Collaborative Bioethics 3

Erick Valdés
Juan Alberto Lecaros *Editors*

Handbook of Bioethical Decisions. Volume II

Scientific Integrity and Institutional Ethics

Springer

Collaborative Bioethics

Volume 3

Series Editor
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The aim of **Collaborative Bioethics**, is to draw attention to an underexplored but increasingly important area of scholarly thought and action: bioethics as a co-creative activity of ethicists working with scientists rather than as always a reaction to biomedical developments after the fact. The scope of this series is determined by each major subfield of science and medicine that raises ethical uncertainties for researchers, regulators, and the public.

Collaborative Bioethics is a series that will provide a central hub for timely publications addressing ethical issues that are emerging right alongside the science. As such, this series will be of interest to a wide swath of readers: bioengineers and scientists at all professional levels; bioethicists intrigued by bioengineering and medical advances; research regulators and funders; and the general public.

Erick Valdés • Juan Alberto Lecaros
Editors

Handbook of Bioethical Decisions. Volume II

Scientific Integrity and Institutional Ethics

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Foreword: On Handbooks

> Handbook: "Old English *handboc* "handbook, manual;" see **hand** (n.) + **book** (n.). It translates Latin manualis and was displaced in Middle English by **manual** (from French) and later in part by **enchiridon** (from Greek). Reintroduced 1814 in imitation of German *Handbuch*, but execrated through much of the 19c. as "that very ugly and very unnecessary word." [1]

The noun "manual" dates in English from the early fifteenth century as "a small service book used by a priest," stemming, through French, from Latin for "of or belong to the hand." By 1530 it was being used to mean "a concise handbook." "The etymological sense is 'a small book such as may be carried in the hand or conveniently used by one hand."[2]

Whatever else may be true of *The Handbook of Bioethical Decisions*, it cannot be said that its two volumes, 68 chapters, over one thousand two hundred pages, and unknown number of grams "may be carried in the hand or conveniently used by one hand"—except, possibly, in its digital forms by skillful manipulators of electronic devices. But as handbooks have expanded in size far from their etymological roots, their numbers seem also to have escalated. From a search of its website, Springer, the publisher of these volumes, lists 2,643 books whose titles contain the word "Handbook," from *The Alien Communication Handbook* to *The Handbook of Esports Medicine*. Meanwhile, a search of the website for Oxford University Press shows 2,185 books with the word "Handbook" in their titles.

So what *are* these handbooks, and what are they good for? Many of them, like this one, are no longer short summaries of a topic. Instead, they have become almost encyclopedias centered on a subject, reference works where one can turn to read thoughtful discussions on a wide range of questions related to a central theme. To be truly all encompassing will prove impossible; the contents of any such handbook can always be criticized as over- or under-inclusive. But unattainable perfection is

[1] https://www.etymonline.com/word/handbook

[2] https://www.etymonline.com/word/manual?ref=etymonline_crossreference

not the goal; the driving motivation for a "handbook" of anything should be its usefulness.

The Handbook of Bioethical Decisions is not exempt from arguments about what it does and does not include, but it clearly, to me, meets the prime directive: to be useful. Volume I, ably introduced by Peter Singer, comprises 40 chapters grouped in two largely different parts: Biomedical Research and Animals, Food, and Environment. The first Part has four sections—Genetic and Cell Research, Enhancement Research, Research with Human Biological Samples and Health Data, and Research with Human Biological Samples and Health Data, and Biomedical Challenges in Research. The second has only three—Using Animals in Scientific Research, Decision Making and Alternatives to Animal Use in Research, and GMOs for Global Challenges. Volume II has four Parts—Research Ethics: Scientific Integrity and Research Misconduct, Research Ethics: Conducting Ethical Research, Institutional Ethics and Bioethics Committees, and Bioethical Issues in Institutional Ethics.

While I might suggest some subtractions from, but more additions to, the topics covered, they do a good job of providing a source for people with a wide range of questions around "bioethics" to find some answers—or, at least, some discussion of their questions. This wide range is particularly important as "bioethics" will not mean the same thing, in different cultures, in different fields, or even among different people in the same culture and field. I regularly argue with the director of Stanford's Center for Biomedical Ethics about the definition of bioethics, whether it is a discipline or a field (a field, I think, but edging, unfortunately, toward a discipline), and whether I am a bioethicist. (I think not, but he disagrees, as, presumably, do the editors of this Handbook.)

I do like the fact that Volume II leads off with six chapters on research integrity—and misconduct. This is not "bioethics" descending from the Nazi doctors' trial, but it is a crucial step in the ethics of bioscience research (and all research, including bioethics research). These questions are often grouped, at least in the United States, with more human and animal subjects research ethics as part of "Responsible Conduct of Research" classes that must be taught to federally funded student researchers, but, too often, I fear they are dismissed as not "real" or "exciting" bioethics. They are—and the six chapters cover most of the important issues.

The second section of Part I, entitled "Conducting Ethical Research," reflects some of that disconnection. Surely the points covered in the first section are indispensable to conducting research ethically. But these shifted the focus more to human subjects of research, with issues of exploitation, participant selection, privacy, and intellectual property. I found the chapter by Jefferson on intellectual property and the effect of "dematerialized" (digital information, and especially "digital sequence information" or "DSI") particularly intriguing and timely—the Convention of the Parties of the Nagoya Protocol to the Convention on Biodiversity is scheduled to meet to discuss that very issue in late 2022.

Part II looks more at the institutions that "do" research and their ethical apparatus, and obligations. The first section looks at the formation and nature of institutional responses to bioethics, from the history of ethics committees at specific

institutions, such as "Institutional Review Boards" and their equivalents in the United States and elsewhere, to the national and international ethics advisory commissions. The second section contains seven chapters that dive deeply into specific activities of ethics committees, both those located at research institutions and broader, national or international bodies. The third section is more of a collection of remaining important bioethics-related issues for research institutions, such as conscientious objection, coercion in mental health treatment, and the ways institutions may be liable for bioethical lapses.

The handbook, from its start in English under the name of a "manual," as a kind of "cheat sheet" manual to help priests through services, can carry the connotation of a little book of answers. Volume Two of the *Handbook of Bioethical Decisions* is decidedly *not* a little book, but, more valuably, it is not a book so much of answers as of explored, and therefore proliferating, questions. The well-grouped chapters do so in an organized and thorough way, complete with substantial references. Bioethics scholars, bioethics researchers, and scientific researchers working in areas that involve bioethics will be able to turn to it to begin, or to deepen, their understanding of important questions about how to make "Bioethical Decisions." All should all find it a useful tool. And "useful" is good.

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We thank Springer and the editors of its new book series Collaborative Bioethics for having invited us to lead the *Handbook of Bioethical Decisions* (Vol. II: Scientific Integrity and Institutional Ethics), aimed at providing robust perspectives for bioethics' professionals to be able dealing with key issues related to integrity in research, and decision-making processes in ethics and bioethics committees.

We are also very grateful to the impressive line-up of authors who participate in this volume, all of them leaders in their corresponding areas. Their commitment, patience and especially their brilliant work have undoubtedly made it possible for the *Handbook* to become a vibrant reality.

Santiago, Chile — Erick Valdés

Santiago, Chile — Juan Alberto Lecaros

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Chapter 1
Introduction: Scientific Integrity and Institutional Ethics: Challenges and Perspectives

Erick Valdés and Juan Alberto Lecaros

Abstract Scientific integrity corresponds to a pattern of conduct in research characterized by the observance and promotion of ethical and deontological principles that inspire and guarantee rigorous and responsible praxis. Consequently, we think that good scientific practices are a set of individual and organizational actions and behaviors based on fundamental values of science expressing principles and responsibilities that scientific integrity entails. Being the set of moral aspirations of an entity, institutional ethics can be understood shaped by socio-cultural beliefs coming from tradition such entity interacts with. Beliefs, laws and cultures are factors that converge and shape social norms that are understood as ethical, in the same way institutional ethics is. In this way, institutional ethics encompasses any department, level or function inside or outside the institution. The emergence of acute decision-making problems in institutional ethics atmospheres is increasingly profuse. Such dilemmas have become progressively complex as controversy of biomedical and clinical practices boosts. For this reason, the relevance of crucial decisions made in the institutional ethics field demands bioethicists to use deliberative devices in tune with unprecedented biomedical inventions. Consequently, a collaborative bioethics must be also aimed at addressing and analyzing the most important ethical concerns and moral quandaries arisen in both research and institutional ethics.

Keywords Scientific integrity · Institutional ethics · Responsible research · Innovation · Scientific research

The possibility of a sole definition of scientific integrity remains open in international scientific community so there is no conclusive unanimity on its meaning. Even so, it is possible to systematize some structural principles for responsible

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research and innovation by observing scientific integrity. Among them we can see truth, rigor and objectivity, independence, impartiality and neutrality, cooperation and honesty, transparency and justice, commitment and social responsibility (UNESCO, 2017). A more specific definition of integrity may be focused on procedures of scientific activities, by evidencing the existence of an enduring link between its theoretical conceptualization and its practical application.

Within the broad set of professional activities scientific research is included, integrity is understood primarily as a duty, namely, as an ethical-legal requirement common to most deontological codes. One operational definition of scientific integrity may refer to different ways it is applied to concrete scenarios in practice. In this fashion, it relates to ideal standards that institutions should meet to promote it. These are the so-called responsible research conducts, quite difficult to demarcate among scientific community. Yet, overall, respectful conducts of scientific integrity are linked to honesty, commitment to truth, preservation of freedom in relation to external pressures, professional standards, and neutrality of professional practice in relation to particular interests, unrelated to research within a framework of responsible research and innovation. In this sense, different institutions involved in scientific research have offered their own specific proposals to ensure compliance with scientific integrity. Some agreed imperatives in scientific integrity settings are related to emphasize principles of honesty, accountability, professional courtesy, justice and good administration, honesty, trust, objectivity, impartiality and independence, openness and accessibility, right to care, fairness and responsibility regarding the future. These criteria (or norms) should establish different levels of responsibility of individual or institutional partners in cross-border collaborative research.

Currently, research integrity is part of a more complex paradigm or model called Responsible Research and Innovation (RRI), which includes ethical issues as well as other more institutional dimensions. That is the reason why we decided to extend the aim of this volume to institution as without encapsulating the issue of scientific integrity in individual practice.

Other dimensions of RRI are public engagement, gender, science education, open science/open access, and governance, among others. More specifically, it has been defined as a transparent and interactive process whereby social actors and innovators hold each other accountable for the acceptability (ethics), sustainability and social desirability of innovation process and its marketable products to enable an adequate integration of scientific and technological advances in our society (Von Schomberg, 2011).

On the other hand, as European Community (2014) declarated, RRI's benefits go beyond societal fit. In fact, it ensures that research and innovation deliver on the promise of smart, inclusive and sustainable solutions to our societal challenges; engages new perspectives, new innovators and new talent from across diverse European society, to identify solutions that would otherwise go unnoticed; builds trust between citizens and public and private institutions to support research and innovation; and reassures society about the adoption of innovative products and services as well as evaluates the risks and how they should be managed.

A negative way of understanding the operational function of scientific integrity, is to comprehend it as those behaviors promoting its violation, by identifying and characterizing specific situations that constitute effective risks of infringement of such integrity. In relation to this point, two types of negative dimensions of scientific integrity have been recognized: scientific fraud and questionable practices. There is a clear consensus in scientific community on the attribution of scientific fraud mainly to three fundamental practices (the FFPs): fabrication of data, through the presentation of results invented by the person in charge; falsification, through the manipulation of research processes and/or results, and plagiarism, through the appropriation of the intellectual work of others without acknowledging their authorship. On the other hand, the so-called questionable practices encompass, according to the OECD: objectionable research practice, objectionable conduct related to data, objectionable conduct related to publications, objectionable personal conduct, financial conduct and other objectionable conduct. Being scientific fraud more serious than questionable practices, there are still no clear criteria to distinguish both practices. As pointed out by Titus et al. (2008), ethically questionable practices in the world of science can occur at all levels of research and many are not denounced. The most common bad practices are data falsification and plagiarism.

Causes that can engender bad practices in scientific research can be grouped around three factors: Individual: associated with inappropriate behavior by scientific community's members; Organizational: related to the nature of interpersonal relationships within an organization; Structural: essentially related to the way of evaluating science and scientists.

Bad scientific practices have a negative impact on different social actors that are related directly or indirectly to scientific research: Researchers: bad scientific practice harms the career and reputation of researchers; Research Participants: participants in clinical trials can suffer dire consequences when the treatments they receive are based on false or incomplete data; Institutions: bad practices can collaterally affect other colleagues in the institution, creating unfounded mistrust among the rest of researchers who belong to it; Society as a whole: bad scientific practices have very negative effects on citizens: mistrust, lack of interest in processes of creating knowledge and its transfer to society.

Nevertheless, there are many mechanisms to promote scientific integrity in institutions. For example, promoting a culture of scientific integrity in the educational community and in the research community, adopting the UNESCO Universal Declaration on Bioethics and Human Rights as a reference text for research and responsible innovation in higher education, encouraging a national policy of scientific integrity, and fostering higher education institutions and research centers to adopt their own code of ethics and good practices, or integrate elements that characterize responsible research and innovation in procedures articulated by higher education institutions, namely: achieve gender equality, involve citizens, promote scientific education, share results through open access policies and promote thoughtful and anticipatory governance of research and innovation. In turn, there also exist the need to promote measures to protect whistleblowers of bad practices, promote

education in scientific integrity at all levels of research and find alternative mechanisms to protect institutions' scientific integrity.

This volume is aimed at showing that scientific integrity corresponds to a pattern of conduct in research characterized by the observance and promotion of ethical and deontological principles that inspire and guarantee rigorous and responsible praxis. Consequently, we think that good scientific practices are a set of individual and organizational actions and behaviors based on fundamental values of science expressing principles and responsibilities that scientific integrity entails. Good scientific practices support responsible conduct in research. Conflicts of interest may arise in situations where the proper fulfillment of public professional obligations and responsibilities, professional criteria or judgment, or the institutional mission's fulfillment may be unduly affected by private or secondary interests. Conflicts of interest should not be identified with research misconduct, but if they are not handled properly they might represent a clear threat to scientific integrity.

In the development of scientific research, there is a whole series of behaviors far from rigorous and responsible praxis categorized from effects and consequences they may cause. Likely, the most serious violation of good scientific practice is fabrication and falsification, even though it is commonly accepted that research misconduct also includes plagiarism. In addition to fabrication, falsification and plagiarism, there are other unacceptable practices that, without falsifying or misrepresenting data recording and results, constitute irresponsible and, therefore, undesirable behaviors.

Integrity control must go beyond the most serious conduits of Fabrication, Forgery and Plagiarism. Although FFP is more studied and referred to in integrity codes, less serious behaviors are more frequent, – sloppy science/Questionable Research Practice (QRP). FF – which due to their low frequency, have a moderate impact on validity. Plagiarism is more frequent and does have a high impact on confidence. Evidence says that selective information use, selective dating, and insufficient mentoring are the most frequent behaviors in this context.

Being the set of moral aspirations of an entity, institutional ethics can be understood shaped by socio-cultural beliefs coming from tradition such entity interacts with. Beliefs, laws and cultures are factors that converge and shape social norms that are understood as ethical, in the same way institutional ethics is. It is common for institutions to make certain general changes to the laws, adjusting ethical standards to institution's needs. Therefore, it is important to know institutional ethics' scope, as because of ignorance some individuals related to the entity my fail when complying institutional ethics. In fact, as institutional ethics implies great commitment of all those related to the entity, it is possible to clarify that it impacts all human resources directly or indirectly linked to the institution.

Institutional Ethics influences every individual who develops activities in an institution or on behalf of it, involved in both hierarchical and subordinate functions and regardless of the employment nature. In this way, institutional ethics encompasses any department, level or function inside or outside the institution. It is intended to examine from an ethical and bioethical perspective, scientific research activities in all areas of knowledge in which human beings participate, including clinical trials, use of human

or animal material and/or available identifiable information, in accordance with current regulations. In addition, it must evaluate, under the same criteria, those research projects affecting the environment and/or future generations.

Among the challenges of scientific integrity and instituional ethics we might certainly include integrity. Yet, today we must take care of the following problems as well: science and risks (how to face uncertainty), science and power (conflicts of power, private sector's intervention, risks for public good, how to create successful public/private alliances), science and sustainability (in one world of global risks – pandemic, climate change- we need complex interdisciplinary science).

How could we put these domains of responsible science into practice? (1) Ethical considerations must accompany research from the start; (2) Seek ethical advice with peers and within the institution; (3) Generate a community of ethical reflection with peers; and (4) Willingness to change our practices, going beyond harm prevention, and being flexible and willing to respond.

While integrity threats from behaviors are less serious than FFP, ethics training is not effective in preventing behaviors' problems. Mentoring is more effective, as modeling students by suggesting experiences with different mentors is a more suitable methodology. Challenges to promote mentoring in institutions are: Common barriers: lack of mentoring culture, lack of time, lack of formal training, and lack of institutional recognition of mentoring (remuneration and academic hierarchy). Some solutions: mentoring training programs; formalization and institutional recognition of mentoring; promote a mentoring culture. Institutional leadership, and international collaborative partnership. On the other hand, institutional challenges to promote a culture of integrity in research also appear, such as management of data and professional expectations, among others.

At the same time, journals must be custodians of knowledge, ensure its quality through high standard oversight, and not being mere knowledge disseminators. As a matter of fact, as pandemic went though, there was a considerable number of very questionable retractions. For instance, a study on hydroxychloroquine (reported damage in patients with COVID-19) in *The Lancet*, and an *NEJM* study that linked cardiovascular drugs with increased risk of getting sick with COVID-19, were retracted because their authors were unable to access the database compiled by Surgisphere. The company argued that it was not providing data upon a confidentiality agreement (Ledford & Van Noorden, 2020: 160). Ultimately, retractions call peer review processes into question and undermine credibility of two journals that have been in business for almost two centuries. They question the peer review system as well as contribute to a lack of transparency and reliability.

We assert that any scientific integrity control system requires a very strong institutional policy, efficient committees and robust government agencies of science. Institutional challenges to promote a healthy research culture are well reflected in the *Hong Kong Principles for Researcher Assessment: Promoting Integrity in Research* (Moher et al., 2020). Principle 1: Assess responsible research practices. Principle 2: Value complete results reports. Principle 3: Reward the practice of open science (open research). Principle 4: Recognize a wide range of research activities. Principle 5: Recognize other essential tasks, such as peer review and mentoring.

The emergence of acute decision-making problems in institutional ethics atmospheres is increasingly profuse. Such dilemmas have become progressively complex as controversy of biomedical and clinical practices boosts. For this reason, the relevance of crucial decisions made in institutional ethics field demands bioethicists to use deliberative devices in tune with unprecedented biomedical inventions.

Consequently, the *Handbook of Bioethical Decisions* (Vol. II: Scientific Integrity and Institutional Ethics) is aimed at addressing and analyzing, from a very contemporary perspective, the most important ethical concerns and moral quandaries arisen in institutional ethics. In this fashion, the volume counts on two parts, Part One: Research Ethics, which addresses issues related to Scientific Integrity, Research Misconduct and Conducting Ethical Research, and Part Two: Institutional Ethics and Bioethics Committees, which analyses Institutional Ethics issues, Ethics and Bioethics Committees roles and scopes, and Bioethical Issues in Institutional Ethics.

We are offering a remarkable collection of works by outstanding international experts on institutional and research ethics, in order for bioethics practicioners to address key issues related to integrity in research as well as to decision-making processes in ethics and bioethics committees. We are certainly thrilled to present this volume to them and the general public interested in such bioethical issues.

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Part I
Research Ethics: *Scientific Integrity and Research Misconduct*

Chapter 2
Data Alteration

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Abstract Data alteration requires consideration of: what are data, when should they be available and what is their quality. Alteration may be intended or unintended: scientific misconduct, scientific error, use of questionable research practices, or community-based and cultural interpretations of data relevance. Situations in which data alteration are at risk include those in which conflict of interest (and thus potential for bias) is endemic, and those in which powerful incentives that do not support research integrity are present. Consequences of intentional and unintentional data alteration are morally important but are not uniformly addressed. Norm and governance changes from the current system are in initial stages of development and must address issues of the data revolution. Points of decision address ethical concerns and moral quandaries researchers will likely face in a system of research practice that does not comprehensively support research integrity.

Keywords Data alteration · Data quality · Data relevance · Data availability · Conflict of interest · Moral quandries · Research integrity

Philosophical/Normative Insights

Alteration of research data (fabrication, falsification) is almost universally considered to be the most serious form of research misconduct. Defined in US regulations as: "…fabrication is making up data or results or reporting them; falsification is manipulating research materials, equipment, or process, or changing or omitting data or results such that research is most accurately represented in the research record… Research misconduct does not include honest error or differences of opinion." (42 CFR, 93.103). Importantly, such violation is largely judged as a violation of research norms and not in terms of harm to research participants or to subsequent patients on whom findings from the fabricated/falsified data are used. Such a blind

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spot requires investigation of philosophical/normative bases for research ethics, under which data alteration falls.

Here we review the work of three philosophers whose insights reveal significant shortcomings in the approach to data alteration and suggest much more productive approaches than are currently in place.

Heather Douglas notes that because research ethics developed in response to failure by the scientific community to self-monitor, the full range of ethical considerations in the scientific endeavor have not been mapped. Science cannot be pursued by individuals in isolation from institutional structures which inform collective responsibilities of the scientific community. Such collective institutions should support individuals in the ethical practice of science. The most obvious – institutional review boards (IRBs) – were forced on science and are not clearly collective institutions (Douglas, 2014). Other collectives are severely compromised – universities and others receiving research funds because of unresolved conflicts of interest (funds and reputation) and journals because they have largely capitulated to business models, paying little attention to the core scientific necessity of producing a record of valid scientific findings. In sum, science currently lacks effective collective institutions supporting research integrity, and suggesting that individual scientists therefore have largely sole responsibility to carry these burdens ignores entrapment of individuals in the perverse incentives created by these institutions.

Data alteration provides a case in point. Data fabrication/falsification violates moral requirements for proper knowledge production and should be seen as an absolute floor, firm and clear, with mechanisms of rebuke for those who fall below them (Douglas, 2014). Instead, US regulations depend on whistleblowers from within the scientific community to report evidence of F/F, and great peril to themselves, and contributing to significant under-detection of data alteration.

Allen Buchanan reveals a different perspective by highlighting false beliefs that subvert morality including omission of institutional environments as necessary to support individual scientific virtues. Such institutional virtues are considerably under-developed, not addressed by policy, again leaving individual scientists carrying the burden of research ethics (Buchanan, 2009). A network of false beliefs, largely protective of institutions such as those receiving research funds on behalf of individual scientists, has not been challenged, in part because these institutions do not allow empirical research into their handling of data alteration and other practices.

Finally, Tadros provides insights about responsibility, relevant for rethinking the overwhelming responsibilization in research ethics of individuals, with institutions which sponsor research and hold the funds, holding hardly any responsibility other than accounting for funds. Appropriate distribution of responsibility makes a difference and can be just or unjust. Responsibility depends on prior social decisions and they alter the probability of our conduct (Tadros, 2020). Relevant social decisions that can be expected to influence data alteration are twofold. First, there are very unclear norms about institutional responsibility for assuring scientific/ethical competence of scientists across their professional careers. Second, scientific institutions such as journals and metrics that flow from their decisions provide serious perverse incentives. Universities should provide nonpunitive assessment, support for

continuing skill development and be a haven against perverse incentives. Apparently, neither is reliably the case today.

All three of these analyses question current logic embedded in functional norms and in regulatory policy relevant to data alteration. We first examine varieties of data alteration, intentional or not, but all carrying actual or potential harm to research subjects and subsequent patients whose treatments are outright wrong or less reliable. Some tools/methods to detect data alteration are noted. Finally, consequences to continuing with the current suboptimal, fragmented system and the tortured decisions required of scientists are compared with an optimal system in which all kinds of data alteration are detected and corrected, supported by incentives aligned with research integrity, are considered as is relevant rebirth of research ethics.

What Are Data, When Should They Be Available and What Is Their Quality?

Data frequently are numbers, referring to measurements, which themselves vary in terms of validity and reliability. Images (histological slides, Western blots, and photos) are also data; there are now significant concerns about the kinds and degrees of alteration of them that cross a line into falsification. Objects can also be data.

It is useful to think of the completeness of a data set and how omissions affect interpretation. Hand describes categories of: data we know are missing, data we don't know are missing, choosing just some cases, self-selection of data, no data for a critical aspect of a system, data that change with time, summaries of data that lose relevant details, fabricated data, and extrapolating beyond data. For example, for decades we have known about harms caused by failing to account for sex (biological) and gender (social) in research. Scientists have rarely done so resulting in catastrophic results for women, particularly in drug research. There is little ethical justification for continuing to fund such research, knowing that the "missing data" are highly relevant (Accounting, 2020).

Of course, some data should not be available for privacy reasons, and alterations may be made to them in support of that goal. For example, the European Union's General Data Protection Regulation (GDPR) gives individuals rights over their data, how it can be used, and access to their own data to correct or erase it, or to transfer it to another data controller (Hand, 2020). Other jurisdictions have different regulations. Likewise, data for research can be anonymized (for example remove names, addresses and social security numbers), which does not guarantee non-reidentification. Pseudonymization replaces identifying information with code, which can allow identification to occur if necessary (Hand, 2020). Definitions of these terms come from the GDPR. The term de-identification comes from US legislation HIPPA referring to removal of 18 data elements listed in that legislation. Some types of information such as rare disease and genome sequencing are more identifying than others. The re-identification risk is an estimate (Chevrier and Others, 2019).

Such measures used to protect privacy do distort data, requiring balancing between the two goals. Altering data quality in this way can hinder its use for research (Chevrier and Others, 2019).

Data alteration also occurs through open data practices, which vary in quality. Databases vary in whether they are peer reviewed or curated and as they become interoperable, data linkage makes corruption from unreliable data sources possible (Leonelli, 2019). Open science involves data dissemination through widely available data infrastructures. The assumption is that these data are of sufficient quality to be used in further investigation, even as clear quality benchmarks are lacking. Curators adapt data to common standards and terminology but may not be available because of cost and size volume (Leonelli, 2017). Some may be of a level of quality to support regulatory decisions.

Varieties of Intended or Unintended Data Alteration

Research misconduct, as defined above, is most commonly thought of regarding data alteration, defined in the US in statute which applies only to federally funded research and to that used to support FDA filings, is understood to be significantly under-detected and under-reported. Unintentional errors cannot, by definition, be research misconduct but do carry unfortunate consequences for reliability of the scientific record and for harms from incorrect findings. Next, situations in which safeguards against improper data alteration are common are described. Finally, a wide range of questionable research practices, apparently widely practiced, with a range of severity and almost entirely unregulated reflect lack of norms re methodological quality in science.

Data Fabrication/Falsification

US Office of Research Integrity definitions appear above. Notably, the actions must be shown by a preponderance of the evidence to have been committed by respondent intentionally, knowingly or recklessly (42 CFR 93.106). Institutions, which receive the research funds, must "have written policies and procedures for addressing allegations of research misconduct…respond to each allegation…foster a research environment that promotes the responsible conduct of research, research training…discourages research misconduct…" (42 CFR 93.227). These regulations, as well as most codes for research integrity are directed at individuals, usually researchers but also research staff. Notably, institutions are rarely held to their responsibilities and journals, which supposedly play a major role in assuring scientific quality are responsible to no one.

Some scientists feel this individualization of responsibility is entirely unfair and that systemic issues in science are both triggering misconduct and are in themselves

unfair, noting that "cheating pays off". The problem is located at the level of the structures of science – its reward systems, rather than individual responses to these systems (Davies, 2019).

Boulbes et al. (2018) show, in a survey of graduate students and postdocs performing bench science, a variety of unethical pressures to which they are subjected. Nearly 40% reported having been pressured by a PI or collaborator to produce positive data, 63% admitted that pressure to publish influenced the way they reported data, 24% said they omitted results that did not support their working hypothesis, and 23% felt manipulating their data or withholding disclosure of negative data was demanded, expected or necessary to prove a hypothesis. In part, they were responding to threats of losing their positions and/or visas. These practices may not have risen to the level of data falsification but clearly depict a system actively undermining ethical scientific practice and apparently allowed by institutions to become normative.

Detection of data fabrication/falsification that rises to the definition of research misconduct depends by regulation on a complainant. Because complainants routinely face retaliation and exclusion, few come forward, guaranteeing underdetection. Likewise, agency requirements for detection and notification of data fabrication/falsification are routinely buried. Seife (2015) notes that FDA findings of research misconduct are seldom reflected in the peer-reviewed literature.

Technological and statistical methods for detection of data fabrication/falsification are evolving. Software can detect some image falsification. Carlisle (2017) describes statistical tests which can determine likely data fabrication/falsification or error and hopes to automate the methods he uses (Carlisle, 2021), of interest because this field has experienced a number of high-profile research misconduct cases. Since current ethical guidelines presume that false data are rare, journals rarely routinely employ such screening tools. Both software and statistical tools provide evidence but do not confirm fabrication/falsification.

A famous, protracted case involving surgeon Paolo Macchiarini describes prolonged lack of detection and resolution of data falsification accompanied by significant patient harm. Cast as a conflict and competition among institutional logics (market-oriented featuring institutional brand and image, scientific scrutiny, and medical care), allegations were dismissed and those who raised them harassed, lack of adequate scrutiny by some journals and which should have occurred at the institution, the conflict retards understanding why it occurred and difficulties in exposing it, eventually done by the media (Berggren & Karabag, 2019).

Scientific Error

Over a 7-month period, one journal screened 200 papers that were on a clear path toward acceptance for publication and flagged 57 for issues with statistical tests, 42 with issues with the blots and 55 with image issues; none had been caught by peer reviewers. Revisiting records of experiments and data collected for a given paper

will allow determination of how errors may have been introduced (Williams et al., 2019).

Examination of retraction notices published in Science over the past 35 years found common unintentional errors in data interpretation and in description of the materials or samples for the experiment. These constituted about half of the errors. Intentional "errors" are deliberately hidden and difficult to detect without access to the full data file – they may be considered data fabrication/falsification (Anderson & Wray, 2019). Just as automated screening software is not commonly used for plagiarism, the software called Seek & Blastin can detect errors in manuscripts and publications for dubious mentions of nucleotide sequence and other reagents (Labbe and Others, 2020).

As an example, cell lines are used in research worldwide but are subject to cross-contamination with other cells and change over time in culture, requiring constant quality control and assurance of their identity. Misidentification of cell lines often remains undetected including by peer review. To deal with this problem a consortium of journals required proof of authenticity of cells at the time of manuscript submission (Fusenig and Others, 2017).

While errors are likely for scientific advancement, a significant subset should have been avoided by properly trained scientists working with statisticians. These include mathematical mistakes, statements not supported by the data, incorrect statistical techniques, which may invalidate findings. Such errors can arise from "bad data", errors in long-term data storage and sharing and extrapolation beyond the data and may be labeled "sloppy science". Detection and management of such errors is haphazard, slow, inconsistent. Error detection and correction should be normalized and not stigmatized (Brown et al., 2018).

Questionable Research Practices (QRP)

QRPs are ethically questionable in part because they potentially increase false positive findings and decrease reproducibility but are tempting because they may increase likelihood of publishable results without resorting to deception or fraud (Bruton and Others, 2020). Researchers may not report these practices when disseminating their work and there are often no formal sanctions against using them. If there are reasons for their use, such reason should be reported and justified (Sacco et al., 2019).

While there is no exhaustive list of QRPs, two surveys provide some sense of their use. Perceptions of NIH principal investigators revealed increasing beliefs that QRPs are normative or necessary for career success, to stay competitive in one's field and more ethically defensible than is fabrication/falsification. They include: concealing data or results that contradict one's own previous research; adding additional research participants because the results collected thus far are not yet statistically significant; deciding whether to include or exclude data after looking at the

impact of doing so on the results; failing to report all of a study's outcome measures (Sacco et al., 2018).

An anonymous online survey of health professions educators found 90% reporting at least one qrp. Those relevant to data collection, storage and analysis showed: 7% stopped collecting data earlier than planned because the results already reached statistical significance, without formal stopping rules; 12% decided whether to exclude nonoutlier data after looking at the impact of doing so on the results; 3% to confirm a hypothesis, selectively deleted or changed data after performing data analysis (Artino et al., 2019).

Of note, qrps are difficult to detect in published literature. Kahan et al. (2020) found that for most published trials, there is insufficient information available to determine whether results were subject to bias such as p-hacking.

Community-Based and Cultural Interpretations of Survey Data Relevance/Precision

Community surveys are common ways to obtain demographic and study-related data. For example, they are used in Global Health research by fieldworkers or community-embedded data collectors so as to facilitate community participation. Some level of data fabrication has been found among fieldworkers. Asking sensitive questions was considered a breach of cultural conventions, others modified study protocols (Kingori & Gerrets, 2019): directly fabricating data is also possible.

Generally, an understudied issue, these practices and their causes have been best documented in Sub-Saharan Africa, where scientists from high income countries hire local fieldworkers as data collectors. According to fieldworkers' accounts, data fabrication/falsification was motivated by irreconcilable moral concerns related to research subjects' poverty (a disqualification from a trial benefit which subjects need), poor trial management, unrealistic workloads and inadequate institutional support. As with clinical trials in general, fabrication detection procedures are usually in place. It is likely that such pressures exist elsewhere, especially where highly-stratified research is conducted in areas with social and economic inequality, high unemployment and weak labor laws (Kingori & Gerrets, 2016).

Decision Points

Some evidence shows that misconduct and misrepresentation behaviors have become normalized, leaving an individual who rejects them at a significant disadvantage. There is disagreement about which questionable research behaviors are actually inappropriate. Selective reporting, trimming outliers are common; a

substantial minority of researchers believe they are appropriate. Is this how good science is done? How does one navigate such system pathologies?

- Seek an employer whose incentives are aligned with quality of science and which actively supports and monitors rigorous science.
- Join a research group that shares data, discusses how to ensure quality, and contains the full range of competencies necessary to do quality science.
- Become facile with technologies such as blockchain that prevents data manipulation. Each data blocked is time stamped and connected in a chain, making data modification impossible without changing the entire chain (Osipenko, 2019).
- It is worth remembering that scandals involving abuse of human research subjects often also include data alteration and that individuals who use internal institutional channels to expose the abuse rarely succeed (Elliott, 2017) and are frequently vilified.

Situations in Which Safeguards Against Improper Data Alteration Are at Risk

Data do not stand on their own – they must be analyzed and interpreted. Bias at any step in the process of designing studies, obtaining data and interpreting its meaning can in effect alter it. Long standing concerns about commercial bias have not been resolved. For example, hiding negative trials by pooling them with other trials and not separately publishing them can distort the apparent risk-benefit profile of a drug candidate. This practice is a form of reporting bias which results in publication of many positively framed articles supporting use of a drug (de Vries and Others, 2019). Another form of data alteration is outcome switching – the practice fishing for outcomes that show what the investigator wants instead of pre-registering the trial with outcomes noted and then reporting on those outcomes.

Two-thirds of biomedical research funding in developed countries comes from industry. An industrial selection effect refers to results that favor the funder and suppress or cast doubt on those that threaten their financial interests. The usual pattern is design bias, selective reporting of outcomes, use of post hoc analysis, withholding publication of negative results. This is accomplished by restriction of access to data, materials seen to be confidential business information and by selective funding to those who share their views (Holman & Elliott, 2018). Such practices can skew whole areas of research.

Since much good can emerge from academic-industry research partnerships, it is incumbent on universities to require that investigators share research data and materials even if they are receiving funding from the private sector (Holman & Elliott, 2018). Disclosuire of funding is necessary as is legal guarantee that the academic principal investigator: has the freedom to control the study design, to publish and to have autonomy in analysis and interpretation of results. There should be no linkage of remuneration with outcome of the research. Practices such as ghostwriters

preparing manuscripts under supervision of the sponsor, then assigning authorship to an academic who has never seen the data but does not have to disclose this fact is unethical. In the three psychiatric trials analyzed by Amsterdam et al. (2017), important adverse events were not disclosed. Journals also can be co-opted to publish such flawed studies because of the significant income they receive from sales of such reprints. Safeguards to support academic/industry collaborations include: establish clear quality criteria and make them public, and mandate data sharing subject work to independent oversight before public release (Edwards, 2016).

Similar concerns should be raised about powerful incentives for hiring, promotion and tenure in academic settings which do not support sound, correct and rigorous science. Rice and colleagues found that citations were almost universally used, although Aksnes and Colleagues (2019) have found there is no evidence citations reflect key dimensions of research quality. Changes in criteria have been recommended but not adopted. Faculty can be expected to tailor their practices to the incentives prevalent not only in their work settings but throughout science.

Decision Points

- Require the conditions noted above before accepting industry research funds and assure that your university will back your decision with oversight and proper legal documents.
- Be very careful about choosing an employer that evaluates performance with criteria that truly reflect scientific quality. While such employers will be unusual, the stakes are high that if you are judged by number of publications and citations, you will be trapped by those incentives.

Suboptimal, Fragmented System or Optimal System?

Concerns about and evidence of suboptimal data practice are frequent although how characteristic of the entire scientific landscape is uncertain. Examples follow.

Concerns about data alteration assume clear decision points about research methodologies and data interpretation. Such decisions may not be so clear, particularly against a background of suboptimal scientific practice, intermittently described. Scientists, especially doctoral and postdoctoral students, may struggle to evaluate the quality of their data or whether the hypothesis has been confirmed by the available evidence or whether a replication was successful (Schickore & Hangel, 2019).

A retrospective analysis of randomized controlled trials (RCTs) included in Cochrane reviews (N = 20,571) found nearly 60% used inadequate methods and 35% were poorly reported. Industry funding, top pharmaceutical company affiliation, trial registration, larger authorship teams, international teams and drug trials were associated with a greater likelihood of using adequate methods. National

Institutes of Health funding and university prestige were not so associated (Catillon, 2019).

Possibility of systemic production of fraudulent gene knockdown studies that target under-studied human genes is described by Byrne and associates. The 48 studies were produced in series, characterized by unusual levels of textual, organizational and figure similarity and submitted to different journals. It is possible they were produced by paper mills. Biomarkers are essential to disease management. A number of them fail, thought to be due to unintentional research error; this study suggests that massive research fraud may be misdirecting research necessary to their development (Byrne and Others, 2019).

A telling tale of a group of clinical trials related to osteoporosis and hip fracture shows failure at every level for detecting and correcting the impact of data from investigators eventually found to have committed research misconduct. Ten years earlier, concerns had been raised about work from one research group in Japan; their work was not dealt with for 15 years. Eventually, 27 or the 33 affected trial reports were retracted. Follow-up of the 12 most likely to have impacted clinical practice showed they had been cited in 1158 publications including reviews, guidelines and clinical trials; in 13 guidelines and reviews, this inclusion was likely to change the results. Almost no reassessment was undertaken and it was not possible to establish the effect on patients whose treatment was based on unreliable research (Avenell and Others, 2019).

No overarching body has the responsibility to coordinate the consequences of proven data fabrication/falsification (Avenell and Others, 2019) or of the other egregious practices outlined above. Smaldino and McElreath (2016) note that since calls for improved scientific methods and data analysis have been reiterated for many years with no detectable change, one can only conclude that incentives, not confusion, are holding them in place. A full list of practices that undermine the integrity of research may be found in Wallach et al. (2018).

More Optimal

Suggested approaches require norm changes and independent oversight.

A small study of individuals who had discovered unintentional errors in their publications (not research misconduct) and requested correction found that journal editors often preferred retraction but also were sometimes not helpful. The scientific reputation of the authors requesting correction was not damaged. Most were motivated by honesty, at the same time believing that the literature abounds with flawed articles that are never corrected or retracted (Hosseini and Others, 2018).

Lack of reputational damage for those who honestly correct their data and other errors is evidence of norm change; it is just the beginning of needed changes in incentives and oversight. Others suggest randomly auditing research labs to detect those with a high proportion of false positives (obtained in small underpowered studies and lacking replication). A simulation study showed significant decrease in

false positive studies which could provide an incentive for quality over quantity of papers. Such an approach was not designed to detect those who fabricate/falsify data but rather to provide a strong incentive to produce data that comply with good research practice (Barnett et al., 2018).

Some (Wager, 2020) have suggested a much more substantive alteration in reporting research. "The ideal system would link the underlying data, appropriately labeled, with the full methods in the protocol and the entry on the trial register…Many checking functions would be automated." Current journal practices have led to significant publication bias and thus an unreliable evidence base, as well as partial reporting of results and methods which cannot be detected through journal articles. Shifting publication away from journals seems necessary to ensure accuracy and withholding funds until research is publicly posted would serve as an incentive. Wager also notes that although such changes have been technically possible and proposed for some time, high publisher profits and journal articles as academic currency.

Yet another approach would address research from commercial entities, which are subject to financial reporting but with an increasing interest in requiring companies to report their social impacts. Depending on how such new regulations are framed, could they reverse the misreporting and suppression of data outlined in an earlier section of this paper?

Decision Points

- Replicate your study before publication.
- If you discover an error in your published research, request correction or retraction (if findings are significantly altered). You will likely be judged honorably by the scientific community.

Constant Rebirth of Research Ethics

Data alteration, negative or positive doesn't come out of nowhere. The frames through which it is been viewed are narrow, focusing on misconduct and individual responsibility for data fabrication and falsification. We have considered several points. How data are viewed and managed reflect system-wide incentives that currently undercut research integrity. A culture in which data are quickly corrected as is the scientific record, is greatly to be desired, along with a lack of stigma for doing so including retaliation against "whistleblowers". Institutions that receive research funds generally have not been responsive for their responsibilities in supporting both good data practices and assistance for those who need to learn them. Too often, reputational protection has stood in the way of learning how to do better.

There is some evidence of revolt among scientists wanting to practice in a more ethical manner than they perceive the current system supports. Institutions need to advocate for such changes, supporting the goal of producing valid knowledge within the bounds of subject protection. Data practices are essential to the trustworthiness of science.

The broader view shows that ethical values change over time, often not accompanied by consensus. That was true in Henry Beecher's time in the mid-1960s (Jones et al., 2016); it was true 30 years later when some parts of the world adopted research misconduct regulations, and it is likely true now. What revisions should be next?

First, the harmful aspects of data alteration and the problems it causes should be reconsidered as a governance problem. While self-regulation by science is necessary, the above evidence has shown it to be far from sufficient, and conflicts of interest resulting from institutions being given responsibility for managing their own integrity violations assures lack of data about causes and consequences. In support of these same self-perceived interests of science and of the institutions producing it, oversight mechanisms are hobbled and often do not impose the sanctions at their disposal. The result is an almost total individualization of responsibility for improper data alteration. Instead, the institutions receiving research funds have a full responsibility to assure scientists practicing under their auspices are fully educated to do their work, can obtain immediately available ethics advice, and that the institutional climate is free of bullies but rather acknowledges and helps scientists deal with perverse incentives built into the broader institutions of science such as journals.

Total scientific self-governance may be justified as essential to academic freedom. Such a view is confused as academic freedom is both a public good and accompanied by rigorous accountability (Bunkle, 2015). Perhaps even more damaging is the fact that it is difficult to estimate the cost of not knowing – not having an evidence base of how many errors and how much scientific misconduct occurs, how it is dealt with and its consequences. This is uncomfortable because you will see evidence of error/FFP, having been told it is your responsibility to report it and yet you will often feel/be punished for doing so. This is the price we/you pay in our current system of research governance.

Second, the data revolution means that data are reusable and often turned from private to public goods. Although still early in its development as a reliable tool, data science has the potential to discover many scientific errors, data falsifications/fabrications and questionable research practices, thus providing an opportunity to correct these practices and avoid their harmful consequences. Yet, problems of discrimination, lack of explainability and transparency are common and ways to discover and prevent these serious ethical problems are still being worked out. At what point do we determine that the value data science provides outweighs the risks/problems? There will likely come a time, in part through data science, that we will not believe how unethical past (now current) practices have been (Enriquez, 2020).

Finally, establishment of a new discipline, meta-research, which studies research itself – its methods, reporting, reproducibility, evaluation and incentives – in other

words, its efficiency, quality and bias. The expectation is that meta-research will recalibrate scientific fields toward higher standards (Hardwicke and Others, 2020).

With these considerations in mind, perhaps the best advice is to: (1) beware of the proclivity of current regulatory practices/system to blame individuals who are actually trying to navigate a system of perverse incentives in production/distribution of scientific knowledge, (2) select those colleagues/institutions that provide learning opportunities and supports to practice science ethically, (3) be aware of the benefits and harms that are often unacknowledged and not measured, (4) do what you can to reform the system but understand that it is likely to be a battle as some institutions/individuals are prospering greatly from the current system and will resist change mightily, and (5) understand that data alteration practices and policy should be evidence-based, to which you can contribute.

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Chapter 3
Research Misconduct and Questionable Research Practices

David B. Resnik

Abstract To promote ethical conduct in science, government funding agencies, academic institutions, and professional journals have defined some types of seriously unethical behaviors as research misconduct and have developed policies and procedures for reporting, investigating, and adjudicating allegations of misconduct. Behaviors that are not as egregious as misconduct but are still regarded as unethical are called questionable research practices. Although there is considerable variation in research misconduct definitions used by different organizations and nations, most of them classify data fabrication or falsification or plagiarism as misconduct. This chapter will distinguish between research misconduct, questionable research practices, and fraud; describe policies and procedures related to misconduct; review some famous cases of misconduct; examine the prevalence and causes of misconduct; and discuss ways of preventing misconduct.

Keywords Research misconduct · Questionable research practices · Ethics · Fabrication · Falsification · Plagiarism · Authorship

Introduction

Ethical norms, such as honesty, integrity, openness, accountability, fair sharing of credit, and social responsibility are essential to the advancement of scientific research because they (1) promote the advancement of the goals of science, such as the development of knowledge; (2) create a research environment that enables scientists to work together toward common goals, and (3) foster public support for science. Data fabrication and falsification, for example, undermine the quest for truth by inducing scientists to accept false hypotheses or unreliable data or results; plagiarism negatively impacts the research environment by destroying trust among

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scientists; and fraudulent or socially irresponsible research undermines the public's support for science (Shamoo & Resnik, 2015).

To promote ethical conduct in science, government funding agencies, academic institutions, and professional journals have defined some types of misbehaviors as "research misconduct" and they have developed policies and procedures for reporting, investigating, and adjudicating allegations of misconduct. Behaviors that are not as egregious as misconduct but are still regarded as unethical are called "questionable research practices" (QRPs). This chapter will distinguish between research misconduct, QRPs, and fraud; describe policies and procedures related to misconduct; review some famous cases of misconduct; examine the prevalence and causes of misconduct; and discuss ways of preventing misconduct.

Misconduct vs. QRPs and Fraud

At a very general level, we can think of research misconducts as behaviors that are widely regarded as highly unethical in science, good research practices (GRPs) as behaviors that are widely regarded as ethical, and QRPs as behaviors that are regarded as unethical but not highly unethical (Shamoo & Resnik, 2015). We can construct a behavioral scale, with misconduct and GRPs at opposite ends, to illustrate this idea (Table 3.1).

Table 3.1 Research misconduct, QRPs, GRPs

Research misconduct	Questionable research practices	Good research practices
Data falsification Data fabrication	Selectively reporting data without providing a good explanation Manipulating statistical analyses to obtain a desired result Poor record-keeping Overstating the significance of one's research	Honestly reporting data and providing good reasons for excluding data Appropriate use of statistics for data analysis Good record-keeping Honestly discussing the significance of one's research
Plagiarism	Inappropriate authorship and citation	Appropriate authorship and citation
	Refusing to share data, methods, and materials	Sharing data, methods, and materials
	Poor supervision of the research group	Good supervision
	Negligent or exploitation mentoring	Good mentoring
	Disrespectful treatment of colleagues and trainees	Respectful treatment of colleagues and trainees
	Not disclosing significant conflicts of interest	Disclosing conflicts of interest
	Violating human or animal research regulations	Complying with human and animal research regulations

While this behavioral scale helps us to understand the difference between misconduct and QRPs, it only provides general guidance for researchers. Government agencies, academic institutions, professional associations, and other organizations have their own definitions of misconduct that provide specific details concerning unacceptable behaviors. These definitions have changed over time and continue to evolve.

During the 1990s, the US government commissioned reports on research integrity that eventually led the Office of Science and Technology Policy (OSTP) to adopt a uniform, federal policy on research misconduct in 2000 (Resnik, 2003). According to this definition:

Research misconduct is defined as fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results…Fabrication is making up data or results and recording or reporting them. Falsification is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record… Plagiarism is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit. Research misconduct does not include honest error or differences of opinion (Office and Science and Technology Policy, 2000: 76262).

The OSTP policy defines misconduct as consisting of fabrication, falsification, or plagiarism (FFP) and distinguishes between misconduct and honest error or a difference of scientific opinion. It is important to distinguish between misconduct and honest error, because mistakes in experimental design, data analysis, and record-keeping are not as unethical as misconduct, since they result from negligence, rather than willful malfeasance. It is important to distinguish between misconduct and differences of scientific opinion because disagreements about experimental design, data analysis, data interpretation, authorship, priority, and other issues are part of normal intellectual debate that occurs in scientific inquiry and are not unethical (Resnik & Stewart, 2012).

In arriving at this uniform definition, government commissions eliminated a category of misconduct, known as "other serious deviations," which had been used by some federal agencies, because it was excessively vague, open-ended, and unenforceable (National Academies of Sciences, Engineering, and Medicine, 1992). Other serious deviations could potentially apply to many types of misbehavior that are regarded as QRPs, such as inappropriate authorship, poor record-keeping, and negligent mentoring. Government commissions also distinguished between research misconduct and "other misconduct," which includes misbehaviors that are not unique to the research environment and are already covered by other laws and policies, such as harassment, discrimination, and financial fraud (National Academies of Sciences, Engineering, and Medicine, 1992).

Although FFP is widely recognized as research misconduct, over half of US academic institutions have definitions that extend beyond FFP and include other misbehaviors, such as significant violations of human or animal research regulations, misuse of confidential information, or interfering with a misconduct investigation (Resnik et al., 2015a). Different countries also have definitions of research

misconduct that include behaviors other than FFP, such as unethical authorship, unethical publication practices, unethical peer review, and interfering with a misconduct investigation (Resnik et al., 2015b).

Recently, some commentators have argued that the federal definition of research misconduct should be expanded to include sexual (or other) harassment, sabotaging research, deceptive use of statistics, and failing to disclose a significant conflict of interest (Botkin, 2018; Marín-Spiotta, 2018). However, there is no indication that the federal definition will be changed anytime soon, because categories of misbehavior other than FFP are (1) already covered by other laws or policies, (2) are not a significant threat to research integrity because they are very uncommon, or are (3) difficult to define (Resnik, 2019).

Scientists must be careful when recording, analyzing, and reporting data so that they do not engage in QRPs or misconduct. Poor-recording keeping can seem like data fabrication or falsification to someone who requests access to data in order to validate or reproduce a research finding. If the data are incomplete, redundant, improperly labelled, or disorganized, it may appear to the data requestor that the scientist has engaged in misconduct. Poor record-keeping was a key issue in the Imanishi-Kari case (discussed below) (Shamoo & Resnik, 2015).

Omission of data can also create ethical problems for scientists. Scientists often do not analyze or publish all of the data related to their research because the data are outliers or they are irrelevant to the main findings of the study and do not need to be presented in the paper. While it is acceptable to exclude outliers from the data analysis for legitimate scientific reasons, such as the data points are due to experimental or human error or are more than two standard deviations from the mean, reasons for not reporting data should be discussed honestly and openly in the paper, since deceptive omission of data may be regarded as falsification of data. Data that are not reported in the paper should be made available to other scientists upon request or in a publicly available database (Shamoo & Resnik, 2015).

Scientists must also be careful to avoiding engaging in QRPs or misconduct when using computer programs, such as Photoshop, to prepare digital images for publication. While it is acceptable to make changes to an image that enhance its clarity, it is not acceptable to make changes that are deceptive. Many journals have adopted guidelines for digital image manipulation and require scientists to submit original and prepared images, so that reviewers and editors can determine whether the manipulations are appropriate (Rossner & Yamada, 2004).

The term "fraud" is sometimes used to refer to cases of research misconduct involving fabrication or falsification of data. However, "fraud" has a specific meaning in the law that may not correspond to misconduct. Fraud is the use of a deception to harm a person (or organization) or deprive a person of a right. An allegation of fraud may serve as the basis for criminal prosecution or civil litigation (Resnik, 2008). Findings of research misconduct made by federal agencies involve administrative law, not criminal or civil law. If a federal agency determines that someone has committed research misconduct, the agency could prohibit that person from receiving research funding, but they would not have the authority to send that person to jail or impose a fine on him or her. Findings of misconduct made by academic

institutions usually involve only contract law. If an academic institution determines that someone has committed misconduct, they could discipline that person or terminate their employment, but they could not send them to jail. A finding of research misconduct made by a funding agency or university could lead to charges of criminal or civil fraud, but this rarely occurs (see, for example, the Breuning and Poehlman cases, discussed below).

Investigating Misconduct

In the US and many other countries, academic institutions and government funding organizations have established policies and procedures for investigating and adjudicating misconduct. These policies comply with standards of legal due process and protect the rights of the accused and the accuser (known as the respondent and complainant under federal law). The respondent has a right to know the charges against him or her, to seek legal counsel, to review evidence, and to interview witnesses. The policies require that all parties maintain confidentiality and that institutions protect the accuser (or whistleblowers) from retaliation (Shamoo & Resnik, 2015).

The process begins when the accuser makes a formal allegation of research misconduct to an institutional official, such as his or her supervisor or department chair. The official will refer the allegation to the Research Integrity Officer (RIO). If the RIO determines that the allegation meets the definition of misconduct and has merit, the RIO will appoint an inquiry committee to determine whether there is enough evidence to warrant an investigation. If the inquiry committee determines that an investigation is warranted, the RIO will appoint a committee to conduct an investigation and gather additional evidence. To make a finding of misconduct, the committee must determine by preponderance of evidence (i.e. more than 50% probability) that the respondent committed misconduct intentionally, knowingly, or recklessly (Office of Science and Technology Policy, 2000). If the investigation committee determines that the evidence supports a finding of misconduct, the RIO will recommend that the institution impose sanctions on the accused party and report the misconduct findings to a funding agency (if one is involved). The agency may accept these findings, ask for more evidence, impose its own sanctions, or conduct its own investigation (Shamoo & Resnik, 2015).

Reporting, investigating, and adjudicating misconduct is a legalistic and time-consuming process that can be very stressful for all parties involved. A finding of misconduct usually leads to loss of employment and an end to one's career in academic science. Innocent scientists who are falsely accused of misconduct may spend tens thousands of dollars on legal fees and suffer irreparable harm to their reputations. Whistleblowers may face stigma or backlash or even lose their jobs or funding if their supervisors are found to have committed misconduct. Because the stakes can be very high in misconduct proceedings, would-be accusers may struggle

with deciding whether to make allegations of misconduct against their mentors or peers (Shamoo & Resnik, 2015).

Some Famous Cases of Misconduct or Alleged Misconduct

Although ethical transgressions have occurred in science for many years, beginning in the 1980s some highly publicized cases of misconduct or alleged misconduct have raised awareness of the problem. Below is a sampling of some of these cases.

In the early 1980s, Steven Breuning of the University of Pittsburgh published 24 papers on the use of neuroleptic antipsychotic drugs to treat mentally disabled children. Breuning's research was funded by a National Institute of Mental Health (NIMH) through a grant overseen by Robert Sprague, Director of the Institute of Child Behavior and Development at the University of Pittsburgh. Sprague questioned the validity of data that Breuning had submitted to support renewal of the grant and informed the NIMH about his concerns. When the NIMH did not act quickly on Sprague's allegations, he alerted the media about problems with Breuning's research, which led to Congressional hearings on fraud and misconduct in government-funded science, led by Representative John Dingell (Democrat, Michigan). In 1987, a NIMH panel found that Breuning had committed research misconduct by fabricating and falsifying patient data. In some cases, patients were entirely fictional. The panel recommended that Breuning be barred from receiving federal research funding and referred him for criminal prosecution. In 1988 Breuning was convicted of defrauding the US government and sentenced to 60 days of imprisonment and five years of probation, and ordered to pay the University of Pittsburgh $11,352 in restitution. The NIMH also launched an investigation of Sprague, who lost all of his NIMH grants but was ultimately cleared of wrongdoing (Shamoo & Resnik, 2015).

In 1986, Thereza Imanishi-Kari, an assistant professor at the Whitehead Institute, which is associated with the Massachusetts Institute of Technology (MIT) and Tufts University, published a paper in the journal *Cell* on using gene transfer techniques to stimulate antibody production in mice. The paper had five co-authors, including Nobel prize-winning molecular biologist David Baltimore. Margot O'Toole, a postdoctoral fellow working with Imanishi-Kari, had trouble reproducing the experiments conducted by Imanishi-Kari that were reported in the paper, so she asked to review the data from Imanishi-Kari's lab notebooks. When O'Toole found discrepancies between data reported in the paper and data recorded in the lab notebooks, she accused Imanishi-Kari of fabricating and falsifying data. Shortly thereafter, MIT, Tufts University, and Office of Research Integrity (ORI), and Dingell's Congressional committee began investigating the allegation. At one point, agents from the Federal Bureau Investigation, which was helping Dingell's committee gather evidence, seized laboratory notebooks. Although Tufts, MIT, and ORI concluded that Imanishi-Kari had fabricated and falsified data, in 1996 a Department of Health and Human Services (DHHS) appeals panel found that there was insufficient

evidence to support this conclusion. Throughout these proceedings, Imanishi-Kari maintained that she was innocent and would only admit to poor record-keeping. Baltimore, who was not accused of misconduct but nevertheless suffered damage to his reputation, described the episode as a witch hunt (Shamoo & Resnik, 2015).

In the 1980s, two prominent researchers, Robert Gallo, from the National Institutes of Health (NIH), and Luc Montagnier, from the Pasteur Institute in France, were both trying to isolate the virus that causes AIDS (acquired immune deficiency syndrome). The researchers had isolated different strains of the virus and they exchanged samples. Gallo named his strain HTLV-IIIb and Montagnier named his BRU, after a patient identified as BRU. In 1983, Gallo and Montagnier submitted their papers on to *Science*. Following publication of the two papers, Gallo received top billing for the discovery of HIV (human immunodeficiency virus). In addition to publishing papers claiming to discover HIV, both researchers sought to patent a test for the virus (Shamoo & Resnik, 2015).

After genetic tests showed that HTLV-IIIb and BRU were almost genetically identical, Montagnier charged Gallo with misconduct, alleging that Gallo had taken BRU samples and falsely claimed them as his own. This accusation led to misconduct investigations by the NIH, ORI, and Dingell's committee. Although Gallo was cleared of misconduct, he suffered damage to his reputation because he was not included among the 2008 Nobel Prize winners for the discovery of HIV, an oversight that many scientists regarded as punishment for "stealing" Montagnier's virus. The US and French governments eventually reached a settlement on co-discovery of HIV and sharing of patent rights. The most likely explanation of the genetic similarity between the HIV strains is that they were both contaminated by a different, highly virulent strain the scientists had been sharing (Shamoo & Resnik, 2015).

From 1977 to 1990, Canadian surgeon Roger Poisson conducted research as part of the National Surgical Adjuvant Breast and Bowel Project (NASBP), an organization founded by University of Pittsburgh cancer researcher Bernard Fisher. The project, which was funded by the National Cancer Institute (NCI), produced many important findings, including the conclusion that lumpectomies are just as safe and effective at mastectomies at treating some types of breast cancer. As early as 1977, NASBP statisticians noticed some irregularities in Poisson's records, but it took over a decade to discover that he had been fabricating and falsifying data. An audit of Poisson's research found that he had altered the records of 117 patients to allow them to qualify for the study. In February 1991, Poisson admitted to Fisher that he had altered patient records and Fisher immediately notified the NCI, which launched an investigation. In defense of his actions, Poisson claimed that he changed records in order to benefit his patients, because he believed that they would get better treatment in a clinical trial than they would outside of the study. In 1993, the ORI found that Poisson had fabricated and falsified data and ordered Fisher to reanalyze the data from papers that contained invalid data. Fortunately, the reanalysis did not change the overall results of these papers (Shamoo & Resnik, 2015).

In 1998, British surgeon Andrew Wakefield and 12 coauthors published a paper in *The Lancet* claiming that 12 healthy children developed gastrointestinal disease and developmental regression after receiving the measles, mumps, and rubella

(MMR) vaccine. The paper also hypothesized, based on these findings, that the MMR vaccine can cause autism. The paper had a negative impact on vaccination rates in the UK and other countries because the anti-vaccination community cited Wakefield's results as proof that childhood vaccinations can lead to autism (Shamoo & Resnik, 2015).

In 2004, British journalist Brian Deer began investigating Wakefield's research. Deer published an article in the *Sunday Times* claiming that Wakefield had not obtained ethics board approval for the study and had not disclosed in the paper that he had received financial support from a law firm that was representing clients who were suing MMR vaccine manufacturers. Wakefield also did not disclose that a lawyer for the firm had helped him recruit patients.

In 2010, the UK's General Medical Council (GMC) revoked Wakefield's medical license after an investigation concluded that he had performed risky procedures without appropriate pediatric qualifications and had conducted research on human subjects without ethics committee approval. After the GMC announced its findings, *The Lancet* retracted the paper.

Deer continued to investigate Wakefield's research. Deer examined the medical records of the patients from the 1998 paper and found that five of the children already had autism before they enrolled in the study and that four which Wakefield had said had developed autism after enrolling in the study were healthy. Deer also found that Wakefield had altered pathology tests results in nine subjects. In 2011, Deer published an article in the *British Medical Journal* accusing Wakefield of fabricating and falsifying data in the 1998 paper. Wakefield has denied these allegations and continues to advise anti-vaccination groups (Resnik, 2018).

In 2004 and 2005 Woo Suk Hwang, a professor at Seoul University in South Korea, published two papers in *Science* reporting the derivation of human embryonic stem (HES) cell lines by therapeutic cloning. Hwang, who earlier had successfully cloned a dog, received international recognition for his HES research and became a national hero in South Korea (Shamoo & Resnik, 2015).

In December 2005, an anonymous whistleblower informed the editors of *Science* that two of the photos of HES cells published in the 2005 paper were duplications. Later, Sung Roh, one of Hwang's co-authors on the 2005 paper, told the media that Hwang had fabricated 9 of the 11 cell lines presented in the paper. A committee from Seoul University began investigating the papers and found that Hwang had fabricated data in both. *Science* retracted the papers and Hwang resigned his position at Seoul University. In 2006, Hwang and five collaborators were indicted on charges of fraud, embezzlement, and breach of bioethics laws. Hwang was sentenced to serve two years in prison, but his sentence was suspended (Shamoo & Resnik, 2015).

In 2005, Eric Poehlman, a professor at the University of Vermont, admitted to falsifying data in 17 federal grant applications and 10 publications over a ten-year period. In 2006, Poehlman pled guilty to defrauding the government and was sentenced to serve a year and a day in federal prison. He also agreed to pay the government $180,000 to settle a civil lawsuit related to the research and was barred for life

from receiving federal grants. Poehlman's publications were retracted (Shamoo & Resnik, 2015).

Poehlman's research assistant, Walter De Nino, began to suspect that Poehlman had been falsifying data when he discovered inconsistencies in the data in a longitudinal aging study. De Nino examined patient records and found that Poehlman had changed data in a spreadsheet to provide stronger support for his hypothesis. De Nino spent months gathering evidence pertaining to Poehlman's misconduct before making a formal allegation. After receiving the allegation, the University of Vermont began investigating Poehlman's research and found that he had falsified data on numerous publications. In one of those papers most of the research subjects were fictional (Shamoo & Resnik, 2015).

In 2006, Anil Potti, a faculty member at Duke University Medical Center (DUMC), published a paper (with 16 co-authors) in *Nature Medicine* that described a statistical model for using the genomic characteristics of tumors to predict response to chemotherapy. Potti's research was funded by an NIH grant obtained by Joseph Nevins, the principal investigator on the project. In 2007, three biostatisticians, Kevin Coombes, Jing Wang, and Keith Baggerly, reanalyzed the data presented in the paper but could not reproduce its results. They published a commentary in *Nature Medicine* in which they claimed that the paper contained numerous errors and problems with the software used in the statistical modelling. Potti submitted a correction to the journal and shared computer software code with the biostatisticians (Resnik, 2018).

In 2008, Braford Perez, a third year medical student who was working with Potti and Nevins, began to review Potti's data and statistical model and found problems with both. He also discovered that the model had not been independently validated. Perez brought his concerns to Nevins and DUMC administrators, but they discouraged him from making a misconduct allegation against Potti because they said that his concerns amounted to a scientific disagreement. They also said that making an allegation would harm Perez's career and DUMC's reputation (Resnik, 2018).

In 2009, Baggerly and Combes learned that DUMC had started clinical trials using Potti's statistical model to guide cancer treatment decisions. They informed the Institutional Review Board (IRB) at DUMC about their concerns. The IRB temporarily halted clinical trials but then restarted them again after a review found no problems with the research (Resnik, 2018).

In 2010, *The Cancer Letter* reported that Potti had falsely stated that he was a Rhodes Scholar on his curriculum vitae and grant applications to the NIH and American Cancer Society. DUMC then launched a misconduct investigation against Potti and found that he had fabricated and falsified data reported in the *Nature Medicine* paper. ORI concurred with these findings and ordered Potti to retract the paper and other publications impacted by misconduct. DUMC also terminated Potti's employment. In 2011, the North Carolina Medical Board reprimanded Potti but did not take away his license to practice medicine (Shamoo & Resnik, 2015).

From the 1990s to 2000s, Joachim Boldt, an anesthetist at Klinikum Ludwigshafen, an academic teaching hospital in Germany, published hundreds of articles in medical journals at a rate of about one article per month. Boldt's research

on using hydroxyethyl starch solutions and other colloids to boost blood volume during surgery was highly influential. In 2009, readers raised some issues with an article Boldt had published in *Anesthesia and Analgesia*. The readers said that results were suspiciously consistent and did not have the statistical variation one usually sees in real data. The journal's editor, Stephen Shafer, contacted Boldt about the concerns raised with his research, but Boldt did not respond. As a journal editor, Shafer did not have the legal authority to launch a research misconduct investigation, so he expressed his concerns to the state medical association, Landesärztekammer Rheinland-Pfalz, which in 2010 formed a committee to investigate Boldt's research. The committee found that Boldt had fabricated data in the disputed study, had not obtained ethics board approval for 68 studies, and had forged copyright signatures for coauthors. The hospital terminated Boldt's employment, and the editors of 16 journals began retracting Boldt's articles. In 2012, the committee concluded its investigation and found that Boldt had fabricated data in 91 publications. The committee referred the matter to the criminal prosecutor, but Boldt fled the country (Wise, 2013). To date, a total of 118 articles published by Boldt have been retracted (Retraction Watch, 2020).

Prevalence Research Misconduct

The prevalence of research misconduct, while thought to below, is difficult to estimate, due to issues with survey methodologies. Surveys that ask researchers to self-report their own misconduct are likely to underestimate the prevalence of misconduct, because people may be unwilling to admit, even in an anonymous survey, to engaging in unethical or illegal behaviors. Martinson et al. (2005), for example, conducted a survey of 3247 National Institutes of Health (NIH)-funded scientists and found that only 0.3% admitted to falsifying or cooking research data in the last 3 years. Fanelli (2009) conducted a meta-analysis of 18 surveys that asked scientists to self-report misconduct and found that 1.97% of respondents admitted to fabricating or falsifying data at some point in their careers. Surveys that ask researchers to report misconduct they have observed committed by others may overestimate the prevalence of misconduct because respondents may not have adequate knowledge of the situation they have observed, and different respondents may observe the same act of misconduct. Swazey et al. (1993), for example, found that 6–9% of 4000 faculty and students who responded to a survey said they had knowledge of plagiarism or data falsification. Titus et al. (2008) found that 3% of 2212 NIH-funded scientists who responded to a survey said they had observed misconduct in the last year. Another issues with misconduct surveys is how to define misconduct. As noted earlier, different countries use different definitions of misconduct, and some surveys may reflect this variation. For example, Okonta and Rossouw (2012) found that 68.9% of 110 Nigerian researchers who responded to a survey admitted to committing research misconduct; however, the definition of misconduct used in this survey

included FFP as well as violating human research regulations, falsifying a curriculum vita and authorship disputes.

Causes and Prevention of Misconduct

For many years, scientists claimed that most research misconduct was committed by a few "bad apples" who were inherently immoral or psychologically unstable. However, the "bad apple" theory has been largely discredited by studies that have also identified numerous factors in the research environment that increase the risk of misconduct, including (National Academies of Sciences, Engineering, and Medicine, 2017; Shamoo & Resnik, 2015):

- Pressure to produce results or publish;
- Competition for funding, jobs, priority, or prestige;
- Financial incentives directly linked to research performance;
- Lack of training in research ethics or familiarity with scientific norms;
- Poor supervision of the laboratory or research group;
- Poor communication among members of the research team concerning data management;
- Psychological stress.

Most experts agree that preventing research misconduct requires the implementation of diverse strategies that counteract the causes misconduct and promote an ethical research environment. Some of these strategies include (National Academies of Sciences, Engineering, and Medicine, 2017; Shamoo & Resnik, 2015):

- Education, training, and mentoring in responsible conduct of research;
- Development of research ethics policies;
- Enforcement of research ethics policies;
- Protection of whistleblowers;
- Ethical leadership;
- Auditing of research.

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Chapter 4
Ethics of Authorship

Sofía P. Salas

Abstract Even though the International Committee of Medical Journal Editors (ICMJE) has developed explicit recommendations regarding authorship, the correct declaration of the contribution of each author is not easily accomplished for a variety of reasons. Therefore, authorship disputes have become an increasing problem within the research community, academic institutions, and funding organisms. This chapter will briefly summarize current criteria for authorship, including the importance of its correct declaration; will identify concepts such as "honorary authorship" and "ghost-writing" as well as some emergent subjects, such as patients as co-authors and suboptimal female representation in the author's list. Additionally, we will discuss some cases of authorship disputes and provide ways of preventing and resolve them.

Keywords Authorship · Misconduct scientific · Mentorship · Gender discrimination · Ethics in publishing

Introduction

The correct designation of authorship in a scientific publication is considered an essential part of the research enterprise: it confers credit for the research and identifies those who will take public accountability for the whole process of the research (Marusic et al., 2014). Since 1978, the International Committee of Medical Journal Editors (ICMJE) has produced and continuously updated the document "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" that contains specific proposals "to review

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ethical standards in the conduct and reporting of research and other material published in medical journals" to be used both by authors and journals (International Committee of Medical Journal Editors).

A rapid search in the electronic data base PubMed using the word "authorship" in the title, reveals that although in 1980 there was only one article related to this subject, in 2020 there were 152 and, most probably, the number will increase, thus indicating the importance of correct authorship for the whole research activity. However, the mere list of authors is insufficient to determine the extent of each individual contribution. Therefore, editors as well as the ICMJE, are encouraging to develop a policy that specifies each author role. But, as we will present in this article, even the most brilliant recommendation will fail when authors act in a mischievous way.

The Importance of Correct Authorship

When defining the authors of a paper, it is important to ensure that those that have made relevant contributions are adequately recognized as authors and also that those who are listed as authors can take public responsibility for what is being published (International Committee of Medical Journal Editors), clearly separating those that have made substantial contributions to the work from those that merely deserve to be acknowledged. Consequently, the ICMJE recommends correct authorship based in these four copulative criteria:

1. *Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND*
2. *Drafting the work or revising it critically for important intellectual content; AND*
3. *Final approval of the version to be published; AND*
4. *Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.*

The final responsibility of defining who is an author is an important task that should be done within those that participated in the research, ideally when planning the work. Nevertheless, while the study is done, other authors can be included as long as their contribution is considered as substantial. Similarly, some of the initial authors could be withdrawn if they did not continue with the research in such a way as to qualify as an author.

Correct assignation of authorship is important for several reasons. First, in terms of transparency, it is a formal way of taking public responsibility for the work being published. Second, publications (both in number and in quality of the journal where the paper is being published) have increasing role in academic promotion and award of grants and some universities may even provide economic incentives for each publication in peer-reviewed journals (Macfarlane, 2021). Similarly, public funding to research universities also considers the number of published papers for monetary

support. Third, authors with high number of papers are usually perceived as key leaders in their fields and are consequently invited as speakers in international meetings or are appointed in advisory committees for the government or the pharmaceutical industry.

As recently mentioned by Macfarlane (Macfarlane, 2021), it is not easy to establish which contribution is deemed so important to satisfy the criteria for authorship; therefore, there is still need of "interpretation". Moreover, since research in medical sciences increasingly includes a multidisciplinary team, with many people making small although essential contributions to the work, it is more difficult that each one satisfies the strict four criteria of ICMJE. Additionally, researchers need to face the "local research culture" that includes designating authorship in a way that is sometimes inconsistent with the criteria; examples are authorship assigned to those that merely give financial support or provide general supervision. In Table 4.1 we summarize the most frequent examples of authorship, which we further explain below.

Honorary or "Guest" Authorship

An honorary or "guest" author is somebody who does not meet the authorship criteria but is listed as an author for a variety of reasons, such as reciprocity, to avoid revenge or alterations on the team-work culture, and also because of a wrongly understood concept of who deserves to be an author, among other causes (Condron et al., 2021). It is not easy to determine the extent of this practice, which might also be related to the local environment. As an example, some authors, particularly those in a junior position, feel obliged to include their senior colleagues, even if their contribution has been minimum. If that has been the traditional practice within the working group, it is very difficult for the newcomers to change this habit.

However, from an ethical point of view, the main problem with this kind of authorship is caused by the inclusion of "honorary authors" to increase the chance of having the article published or to influence the public acceptance on what is being

Table 4.1 Types of authorship

Types of authorship	Definition
Honorary authorship	Does not meet the authorship criteria but is listed as an author.
Ghost authorship	Individuals who contribute substantially to a medical publication but do not appear on the byline and are not acknowledged for their contribution.
Convenience authorship	Is an authorship that is offered as a "reciprocity" trade between authors as a way of increasing the number of publications of everyone.
First author	Is the individual who has done most of the work and is also able to write most of the article.
Corresponding author	Is the individual who will be responsible of communication with the journal.

communicated. An example of this practice was the publications related to rofexocib, a selective COX-2 inhibitor, registered by Merck as Vioxx (Ross et al., 2008). The initial publication of the results of the VIGOR study indicated that this drug had a better safety profile when compared with traditional NSAID drugs, as naproxen, in terms of gastric protection. However, there was a greater incidence of myocardial infarction in the group that received rofexocib than those treated with naproxen or the placebo group (James & Cleland, 2004). Soon after the initial publication was released, the FDA reviewed the original data demonstrating a significant increase in serious cardiovascular events in the rofecoxib group, suggesting that this complication outweighed the gastric advantage of Merck's drug. Nevertheless, the sales of Vioxx increased dramatically until information was obtained that indicated that some reviews favorable to the drug were indeed written by Merck's employees. They prepared the manuscript and recruited academically affiliated researchers as authors. They appeared as first or second authors and were offered a payment for their participation. These academic affiliated authors did not always disclose industry financial support, particularly when it was a review article instead of the report of the results of the clinical trial (Ross et al., 2008). This is a good example on how "honorary writers" influence medical practice, particularly when they are hired by "ghost authors".

Ghost Authorship

Ghostwriters are "individuals who contribute substantially to a medical publication but do not appear on the byline and are not acknowledged for their contribution" (Stocks et al., 2018). The main concern with this type of author is that they could be hired -or be part of- the pharmaceutical, medical device, or diagnostic industry, thus potentially influencing the final content of the publication (Sismondo & Doucet, 2010). This type of authorship usually masks a conflict of interests (Kellner, 2021) and potentially could place patients at risk if clinical decisions are based on biased publications (Sismondo & Doucet, 2010), as was observed in the Vioxx case.

It is important to differentiate a ghost writer from a "professional medical writer". Medical writers contribute to language editing, technical editing, writing assistance and, therefore, do not qualify as authors with full responsibility on what is being published, so their contribution could be acknowledged in the corresponding section (Stocks et al., 2018). As shown by empirical data, this writing support is perceived as having an important role in improving the quality of clinical trial reporting (Gattrell et al., 2016).

Convenience Authorship

This type of authorship corresponds to an author that is offered a "reciprocity" trade between authors, with the sole intention of increasing the number of publications of each individual involved in this "transaction" (Kellner, 2021). Although apparently this practice does not alter the quality of what is being reported, it may influence the academic fair play, since an artificial and without merit increment of a researcher's publication record can have great impact on academic promotion, grants assignation and even the chances of getting a good job (Kellner, 2021). This practice is difficult to manage, since some research centers have publication policies where all staff members are listed in the papers being published, as mentioned recently by Kellner (Kellner, 2021). It is difficult to determine how extended this practice is, particularly within younger researchers. As part of an adequate mentoring, it is important to guide them in a proper way to build their curriculum, avoiding the negative ethical implications of being part of an authorship that is not really deserved.

Although probably less extended than the convenience authorship trade, is the unproper way that some universities and potential authors agree to improve the publication record of the academic center in a rather mischievous way. Basically, the author, who may be in another country or even continent, offers the university to be named in the publication as the corresponding "affiliated" center. This practice can dramatically improve the institution's research indicators, usually measured as number of peer-reviewed articles, giving prestige and a better position in the ranking system, as well as monetary return to the university. As part of this exchange, the author receives "pocket money" from different academic sites, depending on how many affiliations they report in their articles; in other situations, they gain access to additional research resources provided by the institution (Hottenrott & Lawson, 2017). The intended effect of academic incentives (researchers "rewarded" either by obtaining a tenure position or by means of a monetary incentive) is to improve research productivity. Nevertheless, the actual effect has been to produce substandard papers, duplicate publications, and even falsification and fabrication of data (Grant, 2021). When the researchers are rewarded according to the number of citations they get -instead of the sole number of papers published-, the reference list increases with the citation of their own work and if they are in a reviewer's position, they request the citation of their work.

Multiple Authorships

There are several factors that contribute to an increased number of authors per article, and not all of them are related to misconduct (Hottenrott & Lawson, 2017; Madiba & Dhai, 2006). Multidisciplinary research is increasing due to several factors, some of which are inherent to the fact that research enterprise is becoming

more complex, and it has been documented an increase in team sizes and institutional collaborations on papers that are co-authored (Hottenrott & Lawson, 2017). An empiric study provided evidence that multiple affiliation authors are more often found on high impact papers, suggesting a positive correlation between collaboration and citations (Hottenrott & Lawson, 2017).

It is also necessary to mention the culture of "publish or perish", by which academic institutions seem to value more the quantity of papers than the quality of each contribution. One problem with these multiple authorships is that it is difficult that each author fulfills the strict criteria of the ICMJE, and therefore the accountability of the whole research process is diminished.

Another problem is determining who should be the first and/or corresponding author. Traditionally, the first author is the individual who has done most of the work and is also able to write a large amount of the article. The corresponding author may be in a different position in the list and is the individual who will be responsible of communication with the journal. Depending on cultural situations, senior authors grant the first author position to junior colleagues that have worked hard and as a way of giving more visibility to younger scholars. To avoid problems within the group, we suggest that even before the experiments are done, these issues are discussed within the group and there is a minimum agreement on how the author list will be determined (see below).

As noted previously, multiple authorships are particularly frequent in certain disciplines, such as physics and clinical research, whereas in social sciences and humanities, single authors or a senior supervisor with a postgraduate student are frequently observed (Marusic et al., 2011).

Emergent Problems in Authorships

Junior Faculty Roles as Co-authors and the Need of Adequate Mentoring

Several articles express the concern of junior faculty regarding authorship, particularly when they don't get the recognition they think they deserve (Fleming, 2021). Given the asymmetric position, it is expected that senior faculty and/or the supervisor of the postgraduate student or young scholar address this delicate issue as soon as they incorporate into the work team, bringing up authorship early on. We suggest that senior faculty not only introduce younger members to the ICMJE criteria, but also provide them with the whole issue of research integrity, including practices such as fabrication, falsification, and plagiarism. Although it has been suggested that the young scholar should promote this discussion (Fleming, 2021), we believe that it is the senior responsibility to bring up this issue and, ideally, to write down (and share with every staff member) the criteria they will use to establish not only the inclusion of some team members as an author, but who will be the first or the corresponding author.

It is important to mention the so called "chaperone effect", caused by the fact that the reputation of co-authors facilitate the chances that a study from a novel researcher get published in a top journal. This effect is more pronounced in medical and biological sciences than in natural sciences, and results in a "higher average impact relative to papers authored by new principal investigators" (Sekara et al., 2018). Sekara et al. have documented that a "novel author" is unlikely to appear as a senior author if he or she has not previously published in that same journal, providing evidence on the role that mentorship has in providing the experience, expertise, and skills to publish in highly reputed journals.

Patients as Co-authors

In the past years, there has been more awareness of the importance of including patient's perspective on the research design, considering them as "partners" that may influence the whole research enterprise (Cobey et al., 2021). However, the ICMJE authorship criteria seems to be unsuitable for including patients as co-authors. As described by a recent article, regarding editors-in-chief perceptions about this subject, only a minority indicated that patients were involved in peer review of submitted articles and only 3.6% mentioned that their journal had a specific policy on how patients should be included as authors (Cobey et al., 2021). New initiatives, such as the Strategy for Patient-Oriented Research Chronic Pain Network, have recently provided guidance on authorship with patient partners in patient-oriented research (Richards et al., 2020). This guideline explains in plain language which are the requirements for authorship that is useful for potential authors that have personal experience of a health problem, either because they are patients, caregivers, family members or friends that are actively engaged in research conduct and "knowledge translation". Interestingly, this guideline explains the four ICMJE criteria, with the corresponding application to patient engagement.

Gender Gap in Authorship

Several articles, recently published, point to a suboptimal female representation in author's lists, far beyond the actual differences in terms of gender proportion in the corresponding field (Fathy et al., 2021; Schumacher et al., 2021). Likewise, females are a minority in the editorial boards of some journals, as was observed for family medicine journals (Jabbarpour et al., 2020). However, in the medical education field, there has been observed a significant increase in women as first and last authors, reaching almost gender equity in 2019 (Madden et al., 2021). During the SARS-Cov-2 pandemic, it seems that gender imbalances in scientific research actually increased (Bell & Fong, 2021).

It has been documented that an increase participation of women as authors has a positive correlation with the likelihood that the study includes gender and sex analysis, thus promoting scientific advance (Nielsen et al., 2017). However, addressing

gender disparities in science is still challenging, because it has a multi factorial component (van der Wal et al., 2021). A recent study demonstrated empirical evidence of a positive correlation between collaboration and career progression, that potentially could benefit female researchers (van der Wal et al., 2021). As an example, family obligations have a greater impact on female researchers, reducing their possibility to travel and make new collaborations, and less associations with different colleagues negatively impact productivity.

Solving Authorship Disputes

It seems that the best way to solve authorship disputes is to prevent its occurrence by having an open discussion within the research team at the starting point. If it is clear which are the responsibilities expected to be fulfilled by each potential author, the likelihood of disputes decreases. In this initial conversation, particularly if there are junior colleagues that may be not familiar with how authorship is assigned, senior faculty members are expected to be as open as possible regarding who will be listed and what are the requirements for being listed as "the first author". When a person cannot predict how the credit for their work will be given, or when individuals with power dictate who will and who will not participate on the final list, there are always problems (Faulkes, 2018). Even if the person who is being treated unfairly remains silent, the damage to the work environment has already been done. This is particularly relevant within academic institutions where the number of publications (including being listed as first and/or corresponding author) impact career development (hiring and promotion) or may even have financial consequences.

Prevention is the best way to solve author disputes. If this fails, it is necessary to have efficient systems to detect that there is a problem. The Committee on Publications Ethics (COPE) has developed an infographic with signs that might indicate authorship problems (COPE Council., 2019):

Table 4.2 How to suspect potential authorship problems

Signs	Explanation
Author unrelated to the research area	This may indicate a guest authorship or a reciprocity trade.
Impossible prolific author	This could be the case of the head of the department, not necessary something incorrect.
Unfeasibly long or short author list	A case report with too many authors or a clinical trial with only one.
Questionable roles of contributors	For example, no one is responsible for drafting the paper or analyzing the data.
Corresponding author is unable to respond to reviewer's comments or responds with different language quality	This may be legitimate if a language editing service was used

CRediT ("Contributor Roles Taxonomy") is a system that quantifies 14 possible roles of potential authors and is intended to contribute to reduce uncertainty regarding their roles. In simply, it requires quantification of the involvement of each author in one or more of these roles: Conceptualization; Data curation; Analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing; and Reviewing and editing (Fleming, 2021). It is expected that the use of this system might provide a more detailed information regarding individual contribution to the project.

Conclusions

In conclusion, correct authorship is a challenge to all stakeholders involved in the research enterprise: scientific community, journal editors and reviewers (Madiba & Dhai, 2006). Disputes regarding authorship are better dealt within the same researcher group and, if they cannot be solved, the institution should provide an independent guidance to disentangle the controversy (Fleming, 2021). It seems better to anticipate possible discrepancies by having early conversations regarding which are the expectations, goals and perspectives of all the team-work (Regehr, 2021). Additionally, it is important to provide every individual who wishes to be listed as an author the opportunity to get involved into a "more central intellectual role" in the research, thus being able to fulfill the ICMJE criteria (Table 4.3).

Table 4.3 Authorship main guidelines

Guideline	Recommendation	References
International Committee of Medical Journal Editors (ICMJE)	Establishes four criteria of correct authorship	International Committee of Medical Journal Editors (2019)
Contributor Roles Taxonomy (CRediT)	Quantifies 14 possible roles of potential authors	Fleming (2021)
San Francisco Declaration on Research Assessment (DORA)	Recommendations to improve the way in which the quality of research output is evaluated	American Society for Cell Biology (2012)
Committee on Publications Ethics (COPE)	Developed Core practices applicable to those involved in publishing scientific literature	Committee on Publications Ethics (2019)

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Chapter 5
Dissemination of Research Results

T. L. Haven and D. Strech

Abstract In this chapter, we sum up ethical reasons for (and available tools to) comprehensively disseminate research results. This chapter is structured as follows. First, we introduce the normative aspects related to comprehensive dissemination of research results, revealing the ethical principles that guide biomedical research practice (§1). In order to do so, we describe our working definitions for 'research results' and 'dissemination' in the context of this chapter. Whilst the focus of this chapter is on clinical research results, we extend our discussion to other biomedical research results where possible (e.g., preclinical research with non-human animals). We then review the status quo data on results dissemination (§2), and go into contemporary challenges (e.g., completeness and timeliness) associated with results dissemination. The chapter closes with an outlook and a brief survey of existing approaches to foster comprehensive dissemination of research results (§4).

Keywords Publication bias · Trial registration · Research ethics · Institutional review boards · Preprints

Normative Arguments for and Against Comprehensive Results Dissemination

It seems straightforward enough that research results should be disseminated. Yet, why exactly is this perceived to be straightforward, and what if results are disappointing? In this section,[1] we discuss (in decreasing order of importance) some

[1] Several aspects discussed in this section have been described in Strech (2012), this chapter builds on that paper, adding and updating the reasoning the face of novel developments.

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normative arguments based on ethical principles that point in favor of comprehensive results dissemination. We then review a few arguments against comprehensive results dissemination that we go on to rebut, or at least show that they lack proportionality.

Normative Arguments in Favor of Comprehensive Results Dissemination

Retrospective Invalidation of a Prospectively Favorable Risk-Benefit Ratio

Biomedical research comes with inherent risks, be it to human subjects or to animals. Since the Declaration of Helsinki (World Medical Association, 2013), it is only ethically acceptable to conduct biomedical research under certain conditions. Important therein is the idea that the risks inherent in the research are outweighed by knowledge that is gained from conducting the research, and that that knowledge is of value to patients and to society at large. This is called the risk-benefit ratio and research is only ethical of the risk-benefit ratio is favorable, meaning that the knowledge and social value generated from the research outweigh the inherent risks.

In the hypothetical scenario that a researcher recruited patients for a clinical trial, but never disseminated the results of that trial, there would be no social value. This would invalidate the prospective risk-benefit ratio that was based on the knowledge gain. Recently this line of reasoning has been extended to discussions around not disseminating animal research results, in addition to ongoing 3Rs discussion (Strech & Dirnagl, 2019; DeGrazia & Beauchamp, 2020).

Limitation for Risk-Benefit Assessments

Independent review boards such as Institutional Review Boards (IRBs) who assess risk and benefits of new human and animal studies would fail to do their job properly if they approved studies based on a false belief that the respective study would produce novel insights and therewith social value, whereas the intervention had been tested before, but the results were not disseminated.

Negatively Impacting Patients' Health

It is not random which results are not disseminated. We will return to publication bias later, but the finding that positive results are more likely to be published and cited has ethical consequences (Wieseler et al., 2010, 2013). If positive results (including false positives) are more likely to be published, the benefits can be overestimated, and the harms underestimated. This can lead to biased systematic reviews

and meta-analysis that in turn lead to biased clinical guideline and policy formation, which would negatively impact the health of especially those already ill.

Suboptimal Resource Allocation

By not disseminating all research results, we risk funding research lines that have already indicated to be non-fruitful. Given that funding resources are scarce, spending funding on research that is basically redundant is unethical, as it would mean those resources cannot be allocated to areas that look more promising or are in need of more research, based on the state of the literature and the needs of society. When evaluating the large amount of interventional clinical trials on Covid-19, many were found to be redundant and at the same time the vast majority of completed trials did not disseminate their results (DeVito et al., 2020; Pearson, 2021; Park et al., 2021). More than 200 trials investigated hydroxychlorquine and while most had too small sample sizes, almost 90,000 patients participated in these trials which paints a clear picture for suboptimal resource allocation.

Losing Trust in Biomedicine

Following a somewhat more consequentialist reasoning, if results (that often are, but need not be, funded with taxpayer money) are not disseminated, it is expected that the public would lose trust in biomedical research. The exact effects thereof are difficult to quantify. Presumably losing trust would be detrimental on various levels, from patients no longer wanting to follow research findings that could promote their health or deter their illness, to the general public no longer allowing part of their taxes to go to biomedical research, which could slow down medical progress altogether.

Normative Arguments Against Comprehensive Results Dissemination

There are some arguments, although often not very explicit, that warn against comprehensive results dissemination. Here we list two arguments that are often either implicit or explicit in the discourse. First, data is a valuable asset for industry sponsors of biomedical research. Detailed and comprehensive information about study results could reveal commercially sensitive information and would jeopardize a sponsor's competitive position (Strech & Littmann, 2012). Second, out of concerns about participants' privacy, patient-level data should not be shared without compliance to further data protection measures (Institute of Medicine, 2015).

The real challenge that these arguments present is that of proportionality. Under what conditions should it be justified that data are not shared, given the normative principles above? When exactly is it that a company's competitive advantage overrides all else? It seems reasonable to suppose that once an intervention or product has received market approval, the commercial interests and privileged position that comes with being the first of bringing a drug to the market are reasonably protected. But after market approval commercial reasons are no longer legitimate to withhold data from unpublished trials (Strech & Littmann, 2012). Reasons for not disclosing clinical trial information in current legislation are often ill-justified, meaning that they give little explicit guidance as to when protection of a sponsor's interests override other ethical principles.

Similarly, it is up to the particularities of the situation to justify whether protection of privacy supersedes the normative principles listed above. There exist various sharing formats where de-identified data can be shared (albeit not widely) provided that the recipient of the data commits to participant confidentiality and relevant consent requirements are met (Institute of Medicine, 2015). In sum, simply appealing to privacy is not sufficient to withhold adequately protected data in the face of other normative principles.

Defining Terms in This Chapter's Context

What Does "Results" Mean

In this chapter, we take research results to mean patient data and animal data that were produced as part of a scientific biomedical study. Note that this includes the narrower definition of results, namely aggregated patient or animal data, such as effects size estimates for the primary outcome of a study. These aggregated results are typically understood as the core study results. Yet only reporting aggregated results is not without its problems (Lo & DeMets, 2016), as differences between meta-analyses and individual patient data meta-analyses showed (Stewart & Parmar, 1996). Therefore, data sharing in general goes beyond aggregated scores and could include various subject demographics. In principle, one could refer to just about every part of a study as a result (e.g., labelling a new way to use missing data as a 'result'), but our focus will be on data directly derived from patients and non-human animals.

What Does Dissemination Mean

In line with the above, dissemination simply means sharing research results. In the context of academic research, the first dissemination format that comes to mind is the peer-reviewed journal publication with the results section presenting the results as aggregated data. A data-sharing statement in the same text describes whether,

how and to what extent the non-aggregated results data are accessible. But dissemination extends beyond publication, and in recent years we have seen a surge in preprint formats. Preprints reflect the same manuscript format as journal publications but without peer-review.

A second route for results dissemination is via review of different results, such as systematic or scoping reviews. An interesting development with regards to comprehensive results dissemination is that of living systematic reviews. Here automated screening tools are used to spot new papers on a particular topic that are then added to a list. This list is reviewed and updated each month to keep the information as 'live' as possible. To date, the Cochrane collaboration maintains six living systematic reviews (Cochrane Community, n.d.).

Another dissemination route for aggregated results data are the so-called summary results in trial registries where key outcomes are reported. Note that data, especially non-aggregated data, can also be disseminated without reference to a parent-publication via various data-sharing platforms (more on these and other tools for comprehensive dissemination below).

Challenges in Research Results Dissemination: Status Quo Research Results Dissemination

Here we review existing meta-research from different biomedical subfields on challenges with comprehensive results dissemination such as completeness (e.g., publication bias and selective reporting), timeliness, accessibility and quality. Our focus is on comprehensive dissemination broadly, readers interested in good dissemination practices related to research data management are referred to the excellent FAIR principles (Wilkinson et al., 2016).

Complete Reporting

Publication Bias

Although research dissemination extends beyond journal publications, journal publications remain standard for researchers to disseminate their results. This makes publication bias a very relevant phenomenon in the context of results dissemination. Publication bias is defined as "the tendency on the parts of investigators, reviewers, and editors to submit or accept manuscripts for publication based on the direction or the strength of the study findings" (Dickersin, 1990). Often this means that positive studies are more likely to get published and cited, especially if the results could be viewed as novel or exciting (Beg & Berlin, 1988; Jones et al., 2013; Duyx et al., 2017). Note that as the definition makes explicit, this bias is due to both the editorial process, but also the authors' submission tendencies, as it might be that authors

believe their manuscript will not be accepted because the results are negative (Song et al., 2010).

This bias can distort the validity of treatment efficacy estimates since when the findings of positive treatment's effect are published more often than findings of studies where the treatment had no effect remain, consumers of that literature may be artificially led to believe the treatment is safe and effective (Eyding et al., 2010; Turner et al., 2008; Whittington et al., 2004). Not publishing research findings could also run counter to ethical obligations as outlined in the WMA Declaration of Helsinki. In the 2013 revision of the Declaration, it is made explicit that negative results have to published or made available. Journal editors whose journals are a member of COPE have a responsibility "to ensure that research they publish was carried out according to the relevant international accepted guidelines, to secure the integrity of the academic world and to encourage debate by not excluding studies reporting negative results" (Ekmekci, 2017).

In a meta-analysis, publication bias can be estimated with funnel plot, but the method has received some critique (Lin et al., 2018). Another approach pioneered by Turner et al. (2008) was to compare clinical trials registered by the Food and Drug Administration (FDA) and the published literature. They found that trials with negative results were less likely to be submitted (and consequently less likely to appear in journals), whereas with the exception of one study, all trials with positive results had been published.

Publication bias is not restricted to clinical research. Out of 525 publications on preclinical animal studies on stroke, just ten reported no effects (Sena et al., 2010). Sena and colleagues' analyses indicated publication bias was highly prevalent and biased estimates of treatment efficacy. They estimated that the data of around 36,000 animals was not published, a practice in direct clash with the 3Rs principles (Replacement, Reduction, and Refinement, see e.g., Aske & Waugh, 2017). More recent studies showed that about 30–40% of all completed animal studies (often including several experiments) do not publish any results (van der Naald et al., 2020; Wieschowski et al., 2019). Besides harm to animals without any knowledge gain, this overstatement of efficacy may also bias commencement of early phase clinical research (Prinz et al., 2011; Van den Bogert et al., 2016).

It should be noted that this challenge is still existing (Wieschowski et al., 2019; DeVito & Goldacre, 2019), but some progress has been made on the side of journals that explicitly accept negative results, meaning that the direction of the results need not hamper researchers in disseminating their work. Some examples include *Trials* and *PLOS ONE*. Lastly, there are even journals that made negative results their hallmark, such as *Journal of Negative Results in Biomedicine.*

Selective Reporting

A related phenomenon is selective reporting. Here, a results publication exists but the reported results are selective because only the outcomes where a significant effect was observed were reported. Sometimes this is called outcome switching,

when there was no significant effect on the primary outcome and the authors report a secondary outcome where significant effect was observed as primary outcome. Selective reporting can also involve presenting a subgroup analyses as the main finding, or selecting a specific time point to report when the primary outcome results looked most promising (Dwan et al., n.d., for Cochrane, 2010). The phenomenon is thought to be widespread (Dwan et al., 2013, 2014; Song et al., 2010) and can distort the scientific consensus on the effectiveness of a treatment (Chan et al., 2004).

SPIN

Even when nonsignificant results are reported, they may be reported in a distorted fashion such that they could misguide the reader, a phenomenon called SPIN (Boutron et al., 2010; Fletcher & Black, 2007). Here the primary outcome results are nonsignificant and reported, but the message is framed in a way that the results seem promising. Boutron et al. (2010) investigated a representative sample of RCTs and found that 18% of articles contained SPIN in the title and 68% of the abstract, although the types of SPIN varied. One detrimental strategy included the authors to claim a treatment was effective, whilst there was no statistically significant effect of the primary outcome of the study. SPIN can be intentional, but it might also result from ignorance or unconscious bias (Fletcher & Black, 2007). Especially when the abstract is tainted by SPIN, busy clinicians that do not have the time to review the full paper might believe a therapy was effective whereas it was not (Shaqman et al., 2020).

Timely Reporting

Researchers build on each other's work and clinicians want to base their therapies on the best currently available evidence. Therefore, it is important that research results, particularly from clinical trials, are disseminated in a timely manner. This would prevent others elsewhere from conducting similar work (thereby unnecessarily burdening patients). Timely results dissemination, according to the World Health Organisation (WHO, 2015), means that publication in a peer-reviewed journal should be within 2 years of the trial's completion. On top of that, key results of the trial should be made available in the study's registry within 12 months.

Wieschowski et al., 2019 put this requirement to the test and followed clinical trials from German University Medical Centres completed between 2009 and 2013. Only 39% of these trials were timely published. A similar study in the United States with a slightly more conservative approach (i.e., the authors did not carry out additional Google hand-searches) found that on 29% of trials completed between 2007 and 2010 published their results within 24 months (Chen et al., 2016). Looking into clinical and preclinical studies, a systematic review by Schmucker et al. (2014) found only about half of the results to be published within 24 months. Especially in

the face of a pandemic, the WHO expects a much faster dissemination than 24 months to mitigate a global health crisis and this has led many researchers to share their results prior to peer-reviewed publications (Janiaud et al., 2020; Salholz-Hillel et al., 2021). The increase in preprint publications during Covid-19, however, did not result into an overall increase in timely reporting. More than 80% of all Covid-19 trials did not report results within the first 100 days after study completion (Salholz-Hillel et al., 2021) (more on preprints below).

Accessibility

Another challenge is accessibility; results can be published with the intention to be disseminated broadly, but if behind a paywall, results remain inaccessible to many interested readers. Different stakeholders have advocated for an increase of open access results dissemination, ranging from publishers initiating large open access journals (e.g., *PLOS ONE*) to funders like the European Union mandating the work they fund to be published open access (see EU *website*).

Since the Budapest Open Access Initiative in 2002 (http://www.opensocietyfoundations.org), two main ways of assuring accessibility of research results are distinguished. First, there is the green route where researchers deposit their peer-reviewed article into a repository. Second, there is the gold option, here the work appears in an open access journal for all interested to read. Recent years witnessed a huge push in the direction of making biomedical research openly accessible (Kurata et al., 2013). Kurata et al., followed the growth of Open Access publications in biomedicine between 2006 and 2010 and found the rate of open access publications to have nearly doubled (in 2010, 50.2% of publications were open access). In 2018, a large group of European funders launched what is called Plan S, where all commit to only fund research that is published openly and is accessible to all (Plan S & cOAlition S (n.d.); https://www.coalition-s.org). These developments could be interpreted as a collective attempt to meet the accessibility challenge.

However, with the increased focus on Open Access also came the growth of predatory journals (Shen & Björk, 2015). Open Access publishers generally charge authors when their work is accepted, so called Article Processing Charges (APCs). Predatory journals are thought to abuse this model, charging the APCs without providing peer-review or other quality checks (Clark & Smith, 2015; Cobey et al., 2018). Although concerns about predatory publishers have existed for a while, an official definition was established only recently and reads “Predatory journals and publishers are entities that prioritize self-interest at the expense of scholarship and are characterized by false or misleading information, deviation from best editorial and publication practices, a lack of transparency, and/or the use of aggressive and indiscriminate solicitation practices” (Grudniewicz et al., 2019, p. 211). An overview of ethical issues surrounding predatory journals is available at (McLeod et al.,

2018) Broadly, predatory publishers are harmful in at least two ways. They harm by potentially misleading clinicians and patients, and they harm the researchers that publish in them because these journals are often not indexed, meaning the work cannot be identified and used in literature searches or systematic reviews (Clark & Smith, 2015).

Reporting Quality

The final challenge relates to the quality of the results reporting. To ensure that others can use or build on the work, there are certain aspects that must be reported so that readers can critically appraise the study (Altman et al., 2001; Moher, 2009; Kilkenny et al., 2010; Percie du Sert et al., 2020). It has become apparent that biomedical research reports across different subfields are frequently incomplete (Kjaergard et al., 1999; Adetugbo & Williams, 2000; Kilkenny et al., 2009; Macleod et al., 2015). Reporting guidelines were designed to bridge this gap and include a list of items that authors must report to allow others to reproduce, critically appraise and build on the work. Although various reporting guidelines exist, we focus here on two guidelines that encompass two large types of biomedical studies: clinical trials (Revised CONSORT) and in-vivo experiments (ARRIVE 2.0).

Reporting guidelines have been endorsed by many leading journals, professional societies and biomedical research funders (http://www.consort-statement.org/about-consort/endorsers1; Percie Du Sert, 2020). However, surveys and reviews examining the adherence to reporting guidelines in journals that endorsed the guidelines found mixed results (Agha et al., 2007; Baker et al., 2014; Avey et al., 2016). This shows that to endorse something is not the same as to enforce something (Baker et al., 2014), and that ultimately individual authors, reviewers and editors are responsible for assuring manuscripts that they submit, review and approve comply with the relevant reporting guidelines. This is why some have argued for mandating the reporting on these items, as this resulted in some improvement but not as much as hoped for (Hair et al., 2019; Macleod et al., 2019).

Fostering Comprehensive Results Dissemination & Outlook

Approaches to Foster Comprehensive Results Dissemination

There are various things researchers and other stakeholders can do to foster comprehensive results dissemination. In this section, we give a brief (non-exhaustive) overview of contemporary possibilities to comprehensively disseminate research results.

Registries

First, since 2005 members of the International Committee for Medical Journal Editors (ICMJ) only allow trial publications of trials that have been registered (DeAngelis et al., 2004). One of the main reasons for this mandate was to combat selective reporting and selective publication. Since the 2008 revision the Declaration of Helsinki requires that "Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject."

In the United States, trials are mandated to be registered in ClinicalTrials.gov that is managed by the National Library of Medicine, but the registry also accepts trials from outside the US since 2005. In Europe, drug trials are legally bound to be registered in EudraCT database. The World Health Organization maintains its own registry, called the International Clinical Trials Registry Platform.

A similar approach is currently being applied to animal research with preclinicaltrials.eu being the first to launch a tailored registry. Germany recently launched another tailored registry hosted by a regulatory body (animalstudyregistry.org). The Advisory Committee to the director of the NIH, the internationally leading funder for health research, recently recommended that the NIH support a prospective registration platform for animal studies (NIH, 2021).

Although the registration of animal studies is not yet mandated, it is argued that by prompting researchers to think about and commit themselves to quality measures when designing their study, preregistration has the potential to improve the reproducibility of animal research (Bert et al., 2019). Because a large proportion of animal research is exploratory, the registry allows researchers to update their preregistration by adding comments (also on experimental failures, allowing others to learn from these) (Bert et al., 2019). The idea of animal study registries is met mixed views, some arguing it could improve transparency and reduce biased reporting, but some also fearing additional administrative burden and conflicts with intellectual property rights (Wieschowski et al., 2019).

Preprints

An alternative to the traditional peer-reviewed publication are preprints that are faster in disseminating their contents. COPE describes a preprint as "a scholarly manuscript posted by the author(s) in an openly accessible platform, usually before or in parallel with the peer review process" (Cope Council, 2018).

These openly accessible platforms are usually preprint servers where manuscripts can be uploaded for free and come with a DOI. This DOI allows researchers to share their work quickly and allows for bundling of citations once the manuscript gets accepted in a peer-reviewed journal, thereby potentially boosting citations (Conroy, 2019). There are a variety of preprint servers, some more general (https://osf.io/preprints/), others intended to cover works in a specific discipline, such as medRxiv for medical research.

Some expressed concerns about the uprise of preprints (Sheldon, 2018). They could distort the public's understanding of science when journalists pick up non-peer reviewed and sloppy research. Others countered that peer review is not fool proof either and that preprints pose no greater risk than peer-reviewed manuscripts (Tennant et al., 2018). The pros and cons of preprints are well documented (Fry et al., 2019) and whereas initially journals pushed back on preprints, the majority now accepts preprints with some even bundling the submission, meaning your manuscript is automatically uploaded as a preprint and submitted for peer review. Especially in the face of the COVID-19 pandemic, preprints and the use of servers like medRxiv have become increasingly mainstream (Nature Cancer, 2020; Janiau et al., 2020; Krumholtz et al., 2020).

Data Repositories

Sometimes used in addition or as a stand-alone for results dissemination, are data sharing platforms or data repositories. Here authors can deposit their data so that others can use and build on the work conducted. Some common examples include Figshare, Zenodo or country-specific data repositories such as the UK Data service. Many journals now require data to be deposited as a condition for publication (following Transparency and Openness (TOP) guidelines, see Nosek et al., 2015), but the majority of the platforms can also be used without an accompanying journal publication.

Other Formats

Some other formats include micropublications and publishing platforms. Micropublications are small reports of negative or neutral results without a full-fledged scientific narrative. Examples include Science Matters and BMC Research Notes. In order to support authors in deciding what to do with their results, especially if those results may not neatly map onto the format of a peer-reviewed publication, there are tools like Fiddle that act like decision trees (Bernard et al., 2020).

Publishing platforms allow manuscripts to be published without editorial filtering and here peer review happens right after the article appears online. Examples include *F1000 Research* where readers can follow the review of the paper.

Outlook

Recent years have seen a great deal of collective efforts to improve dissemination of research results. Various of these efforts can mutually enforce one another, e.g., registration of study protocols supports our understanding of the completeness of publications, whereas completeness of patient level-data is supported by data

sharing platforms. These are contemporary efforts to uphold the longstanding ethical principles. They are not only valuable because unbiased and timely results dissemination improves scientific understanding of a disease or medical need, they can also help to uphold other ethical principles such a valid informed consent and evidence-based risk-benefit assessment. The challenges associated with comprehensive dissemination of research results might not disappear overnight, but the efforts from different stakeholders within the scientific ecosystem as presented in this chapter seem to suggest that the scientific community is ready to meet them.

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Chapter 6
Conflicts of Interest in Research

Camilo Noguera Pardo

Abstract Conflict of interest's guidelines and regulations have been focused on ensuring good science, mainly understood as a science free from external coercion. However, recent major adverse events involving researchers with significant financial interests in the results of their studies have increased concerns about the risks that financial conflicts of interest pose to well-being of subjects who agree to participate in research. In this chapter, I describe what a conflict of interest in research is, sinoptically explore the main ethical concerns related to it, and propose what compelling requirements for policy and governance are.

Keywords Conflicts of interest · Research · Financial interest; · Ethical concerns · Policy and governance

Introduction

In 2019, Facebook announced to be building technology to read minds. The company was funding research on brain-machine interfaces to create a device which picks up thoughts directly from neurons and translate them into words. The research took place at the University of California San Francisco, where scientists published the results of a study in a *Nature* Communications paper. They built an algorithm able to decode words from brain activity and translate it into text on a computer screen *in real time* (Samuel, 2019).

The research short-term goal was to help patients with paralysis, by decoding their brain signals to allow them to "speak" their thoughts without having to move a muscle. Even though that could be a significant breakthrough in biotechnology and bring up so much benefit to millions of people all over the world and significantly improve their quality of life, such Facebook's endeavor raised ethical

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concerns, not only related to the potential to interfere with basic rights such as mental privacy or the ability to determine when we are humans and when we are machines, but also linked to the implications that emerge when private industry funds academic research.[1]

To a large extent, conflict of interest's guidelines and regulations have been oriented to ensure good science, mainly understood as a science free from external coercion. However, recent major adverse events involving researchers with significant financial interests in the results of their studies have increased concerns about the risks that financial conflicts of interest pose to well-being of subjects who agree to participate in research. The most paradigmatic case of omission of potential conflict of interest in research was that of Jesse Gelsinger. In 1999, Gelsinger, an 18-year-old, died as a result of his participation in a gene therapy study at the University of Pennsylvania. In the following investigation, it was discovered that both the researcher and the institution had shares and interests in the company that produced the therapy, information misplaced in the informed consent presented to Gelsinger and his parents. In response to this calamity, the American Society of Gene & Cell Therapy adopted as a policy that any researcher directly involved in patient selection, in the process of obtaining informed consent and/or in the clinical management of the trial, cannot have shares in the company sponsoring the study (Groeger & Barnes, 2003).

In the last 30 years, private capital has increased its participation in research projects by providing substantial economic support to them (Lo & Thakor, 2022). The increasing cost of research as well as its need for complex technologies and equipment has triggered an economic collaboration between private industry and biomedical and clinical research at universities, as in other public academic environments. This interaction has allowed a rapid transfer of scientific knowledge and technology, by developing new treatments and diagnostic techniques for numerous diseases. Yet, private funds may influence researchs' direction and the quality of publications emerged from them. This influence could harm scientific integrity and interfere with the impact of research on public health.

Existing guidelines have failed to compellingly address problems related to conflicts of interest and additional measures are required to ensure the validity of research and the protection of human subjects.

In this chapter, I describe what a conflict of interest in research is, sinoptically explore the main ethical concerns related to it, and propose what compelling requirements for policy and governance are. While the focus here is the researcher's personal financial relationship, other concerns regarding institutional research ethics committee members, authors and editors of scientific journals, and research institutions, are above the range of this work.

[1] In 2021, Facebook stopped funding the research by saying that this "is over, for now".

What Is a Conflict of Interest?

Professionals have a conflict of interest when their interests or commitments may affect their judgments, research reports or communications to research subjects, participants, patients or clients (NHRPAC, 2001). There are two major types of conflict of interest (Rodwin, 1993): Conflicts between the financial or personal interests of the professional and the interests of a subject/participant, patient or client. Conflicts involving competing loyalties to two or more subjects, patients or clients. Alternatively, the conflict may be between a subject/participant, client or patient and a third party to whom the professional owes contractual obligations, for example, research sponsors, insurance companies, and employers, among others.

As it is controversial that significant conflicts of interest increase the likelihood that professionals engage in misconduct when researching, some prefer the term competing interests rather than conflicts of interest as a way of diminishing any implicit sense of professional misconduct. Law and professional ethics generally require avoiding situations of conflict of interest as a means of protecting oneself from wrongdoing. Scientific misconduct is not always related to conflicts of interest, but conflicts of interest increase the possibility of scientific misconduct.

Distinguishing conflicts of interest from missing obligations is necessary (Rodwin, 1993). A conflict of interest describes a relationship, commitment or interest that imply a moral or legal duty. When a researcher fails in meeting such obligations may incur in violations of human rights, negligence of fiduciary responsibilities related to the professional role, and failure in recognizing the existence of conflict of interest situations. Adopting the distinction between conflicts of interest and lack of obligations may trivialize reasoning, argumentation and debate about the existence of conflicts of interest in research as their recognition would not entail declaring misconduct. In short, a conflict of interest is better understood as an objective situation in which there is greater potential for harm or misconduct as a result of compromising independence when conducting research.

Therefore, a conflict of interest is when "financial or other personal considerations have the potential to compromise or bias professional judgment and objectivity" (Lo & Field, 2009: 46). A conflict of interest exists whether or not decisions are affected by a personal interest, as a conflict of interest entails the potential for bias, and not necessarily its probability. Likewise, a conflict of interest does not imply misconduct in research, as this is limited to fabrication, falsification, and plagiarism (Romain, 2015).

There may be several ranges of conflicts of interest, as they appear in different settings and across all disciplines (Romain, 2015: 122). While conflicts of interest apply to a broad constellation of behaviors and circumstances, they all encompass the use of a person's authority for personal and/or financial gain (Bradley, 2000: 136). In this fashion, conflicts of interest may involve individuals as well as institutions. Moreover, individuals, in certain cases, may have conflicts happening at both an individual and an institutional level. These scenarios may be seen some often

among members of an Institutional Review Board (IRB) and even among those who work on a smaller scale, such as hospital/clinical bioethics committees.

Conflicts of interest have generally divided into two categories: intangible, namely, those involving academic activities and scholarship; and tangible, for instance, those involving financial relationships (Fischbach & Plaza, 2000). For reasons of space, I will focus on the latter.

Conflicts of Financial Interest

The paradigm of conflict of interest is financial interest. Non-financial (or only indirectly financial) forms of bias can pose a serious risk to research and human safety and dignity, yet regulations and institutional supervision are primarily geared towards financial conflicts of interest (GAO, 2001). Significant financial interests must be declared to institutional executives and properly managed. A "significant financial interest," according to the U.S. Public Health Service, is one that could directly and significantly affect the design, conduct or publication of research and thus affect protection of human subjects' issues. While the Public Health Service establishes a minimum monetary interest of $10,000 or 5% ownership in an entity that would reasonably be affected by the investigation, neither Public Health Service nor FDA regulations specify the types of financial interests that can be maintained, or those that cannot be maintained. Financial interests include, but are not limited to: Employment compensation (by another institution than the one funded), payment per consultation, advisory committee service, ownership of shares or property options, intellectual property rights (patents, copyrights, trademarks, license agreements and patent rights agreements), paid expert testimony, fees, keynote speakers fees, gifts, and travel.

The protection of human subjects is key to determining whether a financial interest is ethically significant or not. Property interests (intellectual property rights and equity) are particularly important, not only because they offer potentially huge financial rewards, but also because financial gain depends on the study's outcomes.[2] The main concern is that if researchers have any link to the success of commercial projects, their judgment and objectivity about research's conduct may be affected in detriment of research subjects' welfare. Some basic issues that help reveal significant financial conflicts of interest are when the compensation is affected by research's outcome and when a financial relationship suggests, for a reasonable person, that the researcher or the institution prefers one outcome to another.

Financial conflicts of interest are tangible conflicts, as they can be perceived and measured (Fischbach & Plaza, 2000). While tangible conflicts seem to be easier to deal with than intangible conflicts of interest (such as, academic conflicts or

[2] Researchers may have interests in competing products that are not under study and have a conflict of interest despite not being directly financially associated with a particular study.

intellectual bias, among others), they may not be. Financial arrangements with sponsors may affect many areas of scientific life. Entrepreneurial environment certainly modifies publication practices and sets patterns of investigators and clinicians (Bodenheimer, 2000: 1539–1544).

On the other hand, Romain (2015: 123) states that many reports have shown that industry sponsorship of trials of drugs or devices is strongly related to significantly better outcomes (Bekelman et al., 2003). Even well-designed studies of the efficacy of drugs or devices, without evidence of sensitive risk of bias upon analysis of research model, have obtained better results by showing greater efficacy and fewer harms when they are industry sponsored rather than non-industry sponsored (Romain, 2015: 123; Lundh et al., 2012).

Nevertheless, the evidence is persuasive that researchers with financial links in companies whose products they are studying are much more likely to publish studies favorable to those products (Bodenheimer, 2000). Ideally, researchers should be paid based on time and effort, not on test results. There is broad consensus to prohibit academic researchers and their families from having financial interests in companies that sponsor their research, in companies that manufacture a product or test devices, and in companies that manufacture competing products. Yet, current regulatory approaches, which depend on individual research institutions ensuring that conflicts of interest are handled, cannot ensure that regulations are consistent across institutions. Without mandatory regulations or voluntary agreements, institutions fear that they risk losing researchers to institutions with less stringent regulations. Some have recommended that share ownership bans be imposed only on key researchers in the study such as those in charge of selecting subject-participants, obtaining informed consent, or clinical management. Critics have responded that bias can also occur in the design of the study itself and in the interpretation of study results, and have thus passed broader bans on the fact of being a shareholder of the sponsor. (Lo et al., 2000).

There is general agreement that most of the problematic financial interests are asset holdings and consulting fees. However, internal compensation for researchers and institutions funding research may be equally significant as a source of conflicts of interest (Brody, 1996). Because grants and funding typically cover more than marginal research costs, any situation affecting them, such as the decision to stop a trial or the failure to enroll enough patients with the consequent closure of a research facility, has both financial and professional implications (Fiore, 2012).

Ethical Concerns

There are two important ethical concerns related to conflicts of interest: the preservation of a valid science and the protection of human subjects. In fact, protecting human subjects and those who use the products of science depends on ensuring the validity of research.

Preserving a Reliable Science

Conflicts of interest imply threats to scientific integrity by introducing forms of bias that affect science itself. First, financial relationships between researchers, academic research centres and private industry create incentives to serve commercial interests rather than advance scientific knowledge. Sponsors may try to restrict publication to prevent competitors from advancing. They may also hide negative study findings by keeping control of the publication, or avoid reporting adverse events and side effects to the public. Furthermore, restricted or partial publication increases the cost of clinical progress and may endanger future subjects and patients' health. It also disrupts the work of other scientists who might otherwise improve from censoring previous research (Fiore, 2012).

Second, the validity of study's aftermaths may be influenced by study design decisions: test treatments, placebo or active control, favorable and adverse endpoint, and characteristics of eligible and ineligible participants to finish or modify a trial, among others (Brody, 1996). Conflicts of interest may influence research design and behavior in ways that make study's results invalid, with the potential to misinform many doctors' practice and affect patients' health (Fiore, 2012).

Third, payment of fees by study sponsors to physicians for each patient enrolling in may increase the likelihood that basic scientific research becomes less attractive to researchers and institutions than most immediate application projects preferred by commercial sponsors. As grant payments exceed actual labor costs, profit benefits researchers and/or the institution by providing a discretionary source of income. Indeed, as Fiore (2012) has asserted, overpayments of subsidies can serve as coercion for researchers and research institutions to choose projects that are stimulating for generous sponsors rather than alternatives that could benefit patients or society.

Protecting Human Subjects

As relationships between industry and academic environments become more complex, clinicians can take on multiple roles as a physician, researcher, sponsor, as well as institutional directors and members of ethics committees of institutional research. However, the main role must be that of trustee, which is a person who is trusted to act for the good of others or for the public interest. Therefore, committed loyalties are inconsistent with acting as trustees. Professionals with fiduciary responsibilities should avoid interests (or roles) implying threats to their fiduciary role.

The recruitment of human subjects in industry-sponsored trials conflicts with the fiduciary role. Researchers, sponsors, subsidized institutions and doctors in private practice can benefit from patient participation in research. As studies must recruit a plenty number of subjects to obtain funding, there is an inevitable conflict between potential subject/participants and researchers' interests. In these scenarios,

researchers, pressured to recruit, may interfere with the consent process by misexplaining the research or unduly influencing patients to participate. One of the most objectionable financial provision in clinical research includes introducing patients or their medical information into commerce, being John Moore's case a paradigmatic milestone in this regard.[3] Other recruitment techniques, such as appointing private practice physicians as co-investigators, or retaining them as consultants to gain access to their patients, increases the likelihood that financial considerations may influence clinical judgment as to whether patients benefit from entering a study (Fiore, 2012).

Policy and Governance

Before starting a study, individual researchers must be required to declare financial interests to designated institutional officials that may be affected by the research results. At the same time, institutions are required to report conflicts of interest to Public Health Service funding agencies and take steps to reduce, eliminate or manage conflicts of interest. In US, the FDA requires sponsors and individual researchers to report certain financial agreements as part of commercial applications of drugs, biologics and devices (Fiore, 2012).

International regulations state that information regarding financial conflicts of interest must be obtained from all researchers according to institutional regulations and procedures. In this way, research institutions are formally responsible for developing and communicating the process of evaluation, authorisation and monitoring of agreements that present conflicts of interest. However, specifications are left to each institution and vary widely. In fact, responsibility for conflict of interest regulations tends to be distributed among various administrative units, in such a way that researchers are advised to ensure that they comply with all institutional regulations regarding conflicts of interest (GAO, 2001). In the event that investigators do not comply with conditions or restrictions imposed to handle conflicts of interest, the institution must report the crime and how it is being handled. Improperly handled conflicts of interest may result in the suspension of funding. The corresponding

[3] Moore was near death in 1976 when diagnosed with hairy cell leukemia, a rare and potentially fatal form of cancer. Concerned that Moore's dangerously swollen spleen might burst, surgeons at UCLA Medical Center removed it. Within days, Moore's doctors were amazed to discover that his blood profile had returned to normal. His disease remained in remission until 1996.When Dr. David Golde, a UCLA researcher, examined Moore's spleen, he found that it contained unique blood cells that produced a type of protein that stimulates the growth of white blood cells that can help fight infections. Using new biotechnology, Golde and other researchers developed the cells into a replicating cell that makes the protein in large quantities. In 1984, the regents of the University of California patented the cell line, dubbed "Mo," and named Golde and research assistant Shirley Quan as the inventors. Once he learned of the patent, Moore filed a lawsuit seeking a fair share of the potential profits from products or research derived from the "Mo" cell line (taken from: McLellan, 2001).

Public Health Service may also require the institution to ensure that researchers report the conflict of interest in each public presentation of research results.

Regarding strategies for managing conflicts of interest, declaration and prohibition play a key role. Several influential professional societies, researchers and institutions have advocated the total prohibition of payment to consultations and equity possessions in entities related to their research; some have recommended banning researchers from investing in fields where they do research. Some less drastic approaches are peer review of study design, independent monitoring of research, isolate the researcher from knowledge about the impact of financial interests through blind-confidence provisions, isolate the subject/participant from the influence of financial considerations, and declaration of financial interest to subjects in informed consent, among others (Fiore, 2012).

Critics of current regulations argue that failure to declare financial conflicts of interest violates the ethical obligation to provide potential subjects with relevant information to decide whether or not to participate in research (Korn, 2000). In addition, some argue that failure to declare is fundamentally deceptive and that without complete information about the risks to enroll in research, including the possibility that financial arrangements of the investigator might influence his judgment, consent is invalid (Parker & Satkoske, 2007). Sometimes, the statement confuses or bothers participants and has no effect on eliminating or reducing conflicts of interest. From this point of view, it is unlikely that subjects will be able to make effective use of information on conflicts of interest because, in many ways, they may confuse the nature of clinical trials and the relative and objective risk or have no information enough about financial interrelationships between researchers, institutions and industry.

The U.S. Committee on Conflict of Interest in Medical Research, Education, and Practice, and the Board on Health Sciences Policy of Institute of Medicine of the National Academies recommends that institutions carrying out medical or biomedical research should implement and make public conflict of interest policies for individuals (Lo & Field, 2009: 88–89). Oversight and managing are key at this point as creating create a conflict of interest committee may be also significant. Such committee should apply a wide range of instruments to eliminate conflicting financial interest, and prevent individuals from involving in conflicts of interest as well as to provide additional disclosures of the conflict of interest (Lo & Field, 2009: 89).

Likewise, as part of their conflict of interest policies, institutions should require individuals to disclose financial relationships with pharmaceutical, medical device, and biotechnology companies to the institution annually and when an individual's situation changes significantly. In this fashion, compelling policies should request specific and comprehensive disclosures to allow others to assess conflicts' nature and scope; avoid bureaucracy when individuals making disclosures; and require further disclosure, when needed, to the conflict of interest committee, the institutional review board, and the contracts and grants office (Lo & Field, 2009: 90).

Final Remarks

Clinical, medical and biomedical actors must judge, weigh and balance harsh and uncertain scenarios in research involving actual or potential conflicts of interest. People working in clinical and biomedical settings, as well as society needs to trust that research is being conducted responsibly and free from financial and other constraints. As relation to industry are, now than ever, common in biomedicine, virtuous aftermaths have been produced, such as notable advances in individual and public health. Yet, at the same time, such ties have created risks especially when individual and institutional financial interests may unduly influence professionals' judgments about the primary interests that biomedicine should aimed at. Such conflicts of interest not only threaten research's integrity but also its objectivity and the quality of patients and subjects' care.

Therefore, the goal of conflict of interest management is to minimize its influence on the design and conduct of research for financial considerations. However, simply complying with current conflict of interest regulations, institutional regulations and lax policies does not guarantee to achieve goals of maximizing the protection of human subjects and ensuring valid science. Responsible research conduct requires strong policy and governance for researchers to exercise their best judgment when entering into financial relationships that constitute conflicts of interest, recognize non-financial biases, and, at the end of the day, distinguish the good from what is not.

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Chapter 7
A Priori Publication Agreements to Improve Adherence to Ethics in Research Publications

Lorraine E. Ferris, Rachel Zand, Anamika Mishra, and Paula A. Rochon

Abstract The field of ethics in research publications focuses on creating generally agreed-to academic standards, values, and norms for conducting and publishing research. Publication is the final stage of research, so all those involved in research should have a common understanding of publication ethics before undertaking any research. This common understanding is even more important, given increases in the number of research collaborations, team members, and global networking and multi-disciplinary teams. In this chapter, we advocate for the use of *a priori* written publication agreements as a way to ensure this common understanding. We present some overarching principles that should guide such agreements and discuss several aspects of the research and publication processes that should be addressed in such agreements.

Keywords Research ethics · Power dynamics · Partnerships

Introduction

Publication is the final stage of research; the two cannot be separated. The number of publications involving research networks, partnerships, and collaborations among multiple individuals, groups, and institutions continues to increase, such that

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research is rarely an individual activity anymore. Some of these collaborations are national and international, whereas others are more local, but many involve large teams whose members do not routinely work together and may not be in the same location. Jones, Wuchty and Uzzi's (2008) analysis shows that since 1975, the number of publications in science, engineering, and social sciences with authors based at different universities has increased. The number of authors has also increased (Mongeon et al., 2017; Wuchty et al., 2007). Researchers on many multidisciplinary teams who have not traditionally worked together are now collaborating, in fields as diverse as lab science, technology, and social sciences; humanities and computer science; and life sciences and machine learning.

The heterogeneity of these working groups and lack of physical proximity highlights the need for good communication and for more formal agreements on fundamental ethical and procedural issues before beginning the research. In the absence of such agreements, research can easily be hampered by misunderstandings, discontent, and disputes that may not surface until the manuscript is prepared for publication or even after publication. Preparing the final manuscript is certainly not the time for researchers to discover that their collaborators have important conflicts of interest; have incorporated research data, materials, or the intellectual property of others; or have already published some of the data.

This chapter focuses on ethics in research publications - the codes of conduct governing research and its publication—and discusses some common issues and concerns that arise during these activities. We advocate that researchers use *a priori* written agreements to create a common understanding of research and publication ethics and, in so doing, to prevent or minimize any misunderstandings, conflicts, or ethical violations that may occur at any time in the research process. Publication ethics is often equated with rules to avoid research misconduct and, although misconduct is a major component of research ethics, in this chapter we also consider preferred conduct: "the right thing to do." Finally, we suggest some items to be included in such publication agreements. However, these publication agreements are not the same as the agreements between those who sponsor research and those who conduct it. Here, we focus on the relationships among researchers and the cooperative—not legal—agreements about how they will collaborate in the course of their research.

Establishing Successful Research Teams

Team Dynamics

Research is almost always a collaborative endeavour, often involving teams of individuals with different types and levels of expertise who work toward common goals. Over the past 30 years, multidisciplinary and inter-institutional research teams have become the norm. Inter-institutional collaborations involving a top-tier university produce high-impact articles (Jones et al., 2008). However, conflicts can arise

among team members when a lack of communication, poor coordination, different scholarly practices, and weak group cohesion result in ethical dilemmas. Many conflicts can be prevented by putting more time and effort into creating and fostering team dynamics, setting accountability norms, and implementing constructive methods of conflict resolution. Cultural differences may enhance the quality of research, but they can also be detrimental if, for example, they induce an unconscious bias into the research. These possibilities highlight the need to educate the team about unacceptable behaviours in research and publishing (Thurow et al., 1999) and to ensure that violations have clear consequences.

Frassl et al. (2018) describe ten actions to establish a successful research team, all of which are applicable in the initial stages of establishing the research. These actions include choosing team members wisely, having strong leadership, and cultivating equity, diversity, and inclusion. From there, creating the infrastructure for ethical authorship includes providing digital tools for sharing data and manuscripts, a writing strategy, a data management plan, and criteria for authorship and contributorship. Common sources of conflict include perceived unevenness in member responsibilities and workload, differential access to resources, and perceptions of unequal treatment. It is important for the principal authors to maintain open communication among team members and to provide ample opportunities to troubleshoot small concerns before they fester and grow (Levine, 2005). Fitzsimons and Krahl (2018) tell of a postdoctoral fellow in conflict with the team leader and who chose avoidance over communication. The postdoc attempted to publish data without the leader's permission. If the leader had been sensitive and proactive, the conflict might have been resolved before any damage had been done.

Creating productive team dynamics often requires effective management skills. Many researchers are not trained in these skills, which include effective communication, interpersonal management skills, motivational strategies, and conflict resolution. Such skills can be acquired in several ways, including taking courses in team management, some of which are offered online specifically for researchers (see for example, pimpyourscience.org team building lessons).

Establishing Overarching Principles

An effective way for research teams to work together is to establish some common, overarching principles to be observed during the research. Deciding on these principles at the outset will help establish the ground rules for working together. Examples of such principles include those addressing scientific integrity, the ethical conduct of research, transparency and disclosure, professionalism, and the importance of equity, diversity, and inclusion of authors and team members (Table 7.1).

One of the most important overarching principles is a commitment to scientific integrity, including intellectual honesty, accountability, and taking personal responsibility for one's actions. Scientific integrity is often defined by codes of conduct, and having team members agree to follow one or more of these codes is vitally

Table 7.1 Examples of overarching principles that can be included in an *A Priori* publication agreement

Scientific integrity
Adopt recognized scientific integrity statements or codes. **Resources:** The Singapore Statement on Research Integrity (2010) from the World Congress on Research Integrity (https://wcrif.org/documents/327-singapore--statement-a4size/file). The four principles (honesty; accountability; professionalism; and stewardship) and fourteen responsibilities provide a strong framework for promoting the responsible conduct of research. International Ethical Principles for Scholarly Publications Council of Science Editors have a white paper on publication ethics which promotes integrity in scientific journal publications https://www.councilscienceeditors.org/resource-library/editorial-policies/white-paper-on-publication-ethics/ NIH Office of the Director. National Institutes of Health – Guidelines and Policies for the Conduct of Research in the Intramural Research Program at NIH (2019) The European code of conduct for research integrity (allea.org/code-of-conduct/) Committee on publication ethics (COPE) provides guidance on a variety of issues regarding publications including data fabrication, undisclosed conflict of interest, and image manipulation (publicationethics.org).
Ethical conduct of research
Adopt recognized codes of conduct for protecting human participants and use of animals in research **Resources:** Declaration of Helsinki – Ethical Principles for Medical Research involving Human Subjects Belmont Report – Ethical Principles and Guidelines for the Protection of Human Subjects of Research (1979) Directive 2010/63/EU on the protection of animals used for scientific purposes PHS Policy on Humane Care and Use of Laboratory Animals, 2015

Transparency
Transparency between members of the research teams is critical. Financial conflicts of interest need to be made clear from the start of the research study and added as new conflicts are identified (Rochon et al., 2010). Any personal or professional relationships that could interfere with, or be seen to interfere with, the integrity or the quality of the research need to be declared and managed appropriately. **Resources:** The *Financial Conflicts of Interest Checklist 2010 tool [*to facilitate the structured reporting of conflicts of interest throughout the research process (see Rochon et al., 2010) Memorial Sloan Kettering created a comprehensive set of principles with a section that focuses on disclosure and transparency to external groups and in particular journal disclosure. These sections include disclosure of personal financial interests, public transparency of this information and principles related to following the existing journal disclosure requirements (see Dyer, 2019).
Collegiality
Collaboration and cooperation are key to successful research projects. This includes transparency, open communication and resolving conflicts fairly as they arise **Resources:** NCIC team science field guide https://www.cancer.gov/about-nci/organization/crs/research-initiatives/team-science-field-guide/collaboration-team-science-guide.pdf Collaboration and Team Science: A field guide (see Bennett et al., 2010)
Equity, diversity and inclusion
It is important that research teams are actively established using the principles of EDI and that core members have an ethos that embraces diverse perspectives and recognizes the importance of equity and inclusion on the team and in decision-making. This includes identifying and addressing unconscious bias and ensuring that ensuring that all members feel respected for who they are and what they bring to the team. Resources: Government of Canada. Best practices in equity, diversity and inclusion in research https://www.sshrc-crsh.gc.ca/funding-financement/nfrf-fnfr/edi-eng.aspx Urban Institute Guide for Racial Equity in the Research Process Diversity, Equity, and Inclusion Council Working Group on Content and Communications September 2020 draft https://www.urban.org/sites/default/files/publication/103102/urban_institute_guide_for_racial_equity_in_research_process_0.pdf

important because the codes establish common expectations for the responsible conduct of research.

Although many of the other principles in Table 7.1—ethical conduct of research, transparency, and professionalism—are often part of scientific integrity, highlighting each principle separately allows the team to consider more details about what these principles mean for the specific research being undertaken.

Finally, equity and diversity, are rightfully receiving more attention from institutions and funding agencies as they strive to create more inclusiveness in research environments. From a principled perspective, it is the ethical thing to do, but there are other advantages. Nielson et al. (2017) highlight the gains of having gender diversity on research teams. In 2018, *Nature* talked to research groups who promoted diversity and identified some key features that made these group successful (Powell, 2018). Clearly, having core team members who believe the best research is produced by diverse teams seems to be a factor in their success. Striving for equity in how the research is conducted (e.g., have representative samples) has been receiving attention, and some have called for, among other things, diversity in stakeholders and equity in the design of the research (Hirchhorn et al., 2021).

Detailing the Research Collaboration

Creating overarching principles is an important objective, but early discussions about the details of the collaboration are also important, although it is a complex process, and consulting existing guidelines will be helpful.

Smalheiser et al. (2005) offer guidelines on such topics as sharing reagents and data, designing experiments, division of labour, collaboratively publishing results, and the order of authorship. Gadlin and Jessar (2002) from the National Institutes of Health (NIH) Centre for Cooperative Resolution reflect on their experiences in resolving disputes and offer questions to guide *a priori* discussions on collaboration. These questions relate to the timeline of a project, the expected contributions of group members, intellectual property issues, and authorship. They also discuss issues such as who will handle public presentations and media inquiries and how to handle the loss of a member of the research team with regards to data management, credit, and authorship. Establishing these "scientific prenuptials" can help reduce the need for a third party to get involved for conflict resolution.

Henson-Apollonio (2005) also propose an approach to establishing *a priori* publication agreements among collaborating institutions, emphasizing both the drafting of such agreements and approving the final versions. In particular, they recommend that each institution draft a vision of the agreement that outlines project goals and then submit the draft for discussion among institutions. Each institution is encouraged to define its activities and required resources by identifying their own objectives and activities and highlighting any gaps in tangible and intangible resources that it is contributing to the collaboration.

The authors also recommend having collaborating institutions identify what each will gain from the partnership and including each institution's legal or technology-transfer office in the discussion. Next, they recommend creating a joint work plan that contains detailed and clear guidelines of the tasks and responsibilities of each institution, establishing an intellectual property management plan, and identifying conflict resolution processes. These agreements will likely require amendments as the partnerships develop (Henson-Apollonio, 2005).

Others also believe that proactive discussions through the use of *a priori* publication agreements can prevent disputes (Berndt, 2011; Gold & Bubela, 2007; Delgadillo, 2016). For example, the best way to prevent authorship disputes, according to Sethy (2020), is to have a culture of ethical publication practices, discuss the responsibilities and order of authorship among contributors before drafting the manuscript, and then revisiting the contributions before submitting the manuscript for publication. Because some journals limit the number of authors and collaborators that can be listed for some of their publication types (e.g, comments, viewpoints, editorials), knowing the target journal's policies before this discussion is important.

Albarracínet al. (2020) advocate for getting agreement on the responsibilities of all authors at the onset of the project, recording the agreements and decisions regarding production and authorship, and developing guidelines and checklists to reduce conflict regarding authorship. The importance of such agreements in ensuring that research partnerships are equitable, productive, and oriented toward mutually established goals is especially important for international research partnerships (Lau et al., 2014).

Another approach to *a priori* publication agreements comes from a group of Canadian researchers who created the *Financial Conflicts of Interest Checklist 2010* (Rochon et al., 2010; Table 7.2). This Checklist was designed to ensure transparency among team members by having each member complete the Checklist before and periodically during the research. The Checklist is important because an author's financial interests in the research must be reported to the journal when a manuscript is submitted for publication.

The investigator completing the Checklist describes the study and his or her responsibilities in that study. Information is provided about the study's funder and related contracts. Detailed are the responsibilities of the study team to the funder for research tasks ranging from conceptualizing and designing the study to deciding authorship, authorship order, and who is to be the study guarantor. The Checklist then poses questions, the answer to which create a structured description of the personal financial information of the investigator as it relates to the study. Having each investigator update the Checklist as new and potential financial conflicts of interest arise provides an opportunity to manage potential conflicts early on. This process reduces unnecessary concerns about the objectivity of a study when a manuscript is submitted for publication (Table 7.2).

Using the Checklist or a similar process for disclosing and recording conflicts of interest is important because many times investigators may not be aware of their colleagues' financial relationships and how those relationships might bias the study results.

Table 7.2 Financial conflicts of interest checklist (Abbreviated version)

Study Information: Study Team and Funder Relationship Profile

Item	Descriptor	Response
1.0	Who has ultimate responsibility or authority over following areas of the study?	
1.1	Conceptualize or designing the study†	Study Team☐ Funder☐ Shared‡☐ Don't know
1.2	Approve final design	Study Team☐ Funder☐ Shared‡☐ Don't know
1.3	Approve final data analysis plan	Study Team☐ Funder☐ Shared‡☐ Don't know
1.4	Recruit participants†	Study Team☐ Funder☐ Shared‡☐ Don't know
1.5	Collect or assemble the data†	Study Team☐ Funder☐ Shared‡☐ Don't know
1.6	Analyze the data	Study Team☐ Funder☐ Shared‡☐ Don't know
1.7	Interpret the data†	Study Team☐ Funder☐ Shared‡☐ Don't know
1.8	Study supervision or coordination†	Study Team☐ Funder☐ Shared‡☐ Don't know
1.9	Decide dissemination plan related to study results	Study Team☐ Funder☐ Shared‡☐ Don't know
1.10	If the study is published, who has ultimate responsibility or authority over the following areas of the study?	
1.10a	Draft all or parts of the manuscript(s) †	Study Team☐ Funder☐ Shared‡☐ Don't know
1.10b	Revise manuscript(s) for important intellectual content†	Study Team☐ Funder☐ Shared‡☐ Don't know
1.10c	Finalize manuscript(s)	Study Team☐ Funder☐ Shared‡☐ Don't know
1.10d	Decide where manuscript(s) will be submitted for publication	Study Team☐ Funder☐ Shared‡☐ Don't know
1.10e	Decide timing of manuscript(s) submission for publication	Study Team☐ Funder☐ Shared‡☐ Don't know
1.10f	Decide authorship	Study Team☐ Funder☐ Shared‡☐ Don't know
1.10g	Decide authorship order	Study Team☐ Funder☐ Shared‡☐ Don't know
1.10h	Administrative, technical, or logistic support †	Study Team☐ Funder☐ Shared‡☐ Don't know
1.10i	Act as a study guarantor†	Study Team☐ Funder☐ Shared‡☐ Don't know

† *International Committee of Medical Journal Editors (ICMJE) criteria for author contributorship*

‡ *Study team and Funder shared the responsibility or authority*

Personal Financial Information: Financial Profile

Item	Descriptor	Response
1.0	Does this study provide you with salary support?	Yes☐ No☐
1.1	If yes (to item 1.0), estimate the % of your salary obtained from the funder(s)?	___%
2.0	Will you personally receive direct or indirect financial benefit for your role in this study?	Yes☐ No☐ Don't know☐
2.1	If yes (to item 2.0), what is the amount?	$_____
3.0	Will your department or institution receive financial benefit (direct funding, gift(s), general use (discretionary) funds or other payment above your institution's standard administrative overhead rate) from the study funder?	Yes, currently☐ Yes, past only☐ No, but will in future☐ Never☐ Don't know☐
3.1	If yes (to item 3.0), please specify	_____
4.0	Does this study involve the commercialization of intellectual property (e.g., patents, copyrights or royalties from such rights)?	Yes☐ No☐ Don't know☐
4.1	If yes (to item 4.0), who receives the financial benefit	_____
4.2	If yes (to item 4.0), how is it commercialized (e.g., patents, copyrights or royalties from such rights)?	_____
5.0	Do you have any financial interests with competitor(s) of the funder(s) of your study?	Yes☐ No☐
5.1	If yes (to item 5.0), please specify	
6.0	Do you currently have or expect to have any financial interest related to the study funder(s)?	Yes☐ No☐ Don't know☐
6.1	If yes (to item E.6.0), please specify	
7.0	Do any of your immediate family members (spouse or spouse equivalent; dependent child) currently have or expect to have a financial interest in the study funder?	Yes☐ No☐ Don't know☐
7.1	If yes (to item E.7.0), please specify	_____

Authorship Information: Authorship Profile

Item	Descriptor	Response
1.0	Is there a manuscript submitted for publication?	Yes☐ No☐
1.1	If Yes (to item F.1.0), what is the title of the manuscript?	_____
2.0	Are you an author on this manuscript?	Yes☐ No☐
2.1	If Yes (to item 2.0), which aspects of manuscript development were you involved with? †	
2.1a	Obtain funding	Yes☐ No☐
2.1b	Conceptualize and/or design the study	Yes☐ No☐
2.1c	Collect or assemble data	Yes☐ No☐
2.1d	Analyze or interpret data	Yes☐ No☐
2.1e	Provide study materials and/or recruit participants	Yes☐ No☐
2.1f	Provide statistical expertise	Yes☐ No☐
2.1g	Draft all or part of the manuscript	Yes☐ No☐
2.1h	Revise the manuscript for important intellectual content	Yes☐ No☐
2.1i	Provide administrative, technical, or logistic support	Yes☐ No☐
2.1j	Provide study supervision or coordination	Yes☐ No☐
2.1k	Act as the study guarantor	Yes☐ No☐
2.1l	Act as the ghost author	Yes☐ No☐

† *International Committee of Medical Journal Editors (ICMJE) criteria for authorship. It is intended to capture potential financial conflicts of interest related to authorship responsibilities.*

This table was derived from Rochon et al. (2010)

International Committee of Medical Journal Editors (ICMJE) criteria for authorship includes: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; Drafting the work or revising it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. In addition to being accountable for the parts of the work he or she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

A Priori Agreements

Introduction

We believe that *a priori* publication agreements help researchers decide how they will ensure that specific rules are being followed while also identifying the correct actions to take when publishing. For example, such agreements can determine which researchers will be responsible for data integrity and how they will meet this obligation. In addition, these agreements can also address issues such as what happens if a potential author does not contribute to the work as expected, under what conditions a first author will be replaced, or what happens if a graduate student changes supervisor during the work. What is considered for inclusion in an *a priori* agreement depends on the nature of the research process and if relevant, existing institutional policies.

An *a priori* agreement, by definition, is written before any work has begun and is expressed in plain language, without the text of a legal contract. The purpose of the agreement is to create a common understanding of the collaboration and its details. All core members of the research team (e.g., principal investigators and co-investigators) should discuss the elements of the agreement before it is written and its contents after the agreement is written. Those who have responsibility for supervising graduate students and research personnel should consider the contributions and interests of these groups when discussing the agreement. Ideally, drafts of the agreement will be shared widely with the entire team to address any concerns or issues before it is approved by the team in a final form.

It is important to recognize the various roles people may have on the research team. CASRAI has developed a taxonomy of fourteen contributor roles (CRediT) with definitions of each role. Many publishers and journals are now requiring that submitted manuscripts use the CRediT taxonomy to identify the contribution of each author. Such taxonomies can provide a common vocabulary that can increase the clarity and specificity in an *a priori* agreement (https://casrai.org/credit/).

Unfortunately, it is impossible to anticipate all eventualities. However, having agreements in place before beginning the research should help avoid disagreements, establish some principles that may help in addressing the unexpected, describe dispute-resolution mechanisms, and increase the likelihood that the published article gives credit where credit is due and is transparent about possible competing interests.

Writing the Agreement

Above, we introduced several topics and specifics to consider when writing a publication agreement. Other topics or additional specifics relevant to their circumstances may be necessary (Table 7.3).

Table 7.3 Topics to consider when writing an *A Priori* publication agreement

Description of project or research
Listing of the principal investigator(s), co-investigators, if relevant Name of corporate research sponsor (if relevant) and research funder or names of potential Funders to be considered (if relevant); Identification of the group name (if there is to be one) that will be used to description of the collaboration in the manuscripts (e.g., international collaboration on applications of network theory) Statement about whether there are (or will be) research trainees or post-doctoral fellows involved and if so, details about their participation; indication if, and under what circumstances, this current agreement will be re-visited or re-negotiated
Collaboration rules
Determine who are the "core" members to the a priori agreement and how they will come to decisions (e.g., by consensus). Decide how new "core" members are added, if necessary and under what conditions current "core" members will not continue (e.g., if a member fails to attend meetings and contribute to the work, what will happen) Determine processes for changing or updating the a priori agreement including who votes and what constitutes an agreement; outline processes for dispute resolution and how any the costs will be covered Decide on principles to ensure research integrity, such as the Singapore Statement on Research Integrity (2010)
Conflict of interest
Require all those on the Team to declare all conflict of interest situations followed by a listing of those disclosed; Elaboration as to how new conflicts of interest will be declared Rules as to how the declared conflict of interest situations will be managed [See *Financial Conflicts of Interest Checklist (*Rochon et al., 2010*)* for a framework to record comprehensive structured information about conflict of interest throughout the life of a study leading to publication.]
Description of pre-existing intellectual property and how it will be treated
List intellectual property pre-existing the agreement (e.g., data, methods, tools, measures) Identify who owns the intellectual property and disclose of any prior agreements or other documentation about its usage; elaboration as to how the intellectual property will be used, explicit permission to use it in this way and how credit will be given to those who own the intellectual property
Description of any arrangements or collaborations with 3rd parties, including with communities
Identify any 3rd parties (who are not "core members") to be involved and the nature of that involvement (e.g., Indigenous communities as partners). Determine whether these 3rd parties should be "core members" Determination as to whether any of these 3rd parties need to be engaged in these a priori discussions Determination as to if, and if how these arrangement or collaborations may impact publication ethics (e.g., co-ownership of data)
Determine whether this will be "open science" and if data will be available in public repositories
Consider as to whether these data will reside in public repositories and decide about open science Consider possible journals and their policies about archiving data and public access Determine how data will be anonymized or de-identified and how the team will be assured it is done and done correctly and how the costs will be covered If data will reside in repositories, determine the level of permission and procedure required for other researchers to access; determine who will be responsible for reviewing requests

(continued)

Table 7.3 (continued)

Documentation and archived materials
Consider what documents need to be available to whom and where they will be accessible and archived. Agree on document management process and programs. Agree on who will have responsibility for ensuring appropriate document management and archiving Agreement on where the data will be housed and how it will be backed up and archived (include decisions about whether electronic notebooks will be used)
Budget for the project or research
Determine how the project or research will be funded; Agree on which institution will hold the funds (or institutions) Agree on a budget and how it will be managed. How will the team deal with unexpected costs? Are financial agreements needed?
Power dynamics
Ensure due consideration is given to the power dynamics within teams, including supervisors/trainees and supervisors/paid staff. Ensure the rules of authorship are clear and avoid issues that can arise from these differences in power.
Conflict resolution
Determine a mechanism for resolving potential conflicts within the "core" team and with collaborators

As noted in Section 6.2.3, collecting information about financial conflicts of interest is important throughout the research process, from conception through publication (Rochon et al., 2010). Researchers may not be aware of the financial relationships of their colleagues that could potentially bias, or appear to bias, study results. This lack of awareness may exist within a single laboratory or department but may be even more likely and important among collaborating members of a research team on a multi-site project. Memorial Sloan Kettering, a large research hospital in the United States, created a comprehensive set of principles with a section that focuses on financial disclosure and transparency to external groups and, in particular, to journals (Dyer, 2019).

An email survey of 732 Canadian investigators found that 37% reported having personally experiences or witnessed a situation involving financial conflict of interest (Rochon et al., 2011). In that study, more than two-thirds of respondents reported that ghost authorship was involved in writing the manuscript for their industry-sponsored trials, and more than a quarter indicated that ghost authorship was involved in writing the manuscript for their non-industry funded trials (Rochon et al., 2011). A ghost author is a person, usually a contract writer, who did not participate in the research or even in discussions of the research but who has written a substantial amount of the manuscript and who agrees to not be named as an author. Ghost writers in the biomedical fields are often employed by industry to research and write articles and reviews, processes that involve creating or interpreting content that is potentially biased toward the interests of the company. Ghost writers must be distinguished from professional medical writers-editors who work under the direction of the authors and help draft and revise the text for clarity and consistency and who are not responsible for creating or interpreting content. The draft is

then reviewed, discussed, revised, and approved by the named authors, who are ultimately responsible for all the content in the article.

Although most of the attention around conflict of interest has focussed on financial conflict of interest, several important non-financial competing interests should be recognized. Non-financial competing interests occur when an individual's judgement might be compromised by other factors such as academic, political, or personal gain. These competing interests should also be disclosed.

As data management plans have become required from initial collection to final deposit, research teams should address these plans as part of an *a priori* publication agreement. Details should state how and where data will be stored and secured throughout the project, who will have primary responsibility for day-to-day data management, and who will have access to what level data (identifiable, de-identified, aggregated). Privacy regulations differ across regions but may dictate who has access to identifiable data, depending on where research participants reside, as well as security and format requirements. Team members should discuss these issues with their respective privacy offices and address them into data sharing agreements where required.

Research teams should also agree on where and in what format data will be deposited, where it is appropriate or required to be deposited, and the level of access for secondary use by team members and other researchers. If permission for access is required, the details of who is responsible for granting access and the mechanisms to grant access should also be determined. These decisions will be needed for informed consent for human participant research at the beginning of the study, and for ownership and sharing after the study has ended. Finally, study protocols, statistical analysis plans, datasets, and biological specimens are increasingly made available in public repositories. A publication agreement should also address these arrangements.

Specifics on the Conduct of Research

Depending on the nature of the research, what information or arrangements are included in the agreement may vary (Table 7.4).

Requirements for ethics review by research ethics boards or committees or institutional review boards for human participants and the use of animals in research, depend on the institution and country of the research team members and where the research is taking place. When research teams consist of several institutions or jurisdictions, each "core" member should consult with their institutional administration to determine whether a separate ethics review is required. In some cases, institutions may agree to rely on the approval of another institution's ethics board or committee through a board-of-record agreement. Copies of such agreements should be maintained at every participating institution.

Research involving community partners is becoming increasingly common. Although some communities have developed the infrastructure and knowledge base to be familiar with the academic process and culture, others have not. Discussions

Table 7.4 Topics on conducting research to consider when writing an *A Priori* publication agreement

Methodology used and analyses undertaken and who is responsible
Determine the methods to be used for the entire project and outline the expected analysis to be used Identify whether the team has the necessary expertise, and if not, whether new members will be needed or new hires If more than one site or lab, determine who will do what and in what order. Establish communication mechanisms. Establish a process for deciding if new sites or labs are needed in the future. Agree on who will be conducting what work, where, when and under whose supervision (if relevant)
Registration of clinical trials
Determine as to whether the trial needs to be registered and if so, agreement on who will be responsible for preparing the documentation and registering the trial, and in which registry
Agreement on research ethics
Determine what institutional research ethics boards need to provide their approval and decide who will make the submissions, when, and who will take the lead. Decide on a process for ensuring that team members understand what was approved and what this means for the research (e.g., who obtains consent from participants and how). Agree on who will have the responsibility for ensuring that the information in the a priori agreement relevant to the research ethics is included in the research ethics application and approval has been granted. Ensure everyone has had some research ethics awareness (e.g., through an online webinar) Have one team member with the overall responsibility for recording and tracking approvals
Permissions and approvals
State that wherever the research is undertaken, the relevant team member will be responsible for obtaining permissions and approvals. Have one team member with the overall responsibility for recording and tracking approvals
Data ownership and data sharing
Decide on how (and when) and what data will be shared within the team. Determine who "owns" the data (e.g., co-owned with the community)
Data integrity
Identify processes to ensure the trustworthiness of the data over the life of the project or research (e.g., audit the data, quality assurance mechanisms). Identify who is responsible for ensuring the trustworthiness of the data and who will be the "guarantor" that there is data integrity Ensure the team understands research integrity and what to do if they have concerns or questions

with prospective community partners should be started early and include all pertinent information regarding the research process, the duties and responsibilities of team members, ethical requirements, data ownership, and dissemination of results. Conflict of interest, from an academic perspective, may emerge in the community research context because community researchers may have several roles and have relationships with each other and with research participants. Community team members may not see these relationships as conflicts but as beneficial elements to the project. They may also interpret the priorities of the research differently than do academic team members.

Open and iterative communication is essential to a successful research collaboration (Han et al., 2021). If the research involves community partners, or institutions in regions that do not have a formal ethics committee or board, it is still important that the research conform to the ethics and customs of the location. Team members should identify colleagues and experts who are not involved in the project who may be consulted as needed.

Other aspects unique to community research should be discussed and agreed on from the onset. Community researchers usually engage in projects for the long-term benefits to their communities. These benefits may include capacity building, training for community staff, the acquisition of surplus supplies or resources (e.g. project equipment, collected data), and how the larger community will benefit in the short-and long-term from being involved in the research (Stampfer et al., 2019). Formalizing these discussions into terms of reference or a memorandum of understanding, drafted in plain language to be easily understood by all team members, may be useful and then referenced in the *a priori* agreement.

Specifics About Publishing

Several topics on publications and publishing are suitable for *a priori* publishing agreements (Table 7.5).

An important part of research is the dissemination of findings through peer-reviewed publications. All those involved in the publication enterprise need to know the ethical and scholarly standards of the research and publishing processes. Most scientists want the recognition that comes from publishing an important scientific work, but some may not pay adequate attention to the accuracy of their reported contributions to the work. This lack of attention can have major unforeseen consequences, should concerns be raised about, say, data quality, or worse, alleged research misconduct. For example, if a publication mistakenly states that an author was responsible for analyzing the data and concerns are raised about data falsification or fabrication, being the said author is not desirable. Authors need to be certain that what is reported about their part in the research and their contribution to the manuscript is accurate. All authors must usually approve in writing the final version to be published, including any statements about their contributions.

Several organizations have formulated ethical principles for scholarly publications (The STM trade association, 2018). Among the most cited are those of the International Committee of Medical Journal Editors (ICMJE, 1991a, b). The ICMJE recommendations are designed to assure that publications are as accurate, as clear, and as unbiased as possible. These recommendations address both the conduct of the research and its publication. The *International Ethical Principles for Scholarly Publications* provide both general principles and those that focus on the key actors in the scholarly publication process; specifically, authors, editors, reviewers, and publishers (STM 2013). The Committee on Publication Ethics (COPE) is a non-profit organization whose mission is to define best practices in the ethics of scholarly publishing and to assist editors and publishers to implement these practices [https://publicationethics.org].

Table 7.5 Topics on publishing research to consider when writing an *A Priori* publication agreement

Description of manuscripts
Identify a process to determine possible manuscripts, their scope, expected order in which they will be submitted, and the timelines or if already known, a listing of this information. If there are multiple sites, determine if sites can publish their own data and if so, when in the process Elaborate as to whether there will be a process for proposing new manuscripts not originally envisioned and if so, what process will be used Identify, if known, the first author and senior author and potential authors for each manuscript along with each person's expected contributions to the manuscript. If first author, senior author and potential authors are unknown, agree on how they will be selected. [if research trainees or post-doctoral fellows are involved, an elaboration as to have they will be involved in manuscripts] State whether any manuscripts may be submitted from a member of the team without notice or involvement of other team members. If this is allowed, an elaboration under which this is authorized. Identify group manuscripts versus manuscripts of subgroups (e.g., full publication from the collective and individual lab manuscripts) Identify how manuscripts associated with thesis work will be considered and the rules of authorship
Defining authorship
State who are the potential authors of manuscripts (e.g, all member of the research team versus a subgroup). Agree on what authorship rules will be used, such as those of the ICMJE Require full disclosure as to whether there have been any promises or pledges made about authorship and if so, the nature of them. (these promises or pledges should not be contrary to the authorship rules being followed). Agree as to how potential authors will be notified about the planning of a manuscript so that they can contribute to the manuscript at the level expects for authorship State the rules about "core members" teaching or entering the project or research in terms of their rights/responsibilities to be invited to participate as authors. State the rules about whether revisions to manuscripts will change the authorship order (e.g. what happens when major revisions including cutting out entire work of one potential authors
Determine roles and responsibilities of first author, senior authors and co-authors
Define the roles and responsibilities of the first author, senior author and co-authors including, but not limited to the following: -who is responsible for preparing the first drafts of the manuscript and first draft of the response to reviewers' comments -who will be the "guarantor" (i.e. the person taking responsibility for the integrity of the work as a whole, from inception to published article). Identify what the "guarantor" is responsible for and how the team is to cooperate with these processes -who will be the corresponding author for each manuscript (first author? Senior author?) -who is responsible for identifying other potential authors and who is responsible for inviting them to participate -who will approve the list of authors invited to participate, who will ultimately determine authorship order, and who will make the final decisions (s) as to whether the manuscript will be sent for possible publication -describe what will happen if a potential author does not contribute to the manuscript expected of an author and who will be responsible for communication it to him/her/them. Agreement as to the consequences of such non-participation -statement about the conditions under which authors will lose their right to be a first author (e.g. if not draft of the manuscript if produced within 12 months after data analyses) -agreement that all those who will be authors will cooperate fully with the submission and revision of the manuscript

(continued)

Table 7.5 (continued)

Timelines for manuscripts
Identify the timelines associated with each manuscript including timelines for drafting, responding to drafts etc.
State a process for re-negotiating timelines and documenting the agreed to changes

Despite such guidelines, authorship misattribution occurs often in scientific publishing, in the forms of "gift" or "guest" authorship (authorship awarded to someone who does not meet the criteria for authorship but who is being "thanked" for some reason or whose name is intended to increase the status of the research), and also through "ghost authorship," and unacknowledged authorship. Authorship misattribution is often caused by, and often affects, personal and professional relationships. An estimated 30–50% of publications may have some form of author misattribution (Mainous et al., 2002; Marušić et al., 2011). Authorship is often subjectively established and traditionally has been determined by those with influence in the group (Mainous et al., 2002). As indicated earlier, ghost authorship can also be associated with conflict of interest. Likewise, guest or gift authorship is unethical because the criteria for authorship have not been met.

A priori publication agreements are helpful in multi-disciplinary teams where publication ethics can differ. For example, in the life sciences, the last author is often still considered to be the most responsible author because an old and outdated German practice in which the owner of the laboratory required his name (it was always a him) to be included as an author. (Current guidelines are to let the authors decide where each will be listed, usually ranked in importance to their contribution (http://wame.org/authorship). In the social sciences and humanities, the last author is not the most responsible author. In some physical sciences, authors are always listed alphabetically by last name, irrespective of contribution.

Given the above differences, it is understandable that conflict in academic writing and publishing is common. Claims of ambiguity and unfairness often arise among groups because of the lack of explicit and transparent discussions of the group's decisions. Some approaches to addressing these conflicts focus on dispute resolution in an *ad hoc* manner, often after a manuscript has been submitted to a journal.

Roberts (2017) discusses situations in which the ICMJE criteria do not provide clear-cut guidance; specifically, where team members are involved only at the beginning ("early-career contributors") or at the end ("late-career contributors") of the research. Examples include an undergraduate research assistant who was engaged at the beginning of the project, but graduated and moved on, and a senior laboratory leader who came to the project at the analysis stage and worked directly on interpreting results and preparing the manuscript. In establishing an *a priori* heuristic approach, Roberts provides guidance for considering authorship in these common situations. This guidance falls into two main questions: Did the individual contribute substantive intellectual work to the project, such as collecting, analyzing, or interpreting data or drafting or substantively revising the manuscript? Secondly, will the individual accept responsibility for the content and quality of that work,

such as being accountable for specific aspects of the research and being able to answer any questions or challenges about the integrity of the research? If the answer to both questions is yes, authorship is merited. If the answer is yes to only one of the two questions, the individual should be considered a contributor, not an author.

Additional resources can help teams talk about authorship and its responsibilities. For example, Phillippi et al. (2018) have developed authorship guides, organized by publication type, including manuscripts reporting quantitative research, qualitative research and literature reviews. They are based on guidelines from ICMJE, COPE, the US NIH health data-sharing policies, and the International Conference on Harmonisation: Good Clinical Practice, which concerns the pharmaceutical and medical device industries. Graf et al. (2007) describe the guidelines produced by Blackwell Publishing, "Best Practice Guidelines on Publication Ethics." Also described are the COPE decision trees for handling authorship and integrity issues.

Smith et al. (2020) studied authorship practices among collaborative teams with a survey of multi-authored papers published between 2011 and 2015. Of 8364 responding authors, 1408 answered an open-ended question about whether authorship in research teams was fairly distributed. A qualitative analysis of these answers revealed, among other things, a common lack of fairness, collegiality, and transparency in the awarding of authorship. Although generalizing these conclusions is difficult, it is clear that educating authorship teams about generally accepted authorship criteria and clearly articulating the team's authorship expectations and norms in *a priori* publication agreements should help reduce later disagreements.

How Well Did We Do? Reality Check

One of the best tests to determine whether an *a priori* agreement is robust enough to handle challenging situations is to have team members apply the agreement to various scenarios to determine whether it provides sufficient guidance to resolve the issues posed.

For example, consider the following scenarios.

Scenario A: Researcher A is a short-term researcher for lab Y. She helped formulate the research question and research proposals and was mid-way through the process of data collection when she took parental leave. In the interim, researcher B completed the data collection and worked until the end of the project. The authors complete the project, write the discussion, and submit the manuscript for publication without listing Researcher A as an author. Question: Are the rules of authorship clear as to whether Researcher A should or should not be listed as an author?

Scenario B: A PhD student, who is a team member and is using some of the data for a PhD dissertation, is told that the team wants to delay his PhD defence until a more comprehensive article can be published first. Question: Is the agreement adequate for determining how to respond to the request for delay?

Scenario C: One of the core members of the team has become busy with other research projects and, despite ongoing promises to do so, has not begun drafting the manuscript. Months later, this team member is still unengaged and has not written the draft. Question: Does the agreement adequately communicate the expected timelines and clarify the actions to be undertaken if researchers do not fulfill their authorship responsibilities?

Scenario D: A PhD student who contributed to the research enough to be an author left the graduate program and was known to have conflicts with his supervisor. Attempts to reach the student have been unsuccessful, and the team is ready to submit the manuscript. Question: Does the agreement deal adequately with supervisor-student challenges and how these challenges will be prevented or resolved, including deciding authorship?

Scenario E: When data from several research sites were analyzed, one site's data was markedly more favourable towards the intervention group. The team asked for the raw data from that site. Question: Does the agreement identify who is responsible at each site for data integrity, and is it clear that sites may need, and have necessary approvals (privacy, ethics), to share raw data if asked?

Conclusion

All those involved in conducting and publishing research should have a common understanding of publication ethics before undertaking any research. In this chapter we have focussed on publication ethics in research—the codes of conduct governing research and its publication—and discussed some common issues and concerns that arise during these activities. We believe *a priori* written publication agreements among researchers can address these concerns and considerations to prevent or minimize ethical dilemmas. Although much effort is needed to discuss and finalize an *a priori* agreement, the effort would be far greater to deal with arising issues or disputes if there was no pact detailing how these issues would be handled. We also believe that the process of discussing these agreements could help improve team dynamics and possibly even the quality of the research.

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Part II
Research Ethics: *Conducting Ethical Research*

Chapter 8
Freedom of Scientific Research and Primacy of Human Being: Practical and Epistemological Tensions

Erick Valdés and Juan Alberto Lecaros

Abstract Conducting science, especially nowadays, when biotechnological inventions seem like reaching their pinnacle, encompasses different nuances related to what limits and scopes of scientific human endeavors should be, and how and when protecting human subjects, animals and environment from potential damages caused by conducting research. Even though scientific integrity and research ethics are not only related to our species but also to non-humans' ones, we display this chapter from an anthropocentric key. This decision is not based upon ideological reasons but on methodological ones, as being scientific research a multifactorial object it needs to be analyzed compartmentally to favor clarity and accuracy.

In this fashion, some epistemological and procedural frictions between the principle of freedom of scientific research and that of primacy of human being will be analyzed in order to give some light both to the theoretical debate and biomedical practice.

Keywords Freedom of scientific research · Primacy of human beings · Ethics · Biomedical practice · Scientific research regulations

Introduction

Freedom of scientific research and primacy of human being happen to be competitive principles in bioscientific atmospheres. The latter seems to be lexically preeminent regarding the former, as no matter how important, beneficent, useful and helpful a scientific advance may be, this should not be sought at the expense of human being's interest and welfare.

The above premise is currently reinforced by alluding to infamous examples of our history, such as Nazi physicians inflicting pain and suffering on many innocent

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humans. Certainly, investigating pain's thresholds may be useful for mankind at some point, but doing so by using humans as guinea pigs seems to be out of discussion. In fact, such experiments were widely condemned, including the Nuremberg Trials, which, through the Nuremberg Code, eventually was an epistemological precedent for international biolaw and the extensive catalogue of instruments and provisions of UNESCO, the Council of Europe, and the European Court of Human Rights, created since the 1990s, to regulate bioscientific practices and prevent human subjects from potential abuses that such practices entailed. In fact, the Nuremberg Code became the first official document identifying principles and procedures for regulating experimentation with human beings, a scenario that the Belmont Report addressed paradigmatically upon later.

Performing science, especially nowadays, when biotechnological inventions seem like reaching their pinnacle, encompasses different nuances related to what limits and scopes of scientific human endeavors should be, and how and when protecting human subjects, animals and environment from potential damages caused by conducting research.

Even though scientific integrity and research ethics are not only related to our species but also to non-humans' ones, we display this chapter from an anthropocentric key. This decision is not based upon ideological reasons but on methodological ones, as being scientific research a multifactorial object it needs to be analyzed compartmentally to favor clarity and accuracy.

Moreover, the principle of freedom of scientific research and that of primacy of human being have been given relevance in biotechnological settings, specially attending that while science needs to be fostered, human subjects need to be protected from certain biomedical and biotechnological interventions. Thus, analyzing some epistemological and procedural frictions between such principles might result helpful to give some light both to the theoretical debate and biomedical practice.

Nature, limits and scopes of the principles of freedom of scientific research and primacy of human being are mostly addressed by international biolaw, which is the whole set of UNESCO instruments and European Court of Human Rights' case law, aimed at regulating biotechnological practices and behaviors potentially harmful for human beings. Mainly understood as the intersection between bioethics and human rights (Andorno, 2013) international biolaw is intended to transform such a convergence into a referential framework for governance and oversight of biotechnology.

As international biolaw is plenty of non-binding provisions, it can only be considered as a soft law. Yet, such a feature is not necessarily seen as its weakness. Defenders of soft law argue that it would be wrong to infer that non-binding effects of soft law instruments entails that such legal devices only represent a set of sentences and rhetorical statements lacking legal scope. In addition, even though such international instruments do not reach instant binding outcomes in local jurisdictions, their force is potentially binding, in the understanding that they have been thought as the beginning of a gradual process that requires further steps to obtain an enforced status.

International biolaw instruments share three ideas: (i) Dignity as the overriding principle, (ii) Human rights doctrine as a frame of reference for regulation, and (iii)

The assumption of common moral principles of American bioethics as deliberative criteria to understand biotechnology's potential risks. In this context freedom of scientific research and primacy of human being come into play as an attempt for conciliating legitimate science's interests with a proper protection of human subjects to prevent them from being harming by new biotechnological tools. We will address these principles briefly in turn. Then, we will make visible some practical and epistemological tensions they display to each other.

Freedom of Scientific Research

This principle appears on the Universal Declaration on the Human Genome and Human Rights (Art. 12b); Universal Declaration on Bioethics and Human Rights (Art. 2d); and the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (Oviedo Convention) (Art. 15).[1] It essentially states that while recognizing the relevance of benefits derived from scientific and technological breakthroughs, and emphasizing the need for scientific research, this should be carried out in the framework of ethical principles oriented to respect human dignity, human rights and fundamental freedoms.

In addition, it is understood that freedom of research is necessary to foster progress of knowledge, and as such, it is part of freedom of thought. Research's scopes, including applications in biology, genetics and medicine, and others concerning the human genome (and analogically extended towards scientific and technological practices in general), should be aimed at offering relief from suffering and improving human health.

The principle of freedom of scientific research is understood, in all instruments it appears in, to be restricted by the condition of carrying out research by respecting human dignity and human rights. In this sense, it is possible to affirm that in international biolaw, this principle is subject not only to the principle of dignity, but also, to justice, which is not only meant to work in the field of public health, but it outspreads its epistemological scope into the context of research with human beings.

This principle seeks to achieve an equidistant relationship (if any) between humanity's right to scientific research (as for therapeutic purposes), and the right not to be overwhelmed by such studies. To this end, international instruments correctly undertake that science and technology are not axiologically neutral and that freedom of thought, paradigmatically represented by science and promoted by the Universal Declaration of Human Rights, must not jeopardize human life when scientific research is being performed.

[1] Freedom of Scientific Research is part of right to science, which includes both freedom to *do* science and the right to *enjoy* the benefits of science. Right to science is recognized in Article 27, Universal Declaration of Human Rights (UDHR) and Article 15 (1) International Covenant on Economic, Social and Cultural Rights (ICESCR).

International biolaw's instruments are not specific as to which bioscientific experimentation practices would be dangerous and why. This is not that trivial since it would certainly be foolish to blindly attack new technologies applied to life and to label them as intrinsically dangerous since such a thing, besides being epistemologically pointless, would create a false dichotomy.

As research plays a necessary role in society by developing and boosting knowledge as well as fostering and improving individual and public health, the freedom of scientific research becomes a condition of possibility of this. Consequently, stakeholders (scientists, researchers, subjects and society in general) must be empowered and legitimized to freely determine what and how research should be conducted and how to peruse its outcomes.

In this sense, freedom of scientific research involves, on the one hand, a subjective right of the researcher to prevent himself from being coerced or unduly interfered while performing science. On the other hand, the principle implies an objective facet represented by the State's obligation to enable and, at the same time, rule scientific and technological progress by creating organizational and procedural structures to engender and set policy and governance.

The UN Committee on Economic, Social and Cultural Rights, in its General Comment No. 25 (2020) on Science and Economic, Social and Cultural Rights article 15 (1) (b), (2), (3), and (4) the UN International Covenant on Economic, Social and Cultural Rights, defines freedom of scientific research as including the following dimensions:

> …Protection of researchers from undue influence on their independent judgment; the possibility for researchers to set up autonomous research institutions and to define the aims and objectives of the research and the methods to be adopted; the freedom of researchers to freely and openly question the ethical value of certain projects and the right to withdraw from those projects if their conscience so dictates; the freedom of researchers to cooperate with other researchers, both nationally and internationally; and the sharing of scientific data and analysis with policymakers, and with the public wherever possible. (UN Committee on Economic, Social and Cultural Rights, 2020)

Science and research should not be instrumentalized by political ideologies, economic purposes or partisan interests. However, politics and economics have turned into an intense external pressure to conduct and tendentiously lead research and its results. Pharmaceutical industry in US sponsors universities and medical schools to train future physicians and financially backs research programs. This can clearly color research independency as funds remains as long as investigation takes a specific direction.

The Bonn Declaration on Freedom of Scientific Research (2020) considers research not only as a universal right but also as a public good and, as such, it becomes a "pillar of any democracy." The freedom to conduct research, then, can enable social, cultural, political and economic progress, and substantially benefit people and their social and natural environment. In this fashion, sharing and transferring knowledge are tasks that reach the status of necessary conditions to produce public goods for society's well-being.

Moreover, according to the Bonn Declaration, free scientific research fosters social mobilization, better education, freedom of expression and freedom of association, among others. The researcher has the right to define hypothesis, premises and research questions, as well as he/she is able to decide methods, establish and challenge standards of academic disciplines when new research outcomes question fossilized paradigms and make anomalies visible. In this line, research organizations have some responsibilities too. They should ensure clarity, transparency and comprehensibility when sharing and spreading findings, in order to avoid research diversion, facts distortion and public disinformation.

Also addressing the relationships between freedom of research and democracy, Wilholt (2010: 177) discusses what he calls a "political argument" in favor of freedom of research as it fosters the creation of knowledge, which becomes "an important input for the democratic process." In fact, many times citizens have to make decisions or political choices. When so, they usually rely on beliefs about what the world is like, moment in which science comes into play to resolve doubts and uncertainties. Thus, science becomes an instrument for decision-making at a social and political level.

However, there is an epistemological and methodological fissure both in the political argument and the Bonn Declaration. Considering freedom of research as a guarantee of a strong democracy and a steady society is a conviction that starts from taking for granted that people, researchers, politicians and institutions act always ethically, what is certainly far from reality.

Primacy of Human Being

While the discussion about the scope and limits of this principle is rather scarce, Helgesson and Eriksson (2008) triggered an academic debate about the utility, meaning and role of it for the interpretation of other principles of research ethics, as well as the role it plays as a biolegal principle. Several scholars claimed that the principle of primacy of human being should take precedence over the interests of science and society, and consider it to be the cornerstone of research ethics and bioethics (e.g., Andorno, 2009, 2013; Parker, 2010; Human & Fluss, 2001). However, the discussion begins to have special relevance when evaluating this principle in relation to research that has no potential benefit for the participant, namely, those in which the main benefit is the advancement of knowledge and the interest of society, as well as when this type of research involves vulnerable population which may be exposed to more than a marginal risk (Różyńska, 2021, 2022).

This principle first appeared in the Declaration of Helsinki (1975 version), expressed in two parts: First, in paragraph 5, 2nd sentence, of the section I containing "Basic Principles": "Concern for the interests of the subject must always prevail over the interest of science and society;" and, second, in paragraph 4 of section III pertaining to non-therapeutic biomedical research on volunteers: "In research on man, the interest of science and society should never take precedence over

considerations related to the well-being of the subject." This wording and structure were maintained until the 2000 version and raised interpretive doubts about various aspects of the two formulations, for example the difference between interest and welfare, if applied to the individual or to groups, and the role of each formulation, taking into account the distinction made in the Declaration between therapeutic and non-therapeutic research. With the 2000 version these ambiguities disappear, in part, leaving the principle in a single formulation within the basic principles and eliminating the distinction between therapeutic and non-therapeutic research, supported by the paradigm of the therapeutic beneficence duties of medical ethics brought into research. These changes remain until the latest version of 2013.[2]

In human rights legal instruments such as the Universal Declaration of Bioethics and Human Rights and the Convention for the Protection of Human Rights and the Dignity of the Human Being with respect to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (Council of Europe 1997), also known as the Oviedo Convention, the principle of human primacy is recognized as a general principle guiding all types of research with human beings, encompassing within its formulation jointly the terms interest and welfare of the individual or human being and understanding that these prevail or take precedence over the interests of science and society. The Additional Protocol to the Convention on Biomedical Research (2005) echoes this principle. In all these instruments, the principle of primacy of human being is based upon the notion of dignity and human rights.

As the principle points out the preeminence humans have with respect to the interests of science and society while conducting biocientific research, it also seeks to rethink the relationship between the human being and science, as it orders to avoid considering the subject of experimentation as a simple instrument for the benefit of bioscience. In this line, science and new technologies must serve the human being and not the other way around. Therefore, subject's security and welfare must always overcome any other scientific advance, especially when this is reached at the expense of harm and suffering.

The principle of primacy of human beings is codified with certain vagueness both in the above-mentioned documents and in others.[3] Such a lack of specificity has naturally forced an exercise of interpretation to delimit its meaning, scope and function. At an early stage, the academic discussion faced two dilemmatic positions, between skepticism about its meaning, and the foundational value it has derived

[2] Version 2000: "In medical research on human subjects, considerations related to the well-being of the human subject *should* take precedence over the interests of science and society" (Introduction, paragraph 5). Version 2013: "While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects" (General Principles, paragraph 8).

[3] WHO Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products (1995) (Principle 4); ICH Harmonised Tripartite Guideline for Good Clinical Practice E6(R1) (1996) (Paragraph 2.3); EU "Clinical Trial" Directive2001/20/EC (2001) (Article 4 and 5); EU "Clinical Trial" Regulation No 536/2014 (2014) (Recital 1).

from the Kantian ideas of dignity and autonomy. Among those who hold the latter position it has been argued that the principle's meaning is given by two ideas deriving from the notion of dignity as the overriding standard that founds every value in any social practice. First, science is not an end in itself but only a means to improve the well-being of individuals and society; second, people cannot be reduced to mere instruments for the benefit of science (Andorno, 2009; Parker, 2010). However, this approach neither answer what the operational function of this principle may be in relation to other ethical principles or determines a differentiated normative content for it. In addition, as always participants are exposed to risks for the benefit of others (society), it may be argued that research, by definition, implies certain range of instrumentalization.

Helgesson and Eriksson (2008) argue that the principle of primacy of human beings leads to interpretations that are semantically or logically unsustainable, as well as contradictory to other principles of research ethics, or that the principle is basically redundant. First, it is implausible to interpret this principle: (i) to validate only research with a direct benefit to the participant, as there is ethical consensus in international recommendations about the opposite; (ii) to understand it as a guarantee of the dignity and integrity of individuals and their protection against excessive risks, because it is possible to give such guarantees and protection without always supporting the strong sense of primacy; (iii) understood as if "the entire system of biomedical research should leave the individual on an expected positive balance (compared with a society where there is no biomedical research on human subjects)" (Helgesson & Eriksson, 2008: 55), because this interpretation goes in the opposite direction to that expressed by the principle, that is, to make individual interests prevail over collective ones and not to seek their convergence.

Other interpretations, according to Helgesson and Eriksson (2008), are redundant. If this principle is understood as (i) equivalent to the set of minimum requirements on how research subjects should be treated, it would be an empty principle that says nothing more than the set of rules in a guide or legal instrument provides; (ii) if it is understood as an expression of the requirement of free, voluntary and informed participation of research subjects, it would be a duplication of the duty to express the informed consent of the competent person or his/her representative in the event of incompetence. Finally, this principle could be interpreted as a "main guiding principle," that is, a principle that helps to interpret principles applied to specific situations. While in this case it would not be a redundant principle, it would only make sense as a "main guiding principle" if it could perform that interpretative function, yet, its vagueness prevents it from working that way. Rather, the principle should be understood in the light of the other ethical principles guiding research. For such reasons, Helgesson and Eriksson (2008: 56) conclude that: "the primacy principle does not seem to say anything distinct; rather it seems to be a vacuous figure of speech," therefore, "the primacy principle should not be included unless it is given an ethically relevant, clear and non-redundant meaning."

A way to give meaning to this principle beyond the dilemmatic tension between the ultimate foundational value it allegedly should have for any research with human beings and skepticism about its function given its contradictory, vague or redundant

character, is to remove it from the framework of understanding it was created in. As we pointed out earlier, the Declaration of Helsinki is unclear as to the ethical validity of conducting research that is not beneficial to the participant (following the logic of the principle of therapeutic beneficence), and even does not admit such research on people who are not able to give their consent. Another way of understanding this is in the framework of non-exploitation of participants (Emanuel et al., 2000), which seeks to engender socially valuable research by minimizing exploitation (when health, welfare, autonomy, confidentiality or other interests of the participant are negatively affected). In short, the net risks that subjects withstand must not exceed the social value of research.

In the same sense, other authors have also criticized the ambiguities of this principle in the Declaration of Helsinki, this time in its last version of 2013:

> …The goal of generating new knowledge must not take precedence over the rights of individual research participants. Research participants should not be exposed to high net risks. Yet nonbeneficial research can be ethical when the net risks to participants' interests are low and the benefits to society are sufficiently large. (Millum et al., 2013)

In sum, the importance of this principle is better understood in relation to the principle of proportionality in research. Indeed, the principle of primacy of human being would establish an external limit and within it there would be a discretionary space that allows considering a suitable proportionality between risks and benefits:

> Clearly these limits are relevant and important in the assessment of proportionality between risks, burdens and potential benefits. The fundamental implication is that the assessment of proportionality can be relativistic only to a certain degree. The principle of human primacy thus functions as a constraint against a slippery slope in the assessment of proportionality. This is probably the most important role of the principle of human primacy as a legal norm in its own right. Within the discretionary room, relevant and legitimate interests and factors must be weighed and balanced. (Simonsen, 2012: 55–56)

This reading of the principle, in strict relation to the requirement of proportionality, seems to be the most relevant, notwithstanding the fact that other functions (dependent on the substantive function) can be clarified: (i) the principle as a rule of interpretation, that is, when interpreting an ethical research requirement, the interpretation that most favors participants should prevail; (ii) the principle as a rule of procedure, namely, researchers, sponsors and review committees must observe the duty to identify, quantify, to the extent possible, and assess the risks and benefits expected, by clearly stating it both in the protocol and in the informed consent (Różyńska, 2021: 560).

Practical and Epistemological Tensions

In all international instruments they appear in, the principles here analyzed essentially point out three ideas that can be stated as follows: (i) bioscience is not an end in itself, but an instrument at the service of humanity to increase the well-being of

individuals and society, (ii) subjects of experimentation are not mere means for science to obtain knowledge and benefits, and (iii) bioscientific research cannot be carried out based upon utilitarian criteria. Each one of such premises engenders a tension between the principles, encompassing procedural and epistemological implications. We will refer to them in turn.

Bioscience is not an end in itself, but an instrument at the service of humanity to increase the well-being of individuals and society. This idea is problematic for expressing a tension between the principles of dignity (implied in "primacy of human being") and utility (comprised in "freedom of scientific research"). Indeed, understanding science and new technologies as a set of instruments meant to serve the human being implies, by definition, seeking a utilitarian benefit for our species, not only having the intention or motivation of doing so. Therefore, the overriding principle to determine what science's purposes should be, is utility rather than dignity. Yet such a disharmony is not only conceptual but has procedural connotations since conducting research by respecting dignity (at least in the form all international bioethical and biolegal instruments grasp it), is intrinsically contradictory with "using" humans to achieve utilitarian benefits through research. This tension often comes to play in clinical and biomedical settings, some of them very visible during pandemic, such as human challenge trials and scarce resource allocation.

Subjects of experimentation are not mere means for science to obtain knowledge and benefits. A number of biomedical research mediatize humans to reach their goals. At the same time, the principle of primacy of human being is understood from a Kantian key in international instruments. While research human subjects are not mere means at the science's command, the principle of primacy of human being clearly aims at imposing dignity over scientific goals, as it is internationally considered as an inalienable, inherent and intrinsic condition. From this intellection, any kind of investigation involving human subjects should be prevented from happening. In this sense, virtually all bioscience initiatives should be banned, which seems to be at least counterproductive.

In research settings, the human being has a different ontological status from clinical ones. Research's goals are to test hypothesis and obtain greater knowledge about what is investigated, and human subjects are means to achieve those purposes. Instead, in clinical surroundings, the human being is always the end of treatment and therapy. Thus, if we proclaim the primacy of the human being over science by virtue of his dignity, the epistemological density of such norm weakens and offers several permeable flanks to criticize it as an ethical criterion to conduct science, as well as it is split into two irreconcilable dimensions that should be convergent.

Bioscientific research cannot be carried out based upon utilitarian criteria. As in international instruments dignity does not tolerate a hypothetical interpretation, such a dogma transforms it into a principle on which there can be no discussion, by contradicting the spirit of biomedical research, which also seeks utilitarian consequences that positively impact human life.

It seems like dignity points out, on the one hand, that the end-in-itself status of the human being should be respected only when bioscience has non-therapeutic purposes, and, on the other, that extrinsic utilitarian ambitions should be allowed

when research will result in favor of humanity. This rather cynical understanding (and application) of dignity certainly dwindles its epistemological and procedural intensity as a compelling parameter to conduct research.

Final Remarks

As the instruments of international biolaw were created when biotechnology was rudimentary compared to its current breakthroughs, the intellection of the principles of freedom of scientific research and primacy of human being is clearly anachronistic. In this line, just stipulating that science must develop and be carried out by respecting humans' dignity represents a weak and vague statement that needs further deepening and justification for preventing such principles from falling into epistemological and practical collisions.

Being both principles very used benchmarks when conducting research, some ethical updates need to be made while debating about their connotations and scopes. Likewise, more institutional involvement in building policy and implementing oversight is desirable, not only to advance in configuring key guidelines for research but also to give old principles new meaning more tuned with current scientific and technological achievements.

All research involves risks, yet the current circular dynamic that freedom of scientific research and primacy of human beings display, does not respond the question whether research must be constrained even when risks have been minimized and become proportional to the expected benefits. Such a question remains open until now and definitively claims for an upper level of academic and institutional debate.

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Chapter 9
Exploitation in Biomedical Research

Erik Malmqvist

Abstract Biomedical research on human subjects involves exposing individuals to risks and burdens for the benefit of others, and therefore raises concerns about exploitation. While the concept of exploitation has received significant attention in recent research ethical literature, its relevance and implications in this area remain unclear and contested. This chapter explains how this concept is nonetheless important for understanding the ethical complexities of human subject research and the proper design of subject protections. The chapter provides an overview of research practices often thought to raise exploitation concerns and introduces philosophical exploitation theory, focusing on aspects relevant to research ethics. Against this background, the obligations of non-exploitation held by researchers, sponsors, and third parties such as ethics committees and regulators are outlined. The chapter ends by considering how exploitative research in the past can be retroactively remediated.

Keywords Exploitation · Moral obligations · Research ethics · Social justice · Vulnerability

Introduction

Biomedical research on human subjects requires exposing individuals to risks and burdens in the pursuit of knowledge or interventions aimed at protecting or advancing health in the future. Such research therefore raises concerns about *exploitation*, concerns that some people are inappropriately used for the benefit of others. The exploitative potential of human subject research was already a prominent theme when the field of research ethics started to take shape (Jonas, 1969), and ethical criticisms of various historical and contemporary research practices have often been couched in the language of exploitation (see, e.g., Angell, 1997; Resnik, 2003;

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Elliott & Abadie, 2008). Moreover, avoiding exploitation is widely believed to be the common underlying rationale for concrete subject protections, such as independent review by ethics committees or institutional review boards and the requirement to include participants in research on scientific grounds only (Emanuel et al., 2000). In short, the concept of exploitation strongly shapes thinking about research ethics. Unsurprisingly, therefore, it is the subject of a substantial body of research ethical literature (see, e.g., Resnik, 2003; Hawkins & Emanuel, 2008; Ballantyne, 2010; Wertheimer, 2011; Ganguli-Mitra, 2013; Panitch, 2013; Malmqvist, 2017; Lamkin & Elliott, 2018; Wenner, 2018; Holzer, 2020; Snyder, 2021).

However, despite its influence, the relevance of the concept of exploitation to research ethics and its practical implications in this area are neither obvious nor uncontroversial. This is partly because accusations of exploitation have been directed against many, seemingly disparate research practices. This raises the suspicion that the term 'exploitation' does not identify any particular form of wrongdoing, but is rather a generic label attached to everything that critics find morally objectionable. Moreover, even when the wrong of exploitation is distinguished from other concerns, bioethicists and philosophers disagree about the nature and severity of that wrong. Nor is there much consensus about how exploitative practices (in research and elsewhere) should be reformed.

The aim of this chapter is to explain why the concept of exploitation is nonetheless important for understanding the ethical complexities of human subject research, and how it can help actors involved in research better to understand their moral obligations and inform the design of subject protections. The next section ("Exploitation in context") provides an overview of research practices that have been characterized as potentially exploitative, highlighting features believed to support that judgment. The subsequent section briefly introduces philosophical exploitation theory and makes some distinctions and clarifications of relevance to research ethics. The section "Obligations of researchers and sponsors" shows how the concept of exploitation can help articulate the moral obligations of researchers and sponsors, whereas the section "Obligations of third parties" considers its usefulness for the regulation and oversight of research. The section "Remediating exploitation" briefly discusses how to respond to exploitation after it has occurred. The section "Conclusion" summarizes the chapter's main findings.

Exploitation in Context

While concerns about exploitation potentially apply to all forms of human subject research,[1] including research on human health data and human bodily material, they are most commonly discussed with respect to clinical research, which involves test-

[1] Such concerns may well apply to the use of sentient non-human animals in research too. However, I set this issue aside since it requires delving into the moral status of such animals, which would take us too far afield. Moreover, scientific research may raise concerns about exploitation not only

ing drugs and other biomedical interventions on patients or healthy volunteers. Moreover, some kinds of clinical research are more likely to raise such concerns than others. Common to these is that participants suffer from some vulnerability that is thought to make them liable to being unduly taken advantage of by researchers or sponsors.

One prominent example is Phase 1 pharmaceutical trials involving healthy volunteers. Such trials study the safety of experimental drugs on participants who do not stand to derive any medical benefit from the research but are often paid substantially in return for ingesting potentially harmful substances, undergoing tests, providing samples of bodily material, and following strict routines during days or weeks of confinement. Empirical studies show that healthy volunteers are often drawn from socially disadvantaged groups and treat research participation as an informal job, while lacking protections that are available to workers in other contexts (Abadie, 2010; Fisher, 2020). These circumstances are thought to make them vulnerable to exploitation (Lamkin & Elliott, 2018; Malmqvist, 2019; Walker et al., 2018).

Another example is Phase 1 oncology trials, which (instead of healthy volunteers) enrol terminally ill patients who have exhausted conventional treatment options. Since Phase 1 trials are not designed to test efficacy, the chance that these patients will benefit therapeutically is generally small. However, hope for improved health is a main motivator for them to enrol. This hope for an unlikely but strongly desired outcome, together with the fact that no other treatment provides adequate help, raise the concern that these participants may be inappropriately taken advantage of (Snyder, 2021).

The most widely discussed instance of potentially exploitative research is Phase 2 and 3 trials conducted in low- and middle-income countries (LMICs). Several aspects of such trials have been thought to raise exploitation concerns (Angell, 1997; Ganguli-Mitra, 2013; Hawkins & Emanuel, 2008; Holzer, 2020; Malmqvist, 2017; Panitch, 2013; Snyder, 2021). Since many patients in LMICs are poor and lack access to adequate healthcare, they may enrol in these trials in the pursuit of needed drugs or care that is otherwise unavailable to them (Cooper & Waldby, 2014).[2] Moreover, the trials may not be aimed at addressing health needs of LMICs themselves, but at developing drugs for markets in high-income countries (HICs). An especially controversial issue concerns the use of placebo instead of an active treatment in the control arm of a trial in cases where an active treatment exists but is unavailable in the host country. Such trial designs have been characterized as exploitative given that an active treatment could have been used (though at higher cost to the sponsor), would have benefited participants more, and would have been required in order to pass ethical review had the research taken place in a HIC. In

of *participants* (and their communities), but also of *researchers* (or other contributors to the research enterprise) (Smith, 2018). I set this issue aside as well.

[2] Though most commonly discussed with respect to research in LMICs, the same concern arises when individuals in HICs who lack access to healthcare are enrolled in research (Dal-Ré et al., 2016).

addition, sponsors' failure to make tested interventions available to participants and host communities after trials are over, or to provide other post-trial benefits, has been criticized as exploitative, especially considering the substantial gains that sponsors, researchers, and patients in HICs may derive from the research.

Recently, exploitation has been discussed in regard to "human challenge studies", which involve deliberately exposing healthy volunteers to infection in order to test interventions (Anomaly & Savulescu, 2019). In particular, human challenge studies of SARS-CoV-2 vaccine candidates have been thought to raise exploitation worries. Since the infection in this case can be lethal and therapeutic options are limited, risk-minimization is paramount. Proponents of these studies have recommended recruiting participants among groups whose background risk of infection is high in order to minimize the marginal risk they face (Eyal et al., 2020). However, such recruitment has been characterized as exploitative in cases where this background risk is caused by social injustice, such as, say, a high transmission rate due to poor housing or working conditions (Jamrozik et al., 2021). Moreover, as populations in HICs become immunized, research on SARS-CoV-2 vaccine candidates (whether challenge studies or ordinary trials) may increasingly have rely on participants from LMICs, prompting renewed attention to the exploitative potential of research conducted in such settings (Iyer et al., 2021).

More generally, research involving participants with reduced decision-making capacity (such as children or patients with certain mental illnesses) is sometimes thought to be potentially exploitative, given that these participants may be unable to provide valid informed consent (Resnik, 2003). In addition, charges of exploitation are often directed against research that is outright harmful to participants (Resnik, 2003). However, as explained in the next section, concerns about exploitation are best kept distinct from other ethical worries, including worries about harm and consent. Thus, the objection against research involving invalid consent or outright harm is not only (or primarily) that it is exploitative – though it may be exploitative too, on separate grounds.

Exploitation Theory

We saw in the previous section that concerns about exploitation in human subject research apply broadly. Such concerns seem particularly apposite when participants are in an especially vulnerable condition, e.g., due to economic hardship, social exclusion, or lack of access to needed treatment. However, even when such conditions do not obtain, some form of vulnerability, e.g., related to illness, limited scientific understanding, or dependence on researchers, is arguably a common feature of most research participants' situation. This raises two questions. First, when exactly does the reliance on vulnerable people in research count as exploitation? Second, from a more practical viewpoint, how can exploitative research practices be avoided or reformed? Answering these questions is necessary not only to ensure that

participants are not exploited, but also to ensure that unfounded concerns about exploitation do not impede otherwise legitimate research.

This brings us to exploitation theory, which (among other things) is concerned with determining the conditions under which human transactions and relationships are exploitative, what makes exploitation morally wrong, and how to mitigate it. While exploitation is often associated with Karl Marx's critique of capitalism, these issues remain important in contemporary moral and political philosophy, Marxist as well as non-Marxist. Since such issues are deeply ideologically and morally charged, they are unavoidably controversial. Nonetheless, philosophical debates on exploitation have yielded certain insights, which are helpful for understanding exploitation in human subject research.

We should begin by distinguishing different senses of the term 'exploitation'. In the most general sense, exploiting something simply means using it to one's advantage. For instance, a researcher may exploit her analytic skills in order to make a successful scientific career. However, in a narrower, pejorative sense – the relevant one for ethical discussions as well as for this chapter – exploiting something or someone means using or taking advantage of it or them in some morally inappropriate way.

It is necessary to distinguish exploitation (in this sense) from other moral concerns. While some exploitative practices (such as sexual exploitation) are harmful, people can be exploited also within transactions and relationships from which they benefit overall. As an illustration, consider sweatshop employment, a paradigmatically exploitative practice. Working long hours in unsafe and uncomfortable conditions for meagre pay could be the best available option for workers who would otherwise face unemployment and starvation. However, even in cases where sweatshop employment represents workers' best option (and thus benefits them), it is widely considered exploitative.

Moreover, while some exploitative practices (such as slavery) are coercive, exploitation can occur also within mutually consensual transactions and relationships. In the sweatshop case, for instance, workers could voluntarily agree to the arrangement because they correctly see it as the only way for them to adequately feed themselves and their families. However, even when consented to, sweatshop employment is generally seen as exploitative.[3]

While most theorists agree that exploitation can be both mutually beneficial and mutually consensual,[4] there is less agreement concerning what transactions and relationships are properly understood as exploitative and what is morally wrong with them. On most accounts, exploitation involves two necessary elements (Liberto, 2014; Valdman, 2009). First, one party (the "exploitee") is vulnerable, in the sense

[3] The observation that sweatshop labour can be exploitative despite mutual benefit and consent is commonplace in the philosophical and business ethics literature on sweatshops. See, e.g., Zwolinski (2007), Snyder (2010), and Malmqvist and Szigeti (2021).

[4] Theorists who agree on this include Wood (1995), Wertheimer (1996), Sample (2003), Mayer (2007), Snyder (2008), Valdman (2009) and Vrousalis (2013). Some disagree, though; see Wilkinson (2003).

of lacking reasonable alternatives to interacting on the other party's terms. Second, the other party (the "exploiter") uses this vulnerability to secure an advantage that is in some sense excessive or otherwise inappropriate. The first condition is necessary to distinguish exploitation proper from other bad deals, such as when somebody buys an overpriced used car because they cannot be bothered to shop around (Liberto, 2014). The second condition is necessary to distinguish exploitation from cases of innocuously benefiting from vulnerability, such as when a doctor treats ill patients for a modest fee (Arneson, 2016).

But what exactly is wrong with extracting excessive advantage from the vulnerable? This is the key bone of contention in the philosophical exploitation debate. On the *fairness view*, exploitation is wrong because it results in unfair distribution: the exploiter gains too much from the transaction or relationship compared to the benefits and burdens to the exploitee, from the perspective of some criterion of distributive fairness (Mayer, 2007; Valdman, 2009; Wertheimer, 1996). On the *respect view*, exploitation is wrong because it is demeaning or degrading: the exploiter treats the exploitee merely as means to an end rather than as a person with moral standing in their own right (Sample, 2003; Snyder, 2008; Wood, 1995). On the *domination view*, exploitation is understood as domination for self-enrichment: its wrongness consists in using one's power over others to turn them into one's servants (Vrousalis, 2013).

Returning to the sweatshop case, each view provides a distinct way of supporting the claim that such arrangements are wrongfully exploitative – even when workers benefit and consent. Proponents of the fairness view would locate the wrongness in the disparity between the workers' low wage and onerous working conditions, on the one hand, and the sweatshop owner's gain, on the other. Proponents of the respect view would instead argue that the owner fails to treat the workers as persons by using their need for work as a tool for profit-maximization (Wood, 1995) or by neglecting their basic needs (Snyder, 2008). Advocates of the domination view would argue that the arrangement involves an objectionable form of unilateral servitude on the part of the workers.

In addition to *what makes* exploitation wrong, another controversial issue concerns the *severity* of that wrong. Some doubt that exploitation is seriously wrongful in cases where it is mutually beneficial and consensual and the exploiter has no independent duty to interact with the exploitee (Zwolinski, 2007). If we do not condemn you for *not benefiting* somebody at all, it seems odd to condemn you for *benefiting* them in ways to which they consents. However, many theorists resist this challenge, arguing that exploitation can be seriously wrong even in such cases (Horton, 2019; Malmqvist, 2017; Snyder, 2008; Wertheimer, 1996). Other contentious issues concern the connection between exploitation and social justice and the appropriateness of banning or otherwise interfering with exploitative practices. These issues are discussed in the next section and the subsequent one, respectively.

Obligations of Researchers and Sponsors

We have seen that exploitation is a controversial concept the details of which can be understood in different ways. This may invite the conclusion that has little practical relevance for scientists and other actors involved in research. However, this conclusion would be mistaken: the concept of exploitation is distinctly useful for understanding the real-world ethical complexities of human subject research. On the other hand, its usefulness is limited: not every ethical concern about research can sensibly be construed in terms of exploitation. This section highlights how the concept of exploitation helps clarifying the moral obligations of researchers and their sponsors, along with some limitations in that regard, whereas the next section does the same with respect to the obligations of third parties, such as research ethics committees and regulators.

One important reason why exploitation discourse is useful is that it makes explicit morally relevant features of research that might otherwise escape attention. Researchers and sponsors (as well as ethics committees and regulators) understandably tend to focus their ethical attention on potential harms to participants and the validity of their informed consent. However, since exploitation can be mutually beneficial and consensual, ensuring a favourable risk-benefit profile and obtaining valid consent is not enough to make research non-exploitative. Researchers and sponsors must ask themselves what they owe participants, apart from securing their consent and managing risks.

In this regard, each view on what makes exploitation wrong helps call attention to a distinct set of potentially relevant features. By focusing on the overall distribution of benefits and burdens in a transaction, the fairness view prompts consideration of the *burdens beyond health risks* that participants face (e.g., discomfort, liberty restrictions, and lost time and income) and potential *non-medical benefits* to them (e.g., financial compensation and satisfaction of curiosity). It also requires researchers and sponsors to relate these benefits and burdens to the gains that they themselves and future patients may derive, asking whether the overall distribution is equitable. By focusing on *need*, the respect view prompts consideration not so much of benefits received and burdens incurred in research as of participants' general state of health or wellbeing before, during, and after a study. The domination view makes explicit the significant *power* or *control* that researchers and sponsors often have over participants, prompting them to ask whether this power is legitimate, how to mitigate it if illegitimate, and how to avoid abusing it.

While these views may not be fully compatible when understood as providing a philosophical account of what the wrongness of exploitation ultimately consist in,[5] they may nonetheless all be used as practical tools in the way described here. This is because each one picks out features that are recognized as characteristic of exploitative transactions and relationships on the other views too, and as such

[5] They are not necessarily incompatible though. On pluralist theories, exploitation comes in different varieties which are wrong on distinct grounds (Snyder, 2010, 2021).

constitute as evidence that exploitation is happening. Thus, regardless of which view one prefers on the level of moral theory, applying any one of them to human subject research may help identify practices that are exploitative (on the preferred view) and distinguish these from practices that are non-exploitative (on the preferred view).

Moreover, related to the remarks just made about need and power, the concept of exploitation is helpful because it calls attention to *vulnerability*. To exploit is to extract advantage from the vulnerable, so avoiding exploitation in research requires understanding the ways in which participants may be vulnerable to researchers and their sponsors. Relevant vulnerabilities may take different forms. In Phase 1 oncology trials (as well as many later phase trials in HICs), participants are vulnerable because they suffer from an illness that cannot be adequately managed with existing treatment. Here the vulnerability is mainly of a biological nature. However, other vulnerabilities have structural causes. For instance, healthy volunteers in Phase 1 trials, who mainly participate for money, may be vulnerable due to lack of access to secure employment and social protections. Similarly, participants in Phase 2 and 3 trials in LMICs who enrol in order to access otherwise unavailable care or medicines are vulnerable due to underdeveloped healthcare systems and high drug prices. In each case, the vulnerability consists in a lack reasonable alternatives, which makes participants susceptible to accepting beneficial but exploitative offers. Understanding the vulnerabilities that frame their interaction with participants (and the social, political, and economic context of research more generally) may help researchers and sponsors to avoid making such offers.

Since participants' vulnerabilities often have structural causes, concerns about exploitation tend to be intertwined with concerns about social justice. It is important to understand how these concerns are related, and how they are distinct. Depending on one's conception of social justice, many structural inequalities, e.g., unequal access to income or employment, healthcare or medicines, and adequate housing, may plausibly be considered unjust.[6] This judgment implies that governments ought to counteract these inequalities, but also that individuals and companies have moral responsibilities to contribute to such efforts (see, e.g., Young, 2011). For instance, individual researchers may be morally required to pay taxes to help fund a social security system, support political initiatives aiming to reduce poverty, and possibly devote part of their research efforts to health problems of disadvantaged groups. Similarly, pharmaceutical companies are plausibly considered morally required to develop drugs for conditions afflicting the global poor and facilitate access to the drugs they have developed (Hassoun, 2020). Such obligations are quite independent of the researcher's or sponsor's interaction with participants in a particular study. In addition, however, structural inequalities systematically put individuals, for instance research participants, in a position of vulnerability, rendering them "exploitable" by others (Holzer, 2020; Malmqvist, 2017). This means that whatever independent

[6] Many general egalitarian theories of justice (e.g., Rawls, 1971) and many theories of health justice (e.g., Daniels, 2008) would plausibly consider at least some of these inequalities unjust.

obligations researchers and sponsors may have to counteract structural inequalities, they are also morally required not to avail themselves of the opportunities to exploit participants that these inequalities create. Structural inequalities thus give rise both to obligations of social justice and obligations of non-exploitation. Importantly, however, these are two distinct kinds of moral requirement.[7]

This distinction has important implications. First, research is not exploitative just because the participants are victims of injustice. For instance, it can be acceptable to enrol poor people in need of money in a paid Phase 1 study or to enrol patients with no other way of receiving healthcare in a Phase 3 study – even if the poverty or lack of access to healthcare that motivates them is morally objectionable (Malmqvist, 2013; cf. Wertheimer, 1996, 298–299). There is reason to be especially cautious when designing and conducting studies involving such groups because their vulnerabilities are easily taken advantage of, but this does not render all such studies exploitative. Second, and conversely, research can be exploitative even in perfectly just conditions. Structural injustices are powerful sources of vulnerability, but there are other sources too (Malmqvist, 2013; Vrousalis, 2013). Even affluent participants with excellent access to healthcare can be vulnerable to exploitation due to, for instance, unavoidable illness, desperate hope for relief, or limited scientific understanding. Third, treating participants in a study well does not normally relieve researchers or sponsors of obligations of social justice. Researchers remain required to support just social arrangements as citizens, taxpayers, consumers, and perhaps (in other respects) as scientists, and sponsors to develop interventions that are useful and accessible to developing world populations.[8] Fourth, and conversely, discharging these latter obligations does not normally cancel or weaken researchers' or sponsors' obligation not to exploit participants.

These considerations show that while the concept of exploitation is useful, its usefulness is limited – in research ethics and in other contexts. Many scholars are dissatisfied with the focus of exploitation theory on discrete two-party transactions (e.g., between researchers and participants), and several accounts of exploitation that seek to accommodate structural concerns (e.g., related to global justice) or more complex relationships (e.g., researchers' and sponsors' relationship to host communities) have been proposed (Ganguli-Mitra, 2013; Panitch, 2013; Snyder, 2008; Wollner, 2019). However, the preceding analysis suggests that this transactional focus is not so much a deficiency as a limitation. In addition to exploitation, research ethics (just as any other area of practical ethics) needs to draw on other concepts and perspectives too.

The discussion so far has shown how the concept of exploitation may help refine researchers' and sponsors' moral sensibilities and disentangle their different moral

[7] A qualification: though conceptually distinct, the obligation of non-exploitation overlaps in practice with the negative duty not to contribute to social injustice because exploiters who take advantage of the unjust circumstances of their victims also objectionably risk reinforcing those circumstances (Malmqvist, 2013, 2017).

[8] This is somewhat simplified because researchers and sponsors may sometimes discharge (some of) their social justice obligations *through* conducting non-exploitative research.

obligations in various ways. This is not unimportant, but some might expect more. What concrete practical guidance (if any) does the concept provide? What, more precisely, should these actors *do* in order not to exploit?

There is no quick answer here. This is because the content of researchers' and sponsors' obligations of non-exploitation depends on the type of research they conduct, the context where it is conducted, and the view on the wrongness of exploitation one applies. However, since exploitation is a matter of extracting excessive (or otherwise inappropriate) advantage from the vulnerable, it can in principle be avoided in two ways: by ensuring (i) that those one interacts with are not vulnerable, or (ii) that one's gain is not excessive (or inappropriate). Researchers' and sponsors' ability to pursue the first approach is generally limited since participants' vulnerabilities are often due to structural or biological causes beyond their control. There are some important exceptions though. Due to their influence over drug prices, pharmaceutical companies may well be able to reduce vulnerabilities related to lack of access to medicines. Also, researchers are generally well placed to promote participants' understanding of a study, the broader scientific field, and (often) the nature of their condition. This is important not only for informed consent but also for non-exploitation, because it helps them appreciate the extent to which participating in a study advances their interests compared to other options available to them. That said, as discussed in the next section, other parties, such as regulators and ethical reviewers, are generally in a better position to mitigate participants' vulnerabilities.

Regarding the second approach, what exactly it means to avoid excessive gain partly depends on what one thinks makes exploitation wrong. On the fairness view, the net gain (all benefits minus all burdens from the transaction) of the vulnerable party must not be too small *compared to the net gain of the other party*. On a version of the respect view, the vulnerable party's gain must not be too small *compared to a threshold*, namely the fulfilment of basic needs (Sample, 2003; Snyder, 2008). However, the practical implication is roughly the same: avoiding exploitation when interacting with vulnerable people requires ensuring that they benefit adequately, leaving open exactly where and how the level of adequacy should be set.

What benefits participants should receive varies across different kinds of research. However, in all research, the benefits must be well above what is necessary to offset the health risks they face. Moreover, any kind of benefit is potentially relevant, not just health-related ones. Thus, in clinical trials in LMICs, non-exploitation may require various health-related benefits beyond access to the tested interventions during the course of the research, such as post-trial access to interventions proved effective and certain forms of ancillary care (Mastroleo, 2016). In Phase 1 trials involving healthy volunteers, which typically provides no such benefits and involves temporary confinement, sufficient payment and decent conditions on the trial site are necessary (Lamkin & Elliott, 2018). Sometimes priority access to scarce resources may be required, such as critical care if that is needed following infection with SARS-CoV-2 in a challenge study (Eyal et al., 2020). In all cases, participants should receive adequate insurance protecting them from adverse economic and health consequences of participating (Elliott, 2012).

One way of benefiting participants that is not generally required but that could be necessary when few other benefits are available or the burdens are significant is to support them in their pursuit of important goals or projects. Thus, insofar as participants are themselves committed to the ends of the research they are involved in, whether due to scientific curiosity or altruistic desire, researchers might benefit them by treating them as partners, sharing detailed information about the study and its progress and, when scientifically sound, granting them influence over its objectives, design, and conduct (cf. Anderson & Weijer, 2002).[9] Similarly, researchers can benefit participants in Phase 1 oncology trials who enrol in the pursuit of an improbable therapeutic response by helping them form and sustain realistic expectations about the likelihood of the hoped-for outcome (Snyder, 2021, 147–150). Moreover, benefits to *others* could count as benefits to *participants themselves* when the participants stand in a reciprocal relationship to these other parties or genuinely care about their wellbeing (Millum, 2016). This explains why avoiding the exploitation of participants in research in LMICs may require that studies be responsive to their wider communities' health needs and that interventions proved effective be made available to these communities after the studies are over.[10] As these examples show, a commitment to non-exploitation requires researchers and sponsors to conceive of benefits to participants broadly, rather than just focusing on therapeutic or financial gain.

Obligations of Third Parties

The previous section considered the obligations of non-exploitation held by actors who conduct human subject research, namely researchers and sponsors. This section shifts focus to actors who are not directly involved in the research, but have significant influence over its conduct, for instance ethics committees and regulators. What should such third parties do to prevent and/or mitigate exploitation?

This issue has received less attention than the obligations of researchers and sponsors, and the discussion has mainly focused on the appropriateness of banning exploitative research. While such bans may initially seem attractive since exploitation is morally objectionable, they face a significant challenge. Recall that exploitation can be mutually beneficial and consensual. The victims may benefit because the exploitative transaction or relationship represents the best option available to them

[9] Jonas (1969) famously argued that participants' identification with the ends of the research is necessary for their ethical recruitment. The claim here is much weaker: *when* subjects identify with the ends of the research they could benefit from being treated as partners, which may help make the study non-exploitative. A recent example of such subjects is 1DaySooner (www.1daysooner.org), an advocacy group for people who want to participate in Covid-19 challenge studies.

[10] Such requirements are included in key research ethical guidance documents (NBAC 2001; CIOMS 2016) but sometimes considered difficult to justify from a non-exploitation perspective (Wenner, 2018; Wertheimer, 2011).

and voluntarily agree to it precisely on those grounds. When this is the case, banning the transaction or relationship deprives them of this option, which harms them since their non-transaction alternatives are worse. Also, doing so arguably fails to respect their autonomy since they genuinely want to pursue this option. So, even though exploitation is morally objectionable, permitting it may often be the best policy (Wood, 1995; Wertheimer, 1996, 296–97; Zwolinski, 2007).

In the research context, this challenge concerns not only outright legal prohibition, but also attempts to indirectly enforce researchers' and sponsors' obligations of non-exploitation. For example, ethics committees might reject proposed research that is unresponsive to health needs in LMICs, uses placebo controls when active treatment exists, provides healthy volunteers inadequate pay and insurance, and so on. Alternatively, promulgators of legally non-binding ethical guidance documents might declare such research unethical (as they largely do already; see NBAC, 2001; WMA, 2013; CIOMS, 2016). If effective, these approaches accomplish the same as outright legal prohibition: they block would-be exploitative studies, ensuring that studies that are actually conducted do not involve exploitation. They therefore raise the same challenge: insofar as participants would consent to an exploitative study and benefit from it, for instance by gaining access to otherwise unavailable medicines or income opportunities, blocking the study risks harming the participants against their will.

One possible response to this challenge is to take a *laissez faire* approach to research. On this approach, regulators, ethics committees, and other third parties would ensure that participants provide valid informed consent and are not on balance harmed, but would not block studies on other grounds. Many kinds of research that are widely considered exploitative would thereby likely be allowed (Wertheimer, 2011, 240–44). These include placebo-controlled trials in cases where an active treatment against the condition under study exists but is unavailable at the study location, research in LMICs that is wholly unresponsive to these countries' health needs, and Phase 1 trials offering uninsured volunteers less than a minimum wage for extended confinement in uncomfortable conditions.

Many find this response unpersuasive. Thus, it has been argued that mutually beneficial and consensual exploitation can be justifiably banned or blocked when removing the exploitative option from the table can be expected to prompt the parties to transact on non-exploitative terms (Wertheimer, 1996, 2011) or when the transaction has serious negative impact on third parties (Malmqvist, 2013). The force of these arguments depends on empirical assumptions that may be highly plausible in some contexts and some kinds of research, but less so in others. Thus, their merits need to be considered on a case-by-case basis.[11]

While the question of permitting versus banning or blocking exploitation has received significant attention, it would be a mistake to think that these are the only

[11] A possible additional argument is that exploitative research in the real world is rarely genuinely mutually beneficial and consensual. If this is true, some harm- or consent-based justification for banning or blocking such research is available in most cases, making the problem discussed here moot. This is another empirical issue that must be settled case-by-case.

available responses. There are other ways for third parties – such as, in research, regulators and ethics committees – to address exploitative practices. Recall that exploitation can in principle be avoided (i) by reducing or eliminating vulnerability, or (ii) by ensuring that each party to a transaction benefits adequately. I argued in the previous section that researchers' and sponsors' ability to pursue (i) tends to be limited and consequently focussed on their obligation to pursue (ii). Since, as we shall see, third parties may be better placed to address participants' vulnerability, (i) will be in focus here. Moreover, in addition to these *preventive* approaches, there are ways of addressing exploitation *after it has happened*. These are discussed in the next section.

As noted above, the vulnerabilities rendering people susceptible to being exploited are often rooted in unfavourable structural conditions. In such cases, the most forceful response is to improve these conditions, by reducing poverty, strengthening social protections, improving access to healthcare and medicines, and so on. Such efforts are arguably required as a matter of social justice, independently of exploitation concerns. However, the fact that they may effectively prevent exploitation provides additional moral reasons to pursue them. Such prevention is achieved by expanding the range of options available to people, eliminating or reducing the need for them to accept exploitative offers. Responses of this sort are therefore the opposite of bans: instead of *removing* the exploitative but beneficial option, they *outcompete* it by adding better options. This avoids the concerns about harming and disrespecting the victim that we have seen that bans raise.

In research, one such response is to increase access to healthcare and medicines in LMICs. People obviously have no need to enrol in potentially exploitative research to gain uncertain or temporary access to needed treatment or care if they have more reliable access outside the research context. Similarly, increasing the availability of stable and adequately paid jobs reduces the need to participate in Phase 1 trials offering low compensation and onerous conditions to secure an income.

While attractive, responses of this sort are very broad and unlikely to be motivated solely by a concern to prevent exploitation. Further, they are to a large extent the responsibility of governments (and perhaps of intergovernmental organizations) rather than of actors specifically concerned with human subject research. However, participants' vulnerability can also be addressed in more targeted ways. One approach is to promote their understanding of their condition, the study they participate in, and the relevant research field, as well as their scientific literacy more generally. This helps preventing exploitation by making them less liable to enrol based on an exaggerated perception of the benefits the study will bring or a failure to consider other available options. As noted in the previous section, researchers clearly have an important role in promoting such understanding. However, third parties such as scientific organizations, regulators, and the media can also be expected to contribute to this task.

A controversial way of reducing the exploitative potential of Phase 1 trials involving healthy volunteers would be to introduce protections of the sort available to workers in other areas, for instance rights to a minimum wage, a safe workplace, and compensation and care in case of injury, along with a right to unionize and

engage in collective bargaining (Anderson & Weijer, 2002; Fernandez Lynch, 2014; Malmqvist, 2019; Walker et al., 2018). Such measures would help avoid exploitation by ensuring that participants benefit adequately, but also by reducing their vulnerability. Especially important in the latter regard may be the right to unionize, which would strengthen participants' bargaining position vis-à-vis researchers and sponsors, allowing them to resist exploitative research practices collectively.

Remediating Exploitation

The last two sections focused on various ways of ensuring that exploitative research practices are avoided. However, such preventive approaches are unlikely to be fully effective: participants in human subject research have been exploited in the past and will, in certain cases, likely suffer exploitation in the future too. This makes it important to consider how to *remediate* exploitation, i.e., respond to it after it has happened (Malmqvist & Szigeti, 2021).

Even when exploitation is mutually beneficial, the victims always gain inadequately. When the exploitative transaction is over, they therefore have a valid claim to *additional* benefits: more precisely, to a level of benefits they would have enjoyed in a non-exploitative but otherwise comparable transaction (Malmqvist & Szigeti, 2021). Consequently, researchers and sponsors may, by way of remediation, be required to provide participants with any benefit they owed them as a matter of non-exploitation (see section "Obligations of researchers and sponsors") but failed to provide before. In Phase 1 trials this could mean retroactive financial compensation to underpaid participants. In research in LMICs, remediation could instead take the form of post-trial access to tested medicines or care, or perhaps various community benefits. Indeed, requirements for these latter kinds of benefit in ethical guidance documents (NBAC, 2001; CIOMS, 2016) could be seen as reflecting a recognition that these benefits have objectionably been denied in the past.

While researchers and sponsors who have conducted exploitative research have moral obligations to provide remediation, it is a further question whether and how third parties should enforce such obligations. Sometimes enforcement may raise the same problem as bans (see section "Obligations of third parties"): researchers and sponsors who expect to be held accountable may be discouraged from conducting exploitative studies that participants would actually benefit from and consent to, yet lack the motivation to conduct research on non-exploitative terms. However, it is possible that the risk of such effects is smaller in cases of *retroactively* enforced remediation than in cases of *prospective* bans, making enforcement a viable option.

Conclusion

Biomedical research on human subjects raises persistent concerns about exploitation. Making sense of these concerns is important, both to ensure that participants are treated ethically and to ensure that legitimate research is not unnecessarily obstructed. Exploitation is a curious phenomenon in that even mutually beneficial and consensual exchanges can be wrongfully exploitative, and the precise nature of its wrongness is a philosophically contested issue. However, on most views, victims of exploitation are always vulnerable and always benefit inadequately from the exchange. The implications for research can be summarized as follows: Ensuring valid informed consent and a favourable risk-benefit profile is not enough to avoid exploiting participants. Researchers and sponsors owe them benefits beyond what is necessary to offset health risks, benefits which may take different forms. As for third parties, the most effective response is often prophylactic, aimed at mitigating the vulnerability that enables exploitation. Insofar as participants' vulnerabilities have structural causes, e.g., lack of access to healthcare or poverty, such responses can be considered part of broader efforts to promote just structural arrangements. However, since preventive efforts are unlikely to ever be fully effective, it may be necessary to remediate the effects of exploitation retrospectively by providing benefits that participants were previously denied.[12]

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Chapter 10
Selection of Research Subjects: Methodological and Ethical Issues

José Roberto Goldim and Márcia Santana Fernandes

Abstract Ethics is one of the main components of research process. In order to have social recognition it is not enough generate knowledge, nor that research is reliable, it has to be trustworthy. One of the most delicate activities in research involving human beings is the definition of the selection of potential participants. It is in this set of criteria and approaches that research begins, that connects with society, with people. Research Ethics could be based in many different theoretical approaches. This chapter defends that adequacy of research actions must be evaluated through reflections that allow an integrated perspective of the project's objectives with the well-being of the participants throughout the entire process.

Keywords Selection of research subjects · Methodological issues · Vulnerability · Ethical foundations · Participant selection

Introduction

Research can be understood as a creative and systematic work in the search for knowledge generation (OECD, 2015). In order to have social recognition it is not enough generate knowledge, nor that research is reliable, it has to be trustworthy. To be reliable is the characteristic of those who do well what is expected of them in a specific field of action. However, being trustworthy is associated with certainty and security of actions that will be taken. Researchers and institutions have to be recognized by society as being trustworthy (O'Neill, 2002). It is fundamental to unify the generation of new knowledge with the reflection associated to its practice and

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repercussion, that is, it is necessary to maintain the integrated perspective of Science with Conscience (Morin, 1990).

One of the most delicate activities in research involving human beings is the definition of the selection of potential participants. It is in this set of criteria and approaches that research begins, and connects with society, with people.

Numerous documents establish criteria in the area of research on how to make an adequate selection from a legal, moral and ethical point of view, such as the Declaration of Helsinki (WMA, 2018) and the Belmont Report (US Government, 1979). However, it is fundamental to deepen the reflection on the ethical aspects associated with this issue. The regulatory framework establishes the rules of how and what to do, but the ethical reflection allows the discussion on the fundamentals, on its justifications.

There are many possible approaches to bioethical reflection. Complex Bioethics is one of them. In this perspective, Bioethics is a complex, shared and interdisciplinary reflection on the adequacy of actions involving life and living (Goldim, 2006a, b).

Life and living complement each other, they give the adequate dimension of each person. Life is described by the organic aspects, that is, by the biological characteristics. On the other hand, living refers to the relational aspects, the biography of each one (Agamben, 1998). The ensemble of these characteristics is what gives the uniqueness of each person. Many times, inclusion and exclusion criteria are established in a research project only based on biological characteristics of the potential participants.

Ethical reflection, using different frameworks, about selection of potential participants in a research project, should be based on the facts and circumstances involved. The selection of participants in a research project has some characteristics that need to be properly evaluated, such as the vulnerability of potential participants, the risks and benefits involved, and the number of people who will be exposed to the research interventions.

Vulnerability

To have an understanding on the adequacy of the selection of research participants, it is necessary to reflect on vulnerability, on the need to care for the other (Levinas, 1961). Vulnerability can be addressed in the very process of selection of participants, with the recognition of their characteristics, the type and degree of exposure associated to the research itself.

The selection process must take into account the vulnerability of potential participants in a research. The concept of vulnerability encompasses multiple approaches, such as being understood as fragility, susceptibility, or reduction of autonomy, self-determination, voluntariness, and freedom itself. Recognizing that there is some vulnerability associated to the selection process implies in establishing associated additional protection measures (Kemp, 2004). Basically, there are two approaches to this characteristic: static vulnerability and dynamic vulnerability.

Static vulnerability depends on the recognition of previously established characteristics, such as age, health status, belonging to social groups or other characteristics that may compromise their ability to decide. Different regulatory documents have established, over time, different restrictions for the selection of people who have been considered vulnerable because they possess a given characteristic.

The Nuremberg Code, for example, did not allow research involving people who lacked legal capacity (Nuremberg Trials, 1949). Thus, according to this document, children, adolescents and incapacitated or mentally handicapped people would be prevented from participating in research projects. The CIOMS Guidelines, in its 2016 edition, also establishes specific conditions for research involving incapacitated adults, children, adolescents, women, pregnant and lactating women (CIOMS, 2016). The Declaration of Helsinki, in its 2018 version, does not specify what vulnerable groups or persons are, but states that in the event of vulnerability, appropriate protective measures should be proposed (WMA, 2018). Other groups may also be considered vulnerable, such as elderly people, members of indigenous populations or those living in conditions of lack of resources, or people who are in a situation of restriction of freedom, such as prisoners (US Government, 1979).

On the other hand, there is also dynamic vulnerability, which depends on circumstances associated with the situation in which the person is being exposed to the survey invitation. A person may not fit into the categories considered vulnerable and may become fragile as a result of the situation itself. The presence of elements of coercion can make a non-vulnerable person in a vulnerable one (Gardner et al., 1998).

The use of economic incentives such as remunerating research participants is still a controversial issue. To what extent remuneration can be understood as coercion, deserves further study and research (Brust-Renck et al., 2019; Halpern et al., 2021).

It is always good to remember that coercion exists to the extent that the person who is invited to participate in research perceives the existence of an element of authority or prestige present in this relationship (Piaget, 1977). In this situation a student, an employee of an institution, members of military institutions or religious orders, or even a patient or his family members, may feel embarrassed about the possibility of not accepting the invitation for a research project. Depending on who makes the invitation, or their links to the person who may exercise this role of unequal power, the potential participant may be made vulnerable.

Coercive behavior can be categorized as positive symbolic pressure, which may evolve into negative symbolic pressure until it reaches an action involving the demonstration or use of force itself (Taborda et al., 2004).

Positive symbolic pressure can be expressed by the simple act of asking if this person wants to participate in the research. Depending on the relationship between those who make the invitation and those who receive it, and especially the way in which it is made, it may have an element of coercion associated with it. Persuasion and induction are also considered in this same group. These behaviors may be considered, depending on the circumstances and care of the research team, to be permissible. This can be minimized with disclosure of the research by means of information that allow potential candidates to spontaneously seek the researchers in order to participate in the project (Gardner et al., 1998).

Coercive behaviors, deemed unacceptable in recruitment of potential research participants, involve acts that have the deliberate intention to deceive, to give orders or to threaten, which are characterized as negative symbolic pressures. This situation is aggravated when there is the demonstration or use of physical force or even of a judicial order, considered as behaviors of extreme coercion, for in these situations, the person is deprived of the exercise of his/her freedom (Gardner et al., 1998).

Risks and Benefits

Another important point is the adequate evaluation of the risks associated with research. It is important to differentiate between naturally existing risks and risks created by research (Giddens, 1991). Natural risks are those that people invited to participate are already exposed to in their daily lives. On the other hand, research-constructed risks are those that are added to the natural ones. They are those that participants will be exposed to as a result of having accepted the invitation to be a research participant.

Known risks are based on the evaluation of previous situations, and are expressed by a probability that a harm may occur during the course of the research. This information comes from previously conducted studies. Sometimes, research situations are associated with harms already described, but still insufficient for the calculation of associated probabilities. This characterizes a situation of uncertainty as to the occurrence of a predictable harm. It is important to remember that in clinical research many risks are calculated from studies that do not involve human beings, that is, those performed in the pre-clinical stage. It is fundamental to verify if there is, in fact, the possibility of making this type of extrapolation. In some very innovative research, such as Phase 1 trials, both the harms and their occurrence rates may be unknown. This situation of unknown risk should never be understood as one of no risk (Shrader-Frechette, 1994). Unknown risk is unpredictable.

Before carrying out the selection of the possible participants of a research, all situations involving risks, whether they are known or not, must have the provision of associated contingency measures that may prevent or mitigate their occurrence (Jonas, 1994).

The risk, when understood in the perspective of the selection of potential participants of a research, must be adequately assessed, in terms of identification, quantification and characterization; be managed, in the perspective of being acceptable or not, of being safe and mitigated; and analyzed as to its adequate perception (Slovic & Weber, 2019).

In a complementary manner to the risks, the evaluation of eventual benefits associated must be carried out. That is, the possibility that the research may aggregate some favorable and desirable characteristic in the perspective of the participants. In most cases, the associated probabilities are not presented, and the potential benefits are presented in the form of possibilities associated with participation in the study.

The benefits are presented, most of the time, as an expectation that they will occur, that is, they remain in the perspective of a desirable uncertainty. This hinders an adequate evaluation of the risk-benefit ratio, since on one side we have a probability associated with the risk and on the other an expectation of benefit (Grady et al., 2017).

This becomes even more important when studies with comparative groups are performed. The selection of participants should present the specific risk-benefit ratio for each group that will be exposed to the research situation. The risk assessment of each group and of the research as a whole should ensure that there is genuine doubt on the part of the researchers (Goldim, 2006a, b). That is, there should be no indications of risks or benefits that could characterize a situation of foreseeable inequality (Freedman, 1987). Equipoise between groups should be demonstrated by appropriate assessment of the risk-benefit ratio for the different groups. It is also important to recognize the need to include fallibility as a criterion for adequacy, as evaluations involving uncertainty are always present in these assessments (Miller, 2020). Equipoise does not guarantee that the selection of potential participants is fair, but it greatly assists in justifying the ethical appropriateness of the research project.

Both risks and benefits may have a personal or diffuse perspective, i.e., their occurrence may be directly related to the research participants or have an extended scope for society as a whole. In selecting participants, the primary focus is on the personal risks and benefits of the research participants. Diffuse risks and benefits should be evaluated through the relevance associated with the realization of the project (US Government, 1979). In research, as in other human activities, the greatest risk of all is not taking risks (Doerr, 2018).

Number of People Exposed

The estimation of the number of research participants is by many understood only as a methodological feature of the project. Establishing the sample size of the participants that will be subjected to research-related exposure is both ethically and methodologically important. The ethical and methodological aspects of a research project are inextricably linked. The estimate of the sample size serves to plan the study and adapt how many people will be necessary so that, maintaining the conditions when planning the project, the results are useful, that contribute to the generation of knowledge (Bacchetti et al., 2005).

If the sample studied is insufficient, the research may be harmed in its methodological aspects, and will not have, for this reason, the capacity to generate the expected knowledge. From the ethical point of view, many people, but not enough, were unnecessarily exposed. On the other hand, in experimental research, if the planned sample size is exceeded, there may be an equally unnecessary exposure of participants to research risks, without the counterpart of increased possibility of associated benefits (Bacchetti et al., 2005).

The Ethical Foundations

In the same way as it is important to assess these issues of vulnerability, risk, benefit and sample size to be selected, it is also fundamental to have a solid basis of ethical argumentation for the characterization of its adequacy. The Complex Bioethics model uses different ethical frameworks to elaborate its reflections on the appropriateness of the proposed actions. The ethical framework serves as tool to search for arguments or to verify the validity of arguments used in the evaluation of research projects. The use of multiple frameworks follows the proposal of understanding Bioethics as a "navigation exercise", as a search for possible paths to adequacy. Kant, in 1785, already used the metaphor that Ethics should serve as a "compass for reflection". (Kant, 2005).

The ethical frameworks used are the perspectives of virtues; of wills or intentions; of principles; of responsibility; of rights; of consequences and, finally, of alterity. There are seven different perspectives that complement each other. The integrated use of these different frameworks allows for a better reflection on the adequacy of the proposal for the selection of potential research participants.

The Virtue Ethics

Virtue Ethics is the oldest of the proposed approaches. Virtue is an acquired disposition to do good, which lies at the intermediate point, in a dynamic equilibrium between lack and excess (Aristotle, 2009). Exercising the virtues is always an effort.

Four virtues can be associated with the selection of research participants: Fidelity, Prudence; Temperance and Justice. Prudence and Temperance are associated with the perspective of exposure, of having a reflection based on practical reasoning and ensuring that the sample size is set at the limit of what is necessary. Fidelity is the guarantee that the established commitments will be fulfilled, especially regarding risk prevention and mitigation measures. Justice, finally, is the guarantee of a non-discriminatory behavior, which may differentiate individuals, but which does not establish inequalities based on these characteristics. Justice, as non-discrimination, like any other virtue, requires a continuous effort in the search for the good (Pellegrino & Thomasma, 1993).

The Ethics of Wills or of Intentions

The Ethics of Wills, also known as the Ethics of Intentions, establishes that the moral value of an action depends on the intention associated with the action and the consent for the action to occur (Abelard, 1995).

The researcher must demonstrate his or her genuine intention not to discriminate when proposing a selection of research participants, even if differentiating groups. The researcher must also have the intention to do good for the patient, that is, to have beneficence as the purpose of his or her actions (Abelard, 1995).

On the other hand, the potential participants should have access to information about the risks and benefits associated with their eventual acceptance to be part of the research. The Ethics of Wills is the first to use consent as one of its foundations (Abelard, 1995). The conjunction of the intention of the researcher with the consent of the participant is what allows to verify the adequacy or not of the proposed selection process of a research project.

The Ethics of Principles

The Ethics of Principles allows multiple approaches, but all are based on the notion of duty, of having to do an action. There are two major proposals of Ethics of Principles: The North American (Beauchamp & Childress, 1979) and the European (Kemp, 2004).

The North American perspective, proposed by Tom Beauchamp and James Childress, establishes the ponderation of four principles to verify the adequacy of an action: Beneficence, Non-Maleficence, Autonomy and Justice. This proposal prioritizes one principle, in case of conflict between them, assuming that they are prima facie duties (Ross, 1930).

On the other hand, European perspective, proposed by Peter Kemp and Jacob Dahl Rendtorff, use four other principles: Dignity; Autonomy, understood as Freedom; Integrity; and Vulnerability (Kemp & Rendtorff, 2008). In this perspective, principles are not weighted, but there must be a coherence in their application.

Using principles, it is possible to make reflections on the appropriateness of how to select people for research. In assessing the appropriateness of selecting participants in a research project, the principles of Dignity, Justice and Vulnerability are associated with the very act of selecting. Dignity is the principle that gives the character of humanity to all people, that levels everyone on the same level. It is Dignity that prevents discrimination, by being coherent with Justice. If there is recognition of any inequality between possible participants in a research project, that is, if a characteristic of Vulnerability is recognized, this implies that researchers must take contingency measures in the sense of providing additional protection to these people.

Another extremely important and complementary principle is that of Autonomy, understood as freedom to decide. This decision also depends on information about the risks and benefits associated to the proposed research procedures, that is, an adequate balance between the Beneficence and Non-Maleficence principles. The focus of this evaluation should be the preservation of each individual's integrity. The application of the principles as a whole, either as a weighting or as coherence, is what generates the adequacy of the act of selecting people for a research.

The Ethics of Responsibility

The Ethics of Responsibility is based on the evaluation of the repercussions of actions taken, in terms of the associated facts, whether they are causes or effects of the action (Weber, 2004). Responsibility can be retrospective or prospective. Retrospective responsibility privileges the perspective of the cause, of what has already occurred. Prospective responsibility, on the other hand, directs its perspective to the effects that will be generated. The Precautionary principle generates this need to monitor the data, to continuously re-evaluate the estimates foreseen in the planning phase of a research (Jonas, 1985).

Participant selection involves both retrospective and prospective responsibilities. Non-discrimination should be present both in the selection process, with appropriate characterization of the inclusion criteria, and in the follow-up of participants, with exclusion criteria. Likewise, adequate evaluation and information on the risks and benefits associated with research should precede selection and continue throughout the research. Risks and benefits should be monitored throughout the study. This allows evaluation of the consistency between the data that was used for the estimates and the occurrence of expected and unexpected events verified during the course of the study. The participants should be continuously informed of new risks that have been added to the research, or of changes in the occurrence of previously described harm. Based on these new data, it may be necessary to recalculate the planned sample size, and it may be necessary to stop the study or extend the selection of participants. These changes, if necessary, entail a new consent process to update the information and authorizations previously given.

The Ethics of Rights

Rights are expectations, a person expects other people or institutions to have actions that guarantee them. The Ethics of Rights establishes different scopes: Individual Rights, Collective Rights and Transpersonal Rights. In the process of selecting participants for a research project it is important to guarantee all these expectations.

The most prominent Individual Rights are the preservation of life, liberty, privacy and non-discrimination. The people invited have the expectation of being respected, of being protected as individuals. Collective Rights cover the issues associated with access to health, education and social assistance. Finally, Transpersonal Rights are those that transcend the previous two areas, referring to environmental issues and solidarity (Bobbio, 2014).

In establishing the criteria for selecting participants, several rights stand out and are associated. Non-discrimination and solidarity are an example. Non-discrimination is an Individual Right. Each person has this right not to be discriminated against as an individual, without having to belong to a group: only his very existence gives him this guarantee. On the other hand, there is the expectation of solidarity, that is, that everyone feels responsible for guaranteeing the rights that may be threatened to each person.

Non-discrimination and solidarity are based on an adequate evaluation of the risks and benefits associated with the research project. The focus of this assessment should be on preserving the life of each potential participant and the health of all. The selection of a participant culminates in his or her consent. The basis of this decision to participate or not in research is the expectation of freedom, of being able to make a decision without the presence of associated elements of coercion.

The Ethics of Consequences

The Ethics of Consequences is based on the evaluation of the utility associated with human actions. Utility understood as a relationship between the risks and associated benefits. Risks are not only associated with harm, but also with discomforts or associated additional costs. In assessing benefits, as well as risks, individual or collective repercussions can be evaluated. Micro- and macro-allocation criteria should be adequately differentiated and assessed for their impacts (Singer, 1979).

In selecting participants for a research project, all possible utilities associated with the project must be taken into consideration. The utility analyses must consider all possibilities from the individual and collective perspectives and the associated risks and benefits. Risks associated with individual discomfort or harm must be clearly differentiated from risks of harm and collective costs. Likewise, the potential benefits should be assessed at the individual and collective levels. In the invitation to potential participants the essential information, which allows their understanding and individual and collective level, must be presented in a way that allows an adequate decision.

The researcher should have a macro-allocation perspective while the potential participant makes a micro-allocation. The invitation for participation should be done in a way that does not privilege or exclude one person or group of people over others. Inclusion and exclusion criteria should be clearly established and adhered to. This is the characteristic of the macro-allocation process to be carried out by the researcher. On the other hand, the potential participant of the research makes a punctual and personal evaluation, that is, he associates the eventual harms or benefits to himself, which may be associated to his desires, affections, and system of beliefs and values, besides the more objective decision-making aspects. It is a clear individualized micro-allocation. These two perspectives, which are not conflicting but complementary, guarantee the appropriateness of the process as a whole.

The Ethics of Alterity

Finally, the Ethics of Alterity allows a new perspective, starting from the recognition of the other, without losing the personal dimension of each one. The inclusion of the other, in the individual perspective of each one, implies the establishment of

a conjugation of interests of one's own person and the other person involved. Alterity provides the possibility of a new look, no longer individual but common to all: those of our interests. It is from this interaction that emerges the recognition of the characteristics of ethical co-presence, of co-responsibility, of the impediment of neutrality in front of the other. All of them are Alterity inherent (Levinas, 2000).

Recognizing the other as a person prevents discrimination, makes the relationship between the researcher and the potential participant as an effective interaction. It is not one or the other in isolation, but a respectful conjunction, a presence of each in front of the other, that is, an ethical co-presence.

This genuine interaction also generates a co-responsibility between the people involved. The selection of participants is not the sole and isolated responsibility of the researcher. The Research Ethics Committee, by evaluating and approving the project, becomes equally co-responsible, by validating the proposal forwarded by the researcher. In the same way, the potential participant, when deciding to accept the invitation, also assumes responsibility. The researcher assumes responsibility for the invitation and for the information linked to it, as well as for the follow-up throughout the project. By accepting the invitation, the potential participant becomes part of the project. Accepting the invitation is also taking on responsibilities. It is often misconceived that by accepting the invitation, the participant exempts the researcher from responsibility: consent is not an exemption from responsibility for the researcher. On the contrary, in this effective researcher-participant interaction, there is no longer any possibility for neutrality. The researcher must remain impartial throughout the selection process, but that should never be confused with neutrality. Impartiality does not let my interests dominate the decision-making process, but neutrality disregards the other. There can and should be impartiality on the part of the Research Ethics Committee when evaluating the project. The researcher must also remain impartial in order to avoid embarrassment and coercion on the people invited. In the same way, the participant must be able to preserve his freedom to decide. The researcher and the participant may have their own interests, which may be convergent or divergent. In a genuine interaction, everyone is co-responsible for the actions taken in common.

The Adequacy of Research Participant Selection

The methodological adequacy of research participant selection involves the identification of characteristics or situations of vulnerability related to potential participants, the assessment of risks and benefits associated with research interventions, and the establishment of the number of people who will be exposed.

In terms of ethical aspects, the different perspectives presented above have peculiar characteristics that allow us to generate arguments about the appropriateness or otherwise of selecting participants for a research project. While maintaining methodological rigor, in an interdisciplinary perspective, it is possible to combine arguments from different perspectives, which can generate new possibilities of

understanding and justification of the proposals. These alternatives broaden the possibilities for forwarding the evaluation of the adequacy of the situations involved in the selection of potential participants. The perspective proposed by Complex Bioethics, by considering that this reflection occurs in an interdisciplinary field, enables these integrating reflections among different knowledge (Goldim, 2006a, b).

Complex reflection provides a convergence of the different ethical perspectives on the appropriateness of the selection of participants in a research project. Outside an integrative perspective, there are "seven compasses" pointing to different ways of ethically justifying the appropriateness of the proposal. Instead of seven divergent perspectives, complex reflection provides a new and creative convergent perspective, which allows a more comprehensive assessment of appropriateness.

Final Remarks

Some relationships, which emerge from these complex reflections, are not intuitive. By building an adjacency matrix from the thirty-one different arguments presented throughout the text, which are:

Through an integrated and cross-interpreted analysis of these different arguments [Figs. 10.1 and 10.2 annexed], it was possible to identify different and multiple interactions that must be observed for the recruitment of clinical research participants; using a dendrogram created by UCInet software (Borgatti et al., 2002).

1.Prudence;	2.Fidelity	3.Temperance	4.Justice as a virtue
5.Intention	6.Consent	7.Beneficence	8.Non-maleficence
9.Autonomy	10.Justice as a principle	11.Dignity	12.Integrity
13.Freedom	14.Vulnerability	15.Retrospective responsibility	16.Prospective responsibility
17.Non-discrimination	18.Solidarity	19.Health	20.Life
21.Risk	22.Benefit	23.Utility	24.Macro-allocation
25.Micro-allocation	26.Ethical co-presence	27.Co-responsibility	28.Non-neutrality
29.Researcher	30.Potential participant	31. Research Ethics Committee	

It is worth highlighting:

- the need to consider the ethical co-presence and the preservation of dignity, associated with the researcher, the potential participants and the Research Ethics Committee, as relevant and fundamental elements;
- based on this co-presence, to value, when obtaining the consent, the relationship among autonomy, as capacity; freedom, as exercise of action; and fidelity, understood as fulfillment of the assumed commitments;
- the researcher shall maintain the perspective of non-discrimination associated with impartiality (non-neutrality);

- the researcher's intention must focus on the beneficence and non-maleficence of his actions associated with the research, which is also linked to his retrospective responsibility;
- the appropriateness of the decision-making process of the researcher is associated with justice, understood as fairness, and the recognition of possible vulnerabilities;
- assume the prospective responsibility of the investigator and the Research Ethics Committee for the continuity of the usefulness evaluation, in terms of foreseeable risks and benefits, in the perspective of preserving the integrity of all potential participants involved;
- the decision-making process of the potential participants is associated with the expectation of solidarity and co-responsibility on the part of the researcher, focusing on the preservation of his/her life and health.

These ethical and methodological reflections aim to expand the perspectives of adequacy of planning and execution of the selection process of potential participants in a research project.

Annexes

Actor/Actor	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
1	9	8	8	7	6	6	5	5	4	9	3	8	6	6	9	9	7	6	6	5	7	7	8	6	6	7	6	7	2	2	1
2	8	14	8	12	9	7	7	7	4	12	5	10	8	11	10	11	10	9	6	5	9	9	9	10	10	8	10	11	2	2	1
3	8	8	10	8	8	6	6	6	4	10	3	8	6	7	10	9	8	6	5	4	8	8	9	8	6	6	5	8	1	2	1
4	7	12	8	17	9	6	8	8	4	14	6	12	10	14	12	11	14	13	7	5	9	10	11	13	10	9	9	15	1	2	1
5	6	9	8	9	16	6	9	9	3	9	3	11	6	10	13	12	11	8	7	7	12	11	14	13	9	7	10	10	1	2	1
6	6	7	6	6	6	10	5	5	4	8	4	8	5	6	10	9	5	5	5	4	7	7	7	6	9	5	6	5	2	1	0
7	5	7	6	8	9	5	12	11	3	8	3	11	6	8	9	7	8	7	5	5	11	10	11	9	7	6	8	7	1	2	1
8	5	7	6	8	9	5	11	13	3	8	4	12	6	9	9	7	8	8	6	6	11	11	12	10	8	5	9	8	1	2	1
9	4	4	4	4	3	4	3	3	6	6	3	6	6	4	5	5	3	3	4	4	5	5	5	3	3	4	3	3	2	2	1
10	9	12	10	14	9	8	8	8	6	17	5	14	11	11	14	12	13	10	8	7	12	12	13	11	10	9	9	14	2	2	1
11	3	5	3	6	3	4	3	4	3	5	9	5	5	7	6	6	5	6	4	2	5	5	6	6	6	5	5	5	2	1	0
12	8	10	8	12	11	8	11	12	6	14	5	20	10	12	14	13	12	11	10	10	17	14	17	15	14	8	11	13	2	2	1
13	6	8	6	10	6	5	6	6	6	11	5	10	13	9	10	10	9	7	6	6	10	9	10	8	7	8	7	8	2	2	1
14	6	11	7	14	10	6	8	9	4	11	7	12	9	18	10	10	14	13	7	5	10	9	12	14	11	8	11	13	1	2	1
15	9	10	10	12	13	10	9	9	5	14	6	14	10	10	20	17	11	9	10	9	14	14	17	13	13	10	8	13	2	2	1
16	9	11	9	11	12	9	7	7	5	12	6	13	10	10	17	20	10	8	10	9	13	12	14	13	13	9	10	11	2	2	1
17	7	10	8	14	11	5	8	8	3	13	5	12	9	14	11	10	17	13	6	5	11	10	12	14	9	8	11	14	1	2	1
18	8	9	6	13	8	5	7	8	3	10	6	11	7	13	9	8	13	15	6	4	9	8	10	13	10	7	10	13	1	2	1
19	6	6	5	7	7	5	5	6	4	8	4	10	6	7	10	10	6	6	12	9	9	10	11	8	7	7	8	9	2	2	1
20	5	5	4	5	7	4	5	6	4	7	2	10	6	5	9	9	5	4	9	11	9	10	10	7	7	5	7	6	2	2	1
21	7	9	8	9	12	7	11	11	5	12	5	17	10	10	14	13	11	9	9	9	19	14	17	15	13	7	11	11	2	2	1
22	7	9	8	10	11	7	10	11	5	12	5	14	9	9	14	12	10	8	10	10	14	17	15	12	10	8	9	11	2	2	1
23	8	9	9	11	14	7	11	12	5	13	6	17	10	12	17	14	12	10	11	10	17	15	21	15	12	10	10	13	2	2	1
24	6	10	8	13	13	6	9	10	3	11	6	15	8	14	13	13	14	13	8	7	15	12	15	20	14	7	12	14	1	2	1
25	6	10	6	10	9	9	7	8	3	10	6	14	7	11	13	13	9	10	7	7	13	10	12	14	17	5	9	11	2	1	0
26	7	8	6	9	7	5	6	5	4	9	5	8	8	8	10	9	8	7	7	5	7	8	10	7	5	12	7	8	2	2	1
27	6	10	5	9	10	6	8	9	3	9	5	11	7	11	8	10	11	10	8	7	11	9	10	12	9	7	16	9	2	2	1
28	7	11	8	15	10	5	7	8	3	14	5	13	8	13	13	11	14	13	9	6	11	11	13	14	11	8	9	18	1	2	1
29	2	2	1	1	1	2	1	1	2	2	2	2	2	1	2	2	1	1	2	2	2	2	2	1	2	2	2	1	2	1	0
30	2	2	2	2	2	1	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	1	2	1
31	1	1	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1

Fig. 10.1 Adjacency matrix of 31 different ehical issues using UCINet*. (Zorgatti et al., 2002)

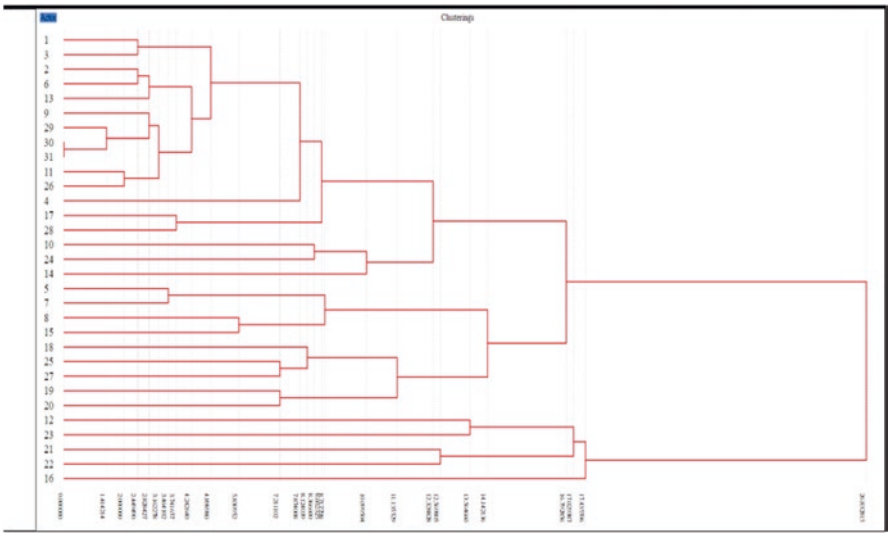

Fig. 10.2 One can observe from the figure 2 the complexity of the relationships established in the conjugation of the thirty-one topics, using UCInet software - their interactions are not linear or even sequentially organized. (Zorgatti et al., 2002)

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Chapter 11
Confidentiality and Privacy in Digital Clinical Trials

Marisa Aizenberg and Andrés Brandolini

Abstract In today's digitalized world, new technologies have been modifying not only the forms of patient care but also clinical research, where handling sensitive personal data is essential to verify the safety and efficacy of drugs or medical products under study and it constitutes a determining factor for research success. There are consolidated regulatory frameworks for the protection of personal data, being the reference those established by Europe and the United States of America, although the Latin American region has also made progress in this regard. New strategies then emerge for conducting clinical trials where digital technologies and safeguarding the privacy and confidentiality of the sensitive data of the participants of such tests are especially important: digital clinical trials, characterized by the use of such technologies in different stages of its realization and with numerous purposes. This modality offers numerous advantages both to researchers, sponsors, patients themselves and the rest of actors involved in studies. However, there are also multiple challenges that must be addressed from technical, legal and bioethical perspectives.

Keywords Digital clinical trials · Confidentiality · Privacy

Introducción

Thanks to the advancement of science, technology and research, great benefits have been reported to the human species, for example, by increasing life expectancy and improving the quality of health care of the population. The exponential and vertiginous characteristics of new technological and scientific developments have a direct impact on traditional schemes (social, economic, cultural and industrial),

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accelerating the invention of new products and services. Such disruption makes it necessary to rethink the way in which the human being interacts with the digital environment that surrounds it: increasingly the boundaries between the biological and the digital are blurred, bringing the human being to a new era of singularity (Kurzweil, 2005). This progress, focused on the interconnection of digital and physical domains gave rise to what we now know as the Internet of Things (IoT), an area in which we find a particular domain, where the coexistence and cooperation of systems integrated with our social life is revealing a new reality of exciting possibilities: digital health. Indeed, the health sector is one of the areas with greatest projections for the development of technological tools and devices to manage information that allow to offer faster, efficient and precise diagnoses, improving people's health outcomes and quality of life, controlling chronic diseases, speeding up research times for new diseases and developing new drugs. All this was dramatically accelerated with the COVID-19 pandemic's outbreak declared by the World Health Organization on March 12, 2020, which forced both governments and the global scientific community to redouble technical efforts to find urgent solutions to stop the virus from spreading, understand and investigate its nature and develop collaborative responses to find a vaccine. In these processes technology and innovation, together with data analysis and artificial intelligence (AI), occupied a central role.

In this context, digital health emerges as a strategy against a knowledge development area that is integrated into a hyperconnected world, through the use of monitoring devices, integration of patient portals and social networks, applications (hereinafter apps), specialized websites, digitized and interoperable health information systems, virtual reality and augmented reality, robotic surgery, AI, algorithms, genomics, 3D printing, biosensors, wearables, and nanotechnology, among others. Each of these digital tools allows connectivity and monitoring, with enormous potential to bridge gaps and inequalities due to geographical, economic or cultural barriers, and provides society with greater access to prevention, care, diagnosis and treatment, together with the timely prediction and monitoring of disease or pandemic outbreaks.

However, the use of new digital tools generates changes that cause unknown problems, which require new theories, principles and ethical norms for both professional exercise by health personnel, as for conducting research with humans. In particular, within the field of clinical research, it is evident the need to reflect on the implications for patient privacy generated by the growing dependence on new information and communication technologies (hereinafter ICTs), the use of internet, and new forms of digital registration. The digital age entails one of the greatest challenges in clinical research and professional practice of medicine and health sciences: the protection of confidentiality and the privacy sphere of the patient.

The use of new technologies, while promoting great benefits, in turn leads to increased vulnerability of people's privacy. Confidentiality concerns are even more sensitive in the digital age, so the issue of personal data protection requires special ethical considerations and precautions. Obliging us to reassess the existing norms and the management in practice in aspects of contract with clients, competence, confidentiality and control of professional practice (Winkler et al., 2018).

Clinical research should seek to promote the well-being of each individual, family, group or community and of the human species as a whole, in recognition of the human person's dignity and universal respect for and observance of human rights and fundamental freedoms. The right to privacy and the obligation of confidentiality are some of the main axes that make up the autonomy of patients and respect for human dignity. Thus, guaranteeing the privacy of the person participating in a clinical trial is an elementary principle, which should be protected throughout all stages of research. Because of its potential for discrimination, the dissemination of health data (sensitive data) in an inappropriate area can cause serious harm to the holder. In addition, this protection must be guaranteed on the basis of the following premise: the human being is constantly evolving and adapting, therefore, the approach to such norms (intimacy, confidentiality and privacy) cannot be carried out in a static manner, but it must go hand in hand with the advance of technology, with new notions of privacy, and it must be updated in the face of every challenge that digitization and new health technologies present.

International Protective Framework for Research with Human Subjects

Before going into the legal scope of the concepts of privacy and confidentiality, we will briefly review the historical-contextual framework from which the main international bioethical instruments were drafted, even applicable to clinical investigations. It should be borne in mind that, after the adverse events leading to human research during the Second World War and also in the post-war period, and with greater visibility during the 1970s, it was necessary and desirable for the international community to establish universal principles that would serve as the basis for a response by humanity to dilemmas and controversies that science and technology posed to the human species and the environment. That is why, throughout history, good clinical practices were defined that establish parameters for the design, conduct, registration and reporting of studies involving human participation. Their observance ensures that rights, welfare, security and dignity of the persons involved are protected and respected.

Nüremberg Code (1947)

Published on 20 August 1947, as a product of the Nuremberg Trials[1] that took place at the end of the Second World War, the Code contains a series of principles governing experimentation with human beings. This text has the merit of being the first

[1] The Nuremberg Trials were a series of judicial proceedings initiated by the victorious allied nations at the end of World War II, in which the responsibilities of leaders, officials and collaborators of Adolf Hitler's National Socialist regime in the various crimes and abuses against humanity committed until the regime's fall in May 1945, were determined and sanctioned.

document that explicitly raised the obligation to request informed consent (hereinafter IC) in experiments with human beings, the maximum expression of the patient's autonomy. In addition, its recommendations also include: the usefulness of the experiment for society as a whole, the need for prior animal testing (preclinical testing) and knowledge of the natural history of the disease, the avoidance of any unnecessary physical or mental suffering or harm (antecedent of the currently established principle of nonmaleficence), the availability of adequate facilities, the conduct of the experiment only by scientifically qualified persons, the possibility for subjects to abandon research at any stage or its conclusion by the responsible scientist.

Declaration of Helsinki (1964)

Adopted by the World Medical Assembly in 1964 and based on the Nuremberg Code, the Declaration of Helsinki (Asociación Médica Mundial. Declaración de Helsinki, 1964) further details the principles governing clinical research. In this sense, it determines as basic principles of investigations respect for the individual, his right to self-determination, respect for his privacy and the confidentiality of his personal information, and the right to make informed decisions both at the outset and during the course of the investigation. In addition, it adds the obligation to have research protocols describing the project and the method of research to be carried out; and provides that such protocols be sent, before starting the study, to a Research Ethics Committee for consideration, comment, advice and approval. In relation to the IQ of the patient participating in the trial, which was considered "absolutely essential" in the Nuremberg Code, it is recognized that when the participant is incompetent, physically or mentally incapable of consenting, or is a minor, IC should be given by surrogation and ensuring the best interest of the individual.

Belmont Report (1979)

Created by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, the *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, was, and is currently one of the most important documents in the field of medical ethics as it determines guidelines, and ethical principles for the protection of human subjects in experimentation. This is on the understanding that, while scientific research has resulted in substantial benefits, it has also raised disconcerting ethical issues. Thus, the *Belmont Report* introduces three "basic ethical principles" into the field of clinical ethics, as general criteria that serve as a basis to justify many of the ethical precepts and particular assessments of human actions. These three principles are: a) respect for persons: which is based on the conviction that all individuals should be treated as

autonomous agents and, on the other hand, that all persons whose autonomy is diminished have the right to be protected, b) beneficence: which requires the effort in ensuring well-being which, in turn, is expressed in two complementary rules: do not cause any damage (Hippocratic maxim *primum non nocere*), maximize the possible benefits and reduce the possible damages, and c) justice: in terms of selection of participants, equitable distribution of resources, burdens and benefits, and access to successful treatments, among others.

CIOMS Guidelines (1982)

The Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (hereinafter WHO), began its work on ethics in biomedical research in the late 1970s. Since then, in cooperation with WHO, it has prepared guidelines for human research (CIOMS, 1982). The aim of these guidelines is to provide internationally accepted ethical principles and detailed comments on how to apply universal ethical principles, with particular attention to research in resource-poor environments. The result of the collaboration between CIOMS and WHO was entitled "International Guidelines for Biomedical Research Involving Human Subjects" and is currently considered one of the most comprehensive, up-to-date and detailed documents for human research. The Guidelines consider it essential to maintain the confidentiality of personal data during and after the study, and also to publish data resulting from the research by respecting the interests of all affected (mainly taking into account the interest of the individual participating in the clinical trial).

Operational Guidelines for Ethics Committees That Review Biomedical Research (2000)

These WHO's guidelines (OMS, 2000) were developed to complement existing laws, rules and practices at the time, and to serve as a basis on which ethics committees (hereinafter EC) develop their own written procedures for their roles in biomedical research. Within the objectives of the EC, the Guidelines state that: (a) they must contribute to safeguarding the dignity, rights, security and well-being of all current and potential research participants; (b) they must provide an independent assessment, competent and timely ethics of the proposed studies, (c) they are responsible for carrying out the evaluation of the proposed research prior to its initiation, (d) they are responsible for acting in the full interest of potential research participants and communities involved.

Universal Declaration on Bioethics and Human Rights (2005)

The Universal Declaration on Bioethics and Human Rights (UNESCO, 2005) was the third normative text developed and adopted by UNESCO on bioethics and deals with ethical issues related to medicine, life sciences and related technologies applied to human beings, taking into account their social, ethical, legal and environmental dimensions. The Declaration establishes common guidelines for dealing with new situations of intervention on life following the progress of biomedical sciences and new technologies available within a framework of scientific integrity, placing dignity and respect for human rights at the forefront. Indeed, it proclaims that the interests and welfare of the individual should take precedence over the exclusive interest of science or society (Article 3).

Privacy and Confidentiality of Health Data in Clinical Investigations

The international documents listed form a guideline for developers and clinical researchers, and show that health depends not only on the progress of scientific and technological research, but also on psychosocial and cultural factors. That is why it is essential that scientific and technological conduct respect bioethical principles. Clinical trials are essential and necessary tools for evaluating the efficacy and safety of new medicines and medical products that are made available to the public for clinical use. These processes are largely based on the recruitment of target patients for the treatment under study and the subsequent collection, processing and analysis of personal data that support scientific results-statistics obtained from research. Clinical trials are an important part of the drug development life cycle and are based on accurate and sufficient data. Thus, the use of personal data is a determining factor in research.

However, because of their potential for discrimination, patient health data are considered sensitive in most regulatory regimes. The same approach is followed by good clinical practice, which defines confidentiality as a duty for every researcher. Hence, respect for the privacy and confidentiality of information should be a guiding principle throughout the clinical investigation, and even after its completion. The same applies to medical care, where the processing of personal data is protected by medical professional secrecy. Access to such information by unauthorised third parties may imply serious economic, social, psychological and health damage to the data subject.

At this moment it is appropriate to make a conceptual distinction between three principles that, in many occasions, are used as synonyms even if they are not, and that have great importance for the subject: intimacy, privacy and confidentiality. All of them form, to a greater or lesser extent, the rights and obligations that arise in the case of the clinical link (either by medical care or by clinical research).

First, intimacy can be understood as that personal, reserved sphere of the public universe, which corresponds to a deep layer of the person and which is absolutely necessary for human development. Privacy, on the other hand, emerges at a less profound level, which gives the subject the right to determine when, how and how much information is communicated to others about himself. In other words, the recognition of the right to privacy allows us to determine and control who has access to information, under what circumstances, and to what extent we want to share it or not. Finally, confidentiality would be:

> …the attitude requested of the subject who is aware of data or fact of the privacy of the person that implies the obligation of the professional to keep secret any information provided by the patient, not being able to reveal it to a third party without their specific permission (Winkler et al., 2018).

In the field of clinical investigations, the researcher is obliged to make a promise of confidentiality to whom he allows access to sensitive information. This is because the subject of the investigation trusts the researcher and presumes him capable of fulfilling his promise of confidentiality because he is responsible for any undue access not expressely authorized by the patient/data holder. Thus, respect for the confidentiality and privacy of information is internationally considered a good clinical practice, and finds its genesis in the bioethical principle of respect for persons, which is often interpreted as respecting the individual's autonomy. It is on the basis of this principle that the protection of confidentiality of research data is required, as well as it is also key in the selection of research subjects and in activities to be carried out for the clinical trial such as interviews or surveys.

In the current context, it is essential to review the issue of confidentiality as it shows a set of new challenges that health professionals and scientists must face.

> In particular, the advances in the media, the electronic clinical record, the possibilities of digital communication between professional and patient and between participant and researcher shape a professional and scientific context never known before, which needs the review of practices, norms and standards governing such relationships (Winkler et al., 2018).

Regulatory Frameworks for Personal Data Protection

European Union: The General Data Protection Regulation (GDPR)

In recognition and understanding of the need to protect people's privacy, there are numerous data protection laws. At the level of the European Union (hereinafter the EU) by Regulation (EU) 2016/679 of the European Parliament and of the Council a new framework known as The General Data Protection Regulation (GDPR) has been introduced (Reglamento (UE), 2016), which provides uniform interpretation and application of data protection standards across the EU. The Regulation is a fundamental change in data privacy management designed to protect and enhance

data privacy for all EU citizens and with implications for how EU organisations address data privacy (Angeletti et al., 2018).

The purpose of the GDPR is to protect personal data in general, that is, any information about an identified or identifiable natural person (the data subject); any person whose identity can be determined, directly or indirectly, in particular by means of an identifier, such as a name, an identification number, location data, an online identifier or one or more elements of that person's physical, physiological, genetic, psychological, economic, cultural or social identity (Article 4 GDPR).

Among the main requirements and guidelines defined in the GDRP regarding processing of personal data are the following: (a) explicit consent: clear and defined conditions are established for obtaining the consent of the data holder in order to move forward with their processing (Article 7 GDPR), (b) data protection officer: a person should be designated to be responsible for the maintenance and monitoring of internal personal data records, (c) sanctions: non-compliance with the provisions of the GDPR may result in serious sanctions for the offender, (d) territorial scope: the GDPR applies to all organisations that process data from holders of personal data residing in the EU (Article 3 GDPR), (e) right to access: the data subject (data subject) shall be entitled to obtain a confirmation from the controller, as to whether or not personal data concerning you are being processed and, where applicable, access to personal data and other information (Article 15 GDPR), (f) right to rectification: incorrect data must be rectified at data subject's request.

Also, and taking into account the purposes of the processing, the data subject shall have the right to complete incomplete personal data, including through an additional declaration (Article 16 GDPR), (g) right to be forgotten: data subjects have the right to request data processors to delete their data (Article 17 GDPR), (h) data portability: data subjects have the right to request their data in a portable format (in a structured, commonly used and machine-readable format), allowing the transfer of data to another data controller (Article 20 GDPR), (i) data protection by design and default: default privacy protection mechanisms must be developed and follow-up processes implemented (Article 25 GDPR), (j) notification requirements: data breaches should be notified without undue delay. If possible, no later than 72 hours after you have become aware of the event violating the security of personal data. If the notification does not take place within 72 hours, it shall be accompanied by indicating the reasons for the delay (Article 33 GDPR).

In the case of clinical trials, which fall into the category of treatment and handling of health data, the Regulation defines three main roles to be taken into consideration: the subject, that is, (i) the resident or individual who provides his or her personal data to the organisation for the clinical trial's purpose, (ii) the controller, that is, the researcher who determines the purpose and meaning of the processing (the clinical trial) of the personal data provided by the subjects, and, (iii) the data processor, who processes personal data on behalf of the controller (Angeletti et al., 2018).

USA: Health Insurance Portability and Accountability Act

For its part, USA does not have federal legislation that protects users' data and privacy comparable to the GDPR but there are sectoral regulations that rule different areas such as the Health Insurance Portability and Accountability Act (known as HIPAA). HIPAA has a "Privacy Policy" that states how protected health information should be shared and with whom it can be shared. The Privacy Policy also grants individuals some rights regarding their health information, such as the right to access or request corrections to their information. In particular, HIPAA stipulates that, with few exceptions, the information is available to doctors and they cannot disseminate data without the written permission of the patient. This regulation is mandatory for doctors, health centers and funders.

The standard protects the following personal information, since these data, associated with any information, allow the assignment and unique identification to a person: name, address, names of relatives, names of employers, mail, fax, telephone, date of birth, fingerprints, photos, social security number, IP address, vehicle or device identifier number, medical registration number, affiliate number, bank account number, website and any other feature that allows unique identification. In addition, within the functions of those responsible for personal databases, the standard provides for ensuring the confidentiality, integrity and availability of protected information entered or maintained in the system (Luna et al., 2018).

Compared to EU Regulation, HIPAA has a narrower scope of coverage and protection of the holder rights. For example, the HIPAA standard allows some degree of disclosure of medically protected information without the patient's consent. This is not the case under the GDPR: explicit consent of EU stakeholders must be obtained for any interaction of medically protected information (referred to as health data under Article 4 of the GDPR) that is outside the direct care of the patient. Another major difference between the GDPR and the HIPAA standard is the approach. The GDPR Regulation focuses on protecting the personal data of EU citizens. Therefore, any organization handling EU patient information may be subject to GDPR regulations. In contrast, HIPAA focuses on organizations (covered entities and business partners) that handle medically protected information within the United States.

Regulation in Latin America

In Latin America, data protection mechanisms are based on European legislation. Thus:

> A common concept in almost all countries in this area is that regulations are based on habeas data, which literally translates from Latin as "you have a right to your data": it is the principle by which every individual has the right to know what personal data are being stored by third parties, and to update, modify or even delete them (Luna et al., 2018).

Argentina is one of the countries that provides extensive protection of personal data, counting such constitutional root protection under the habeas data institute. Article 43 of the Constitution provides that:

> (...) Any person may bring such action to take cognizance of the data referred to him and of its purpose, recorded in public registers or data banks, or private ones intended to provide reports, and in case of falsehood or discrimination, to demand the deletion, rectification, confidentiality or updating of those. The secrecy of sources of journalistic information may not be affected (...).

In addition, like several countries in the region, Argentina has a specific law: Law 25.326 on Protection of Personal Data (LPDP), which in its second article defines sensitive data as those personal data that reveal racial and ethnic origin, political opinions, religious, philosophical or moral convictions, trade union membership and information concerning health or sex life.

With regard to the handling of this category of personal data, their processing is permitted in certain cases authorized by law, with such authorization being given to public or private health establishments and professionals linked to health sciences, who may collect and process personal data relating to the physical or mental health of patients who come to them or who are or have been under their treatment, respecting the principles of professional secrecy (Article 8 LPDP).

In Argentina, both medical professional secrecy, regulated in specific rules and Law 17.132 with the Rules for the Exercise of Medicine, Dentistry and collaborative activities thereof, As the duty of confidentiality required by both the regulations for the protection of personal data, as well as that governing the rights and data of the patient, Law 26.529 of Rights of the Patient, derive from respect for the privacy and dignity of the data subject (Moreno, 2017).

Finally, and following Europe's protection scheme, in Latin America the following countries have data protection laws and account for the space occupied by the issue of data within the legislative agendas at regional level: Peru (Law 29.733 of Protection of Personal Data), Colombia (Statutory Law 1581 of Protection of Personal Data), Brazil (Law 13.709 General of Protection of Personal Data), Uruguay (Law 18.331 of Protection of Personal Data and Action of Habeas Data), Mexico (Federal Law on the Protection of Personal Data in Possession of Individuals), Costa Rica (Law 8968 on the Protection of the Individual from the Processing of Personal Data, Chile (Law 19.628 on the Protection of Private Life or Protection of Personal Data) and Panama (Law 81 on Protection of Personal Data).

Where We Are Going: Digital Clinical Trials

Clinical trials are a fundamental and necessary tool for evaluating the attributes of new medicines and medical devices and other health system interventions. In effect, prospective, randomized, placebo-controlled clinical trials are often the most

powerful tool we have to answer fundamental questions about the safety and efficacy of new medical products (Gottlieb, 2018).

However, traditional clinical trials pose challenges that can hinder the efficient conduct of research to develop a knowledge base that supports products for patient communities. Some of the current operational inefficiencies relate to the identification, recruitment, data acquisition and monitoring of participants, all of which increases costs, increases the burden on participants, extends already extended testing deadlines and contributes to low participation in clinical trials (Inan et al., 2020). In short: clinical trials require major changes in their processes to evolve to a point where they embrace the digitized era.

Thus the concept of digital clinical trial arises (Angeletti et al., 2018; Steven et al., 2019; Brezing et al., 2020; Nissen, 2019), also referred in the literature as digital trials (Deloitte, 2019), enabled clinical trials (Marquis-Grave, 2019), e-technology clinical trials (Rosa et al., 2015), intelligent clinical trials (Deloitte 2020), virtual clinical trials (Alemaheyu et al., 2021) among other names. It has been said that a digital trial is a trial that uses technology to improve patient recruitment and retention, information collection, and data analysis (Inan et al., 2020).

Thus, within such a conception of digital clinical trials are recognized fundamentally 3 elements that align to the axes listed above: (a) recruitment and digital retention, through the use of social media, onl-line consent, bidirectional communication and recruitment diversification, (b) collection of digital health data, with patient-informed outcomes, use of digital biomarkers, wearables and mobile sensing technologies and privacy management and (c) Digital analytics of real world data, interoperability, artificial intelligence and machine learning (Inan et al., 2020).

A similar approach (Sanofi, 2020) proposes to address the issue from three different moments of the trial: (a) planning phase, with the possibility of designing protocols based on real data, from electronic health records, inclusion of synthetic control groups (Thorlund et al., 2020) (or even in silico trials), selection of healthcare and research centres, (b) implementation phase, using social networks for a multi-channel recruitment, entirely virtual or hybrid modality, with the creation of virtual access environments from the research center to the patient, use of wearables with data collection and real-time decision-making, patient-centered approach (or e-patient centricity), using e-consent and e-labelling, optimization of risk monitoring and analysis (risk based monitoring) with automatic and continuous monitoring, data collection and remote testing, (c) analysis phase, using artificial intelligence and data analytics techniques and automated report writing and review.[2]

[2] The same authors highlight the following trends in the digital transformation of health: personalized medicine (or precision medicine) based on the genomic profile of each patient, being big data a fundamental tool, the use of virtual reality, the availability of medical devices (wearables) to obtain health data in real time, health predictions made from data analysis, artificial intelligence as an analysis and prediction tool, blockchain technology and improvement in electronic health records. We could add other tools, such as telediagnosis, telemonitoring, telemedicine and teletraining, among others.

The use of digital technologies in clinical trials in addition to providing advantages in terms of recruitment (Frampton et al., 2020), commitment and retention of participants and data collection, enable the use of electronic platforms for managing patient records, electronic health records (e.g., electronic medical records), health apps and easier communication of results, as well as improving the efficiency of the study and reducing costs, boosting research and development and greater involvement of stakeholders (Marquis-Grave, 2019). It has also been highlighted the novel design of protocols, the use of genomic information, e-consent (Skelton et al., 2020; Iwaya et al., 2019; Wilbanks, 2018), diversity of information sources (e-sources) and device connectivity, therapeutic adherence (Deloitte, 2019) and the possibility of using digital endpoints (Clay, 2017; Kruizinga et al., 2020).

On the other hand, the potential violation of the privacy and confidentiality of participants, the need for permanent updating of the technology used, the possibility of including a non-representative sample have been identified as disadvantages (due to the digital divide still prevailing in society), as well as infrastructure and big data management (Marquis-Grave, 2019).

A fully digital test would also allow access to potential participants regardless of where they live or work, which for researchers means more efficient and real-time remote monitoring. The opportunity to optimize the costs and efforts of clinical trials through the use of digital technologies advances towards a patient-centered trial experience, and designed to accelerate the pace at which we generate evidence (Inan et al., 2020).

The Paradigm Shift and the Tendency to Generate Digital Data: Challenges for Privacy and Confidentiality

In the new era, we constantly leave our digital trail using modern ICTs applications. In fact:

> Every time you click and enter different sites, you audit the time that is there, how long it takes to close advertising, if you access it, among many other behaviors. These digital traces (data) are what are building a kind of artificial identity in constant transformation. The digital self is shaped by intelligent algorithms that constantly store and process such data and, on that basis, make predictions sold to the highest bidder (Corvalán, 2020).

These traces are collected, assembled and used in countless ways that often mean serious implications for people's privacy and intimacy. As we have been developing, information related to people's health is categorized as sensitive, and has special protection globally. Likewise, confidentiality is recognized as one of the main duties to which investigators are ethically bound. Thus, digital data collection, and the formation of digital identities makes it necessary to create and use security protocols that establish mechanisms of action against the potential risks of system violations that protect participants against data violations during the compilation, data transmission and/or storage. While the use of new technologies in medical research

can mean great advances and efficiencies, it can also entail great risks for intimacy and privacy of participating patients. The violation of confidential databases remains a risk, although the use of distributed ledgers, such as blockchain or decentralized databases, could mitigate risk (Inan et al., 2020).

In a simplified representation model of the data collection process (Angeletti et al., 2018) three main domains were identified within patient recruitment, accounting for the times when special computer security measures are required: private space, trust space and public space. The authors explain that, during all phases of the clinical trial, data generated by IoT devices in the private space are transmitted through a secure communication channel to the trusted space. Here, it can be enriched with other relevant data, possibly residing in the public space, such as gender, sex and age. For his part, the researcher is operating within the reliable space and analyzes the data as an integral part of the research, evidencing that the user has a very limited control over the use of his personal data as soon as he leaves his private space. Therefore, it is essential that the trust space complies with all relevant regulations for data protection taking into account the applicable regime; and it is in this instance that the greatest cybersecurity measures should be adopted. For this reason, the data controller and the data processor usually take care to anonymize or pseudo-anonymize the data residing within the trusted space. The current dominant approach to handling health data in clinical trials requires users to rely on a third party, the researcher, who handles their data for trial purposes. It is therefore very important that this area of trust is respected, in order to move towards a research focused on the patient, the owner of the data under treatment and analysis. On the other hand, many important challenges have been identified by adding the use of artificial intelligence in this context (Hlávka, 2020).

Other Issues to Consider in Relation to Personal Data Protection

Some questions relating to the privacy and confidentiality of data processed in the context of a digital clinical trial warrant additional considerations. Without intending to be exhaustive, we can highlight the following:

Need for Specific Regulations

In addition to HIPAA, the United States of America also has the Health Information Technology for Economic and Clinical Health Act (HITECH Act) aimed at promoting the adoption of information technologies in the health field. The country's regulatory agency has also issued related regulations providing guidelines for electronic registries and signatures (FDA, 2003), computerized systems in clinical trials (FDA,

2007), the use of electronic source information in clinical trials (FDA, 2013), regulating interactive promotional materials (FDA, 2014), electronic health records (FDA, 2018) and mobile medical applications (health apps) (FDA, 2019), among others. The European Medicines Agency has also issued regulations on electronic origin information in clinical trials (EMA, 2010), the direct capture of electronic origin information (EMA, 2019) validation and qualification of the computer systems used, documentation of qualification activities and contracts with suppliers (EMA, 2020), among others. Already in 2018 the European Commission communicated its strategy for the digital transformation of health based on three pillars: Access and exchange safe data, connect and share health data for research, Faster diagnostics, improved health, and strengthened citizen empowerment and individual care through digital services (European Commission, 2018).

Novel Bioethical Aspects

Faced with new digital tools available and challenges that arise in digital clinical trials' scenarios, new questions (or novel aspects of already known dilemma situations) that Research Ethics Committees must deal with also appear. Among the most critical issues are those related to privacy, confidentiality and security of health data in digital research. In fact:

> Standard protection mechanisms such as anonymization, notification and consent are limited in this new capability environment. Consent to the use of data can hardly include an exhaustive list of all possible future uses of the information. In turn, anonymization technologies, even if robust, still allow for re-identification if sufficient resources are devoted to that task. Data security also represents a challenge due to cyber attacks, database hacking and data hijacking (Vayena et al., 2018).

That is why in the assessment of compliance with bioethical principles that guide clinical research the type of data involved should be considered, as well as its collection, transmission, form and place of storage, conservation deadlines, privacy, security measures, access, opportunity for disclosure, and authentication for access, among other issues (Eagleson et al., 2017).

Like a traditional clinical trial, digital clinical research must have social value and demonstrate its scientific validity, in this case, contrasting the methodological aspects with current standards and good practices of digital technologies. Consideration should also be given to the possible occurrence of inequitable selection or distribution of participants in the face of possible biases presented by algorithms used, and vulnerabilities in terms of digital capabilities. Digitality should also be taken into account in assessing risk minimization and maximizing potential benefits for participants. As for the independent evaluation to be carried out by the Research Ethics Committee, the suitability of the members in matters of digital health should be verified and, if necessary, the inclusion of new professionals linked to computer sciences and data sciences. Respect for participants should also be evaluated from a digital perspective in the event of changes of opinion, revocation

of informed consent, access to new findings or information during the development of the study, information on the results obtained and study's benefits. In addition, provision should be made to compensate damages suffered by participants for security incidents in the processing of information.

Another fundamental ethical aspect is digital or electronic informed consent.

Digital Informed Consents

Digital, electronic, and computer informed consents or e-consents represent another challenge for digital clinical trials, in bioethical, technical and regulatory fields. Wrong consents may even impact the validity of the entire study and many of the breaches found by health authorities lie in them (Cambridge Consultants, 2018). They contain interactive components intended to confirm the understanding of the purpose and characteristics of the clinical trial and include novel strategies such as video consents or consents through smart phones, tablets or personal computers (Marquis-Grave, 2019). Other modalities that have been foreseen consist of broad consents, opt-out type, dynamic, one click-accept all (UNESCO, 2017), among others. There are also many companies that offer specific services and platforms to implement e-consents tailored to the clinical trial being planned.

In addition to the information usually contained in these documents in their traditional form, an electronic consent must include details as to specific aspects of the digital mode of clinical research and additional steps must be taken as to the identity of the signatory, his age and ability to understand. Regulatory guidelines (FDA, 2016) and numerous important recommendations for implementing this consent modality can be found (Frampton et al., 2020).

Using Artificial Intelligence

It has been pointed out that some elements necessary for successful digital clinical trials are the connectivity of devices and the low costs of IoT, blockchain, sensory technologies, data analytics and, fundamentally, artificial intelligence. The use of the latter could even lead to clinical trials without research centers, guiding recruitment and participation of patients in remote trials with less clinical intervention (Cambridge Consultants, 2018).

Among the many applications of AI in digital clinical trials are those related to advanced data analytics and process automation, such as: (a) in the design of the trial evaluating the feasibility of protocol design and patient recruitment through real-world data, by evaluating the performance of the research center (enrollment and dropout rates) with real-time monitoring, analysing and interpreting information, structured or not, from previous trials and scientific literature, (b) at the beginning of the trial, mining electronic health records and publicly available content,

including clinical and social media trial databases, to find potential participants using natural language processing and machine learning or generating draft contracts, agreements, reports or other documents using intelligent automation, (c) in the conduct of the test, evaluating the site's performance (measuring enrollment and dropout rates) with real-time monitoring, analyzing digital biomarkers and automating information management and (d) at the end of the trial, intervening in the writing of the final report. In addition, AI can also empower mobile applications, wearables, biosensors and other connected devices by improving, early in the study, recruitment and simplifying and accelerating the informed consent process through e-consent and, during the development of the same, favoring adherence through alerts and reminders in smart phones and performing e-tracking of medication's taking, and visits to the research center (Deloitte, 2020).

Finally, it should be mentioned that important recommendations and suggestions of strategies have been made to take advantage of and enhance digital technologies, including artificial intelligence, in clinical trials and, at the same time, facilitate patient participation (NIH, 2019).

Final Remarks

In an increasingly data-driven world, where information exchange, machine learning, social networks, the internet of things, the use of wearables, artificial intelligence, interoperability and connectivity of devices and sensors, robotization, among others, will be key technologies for human-centred mobile e-health, a new modality for clinical research is particularly relevant: digital clinical trials.

Experimentation with humans, under the strict and widespread procidemental and bioethical requirements, is essential for the discovery of new and better diagnostic, therapeutic and preventive alternatives. Although, as initially mentioned and demonstrated later, new technologies are drastically changing the way research is conducted, it is essential to pay attention to bioethical principles and legal guarantees regarding the use of sensitive data, such as health data.

The emergence of multiple challenges makes it necessary to review current regulatory devices, forcing us to think about modifying or incorporating procedures that protect and secure patient data against the greatest vulnerabilities that, as a counterface, digital world brings up. Indeed, digital transformation in health will require comprehensive assessment of current clinical research and personal data management regulations to ensure that relevant trial stakeholders work together to support the uptake of digital technologies by respecting privacy and intimacy rights of participants and, in short, their dignity as human beings.

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Chapter 12
Dematerialization and Intellectual Property in the Biosciences

David J. Jefferson

Abstract Over the past 40 years, modern biosciences coevolved with the expansion of intellectual property, as new laws have enabled life forms that are the products of bioscience research to be claimed as proprietary objects. Numerous bioethical issues have already been raised in relation to claiming biological and genetic materials as intellectual property, including concerns over moral and distributive justice, misappropriation, and access to public good technologies. While many of these issues remain critically important, a new set of problems has emerged following a shift towards "dematerialization" in different areas of research, where genetic information may be able to effectively replace the use of physical biological materials as experimental inputs. This chapter explores the implications for legal and scientific practice that arise out of the increasing reliance upon data rather than tangible biological materials. The chapter argues that while there are steps that researchers can take to respond ethically to dematerialization, individual scientists should not be expected to develop their own bioethical protocols without the support of legal and institutional systems.

Keywords Intellectual property · Biotechnology · Genetic engineering · Digital sequence information · Dematerialization

Introduction

The modern biosciences have coevolved with the expansion of intellectual property. Beginning in the 1980s, changes to laws worldwide enabled life forms to be claimed as proprietary objects, affecting the development of scientific fields ranging from molecular biology and chemistry through to medicine and the plant sciences. Since that time, bioethicists, joined by scholars in science and technology studies, law,

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and the social sciences and humanities, have directed attention to a variety of concerns over how intellectual property laws and related legal regimes might affect the practice of science and the social contexts in which research occurs.

Interdisciplinary scholarship and civil society activism have analyzed and critiqued a range of bioethical issues in this space, including moral and distributive justice questions arising out of claiming organisms as intellectual property (Bagley, 2003; Drahos, 1999; Rimmer, 2008)), and the potential for biological and genetic materials and associated Indigenous and local peoples' knowledge to be misappropriated by scientific and commercial actors (termed "biopiracy" by critics) (Robinson, 2010; Shiva, 2016). Likewise, controversy has erupted over the possibility that access to public good technologies such as pharmaceuticals and the seeds of food crops might be impeded due to the expansion of proprietary rights (Brewster et al., 2007; Heller & Eisenberg, 1998). Other critiques have examined how intellectual property claims can restrict access to technologies that are instrumental to the realization of research in the biosciences, (Graff et al., 2003) and how the increased focus on the commercialization of research outcomes may distort the incentive structure within universities and public institutions (Stiglitz, 2008).

While many of these issues remain critically important today, a new set of problems has emerged with recent developments in the biosciences. This is driven by a shift towards "dematerialization" in numerous areas of research, such that in at least some instances, genetic information can now effectively replace the use of physical biological materials as experimental inputs. For instance, in one high-profile case scientists in Canada were able to chemically synthesize horsepox virus (HPXV) using only digitized genetic sequence information (Rourke et al., 2020). In addition to its significance as a scientific breakthrough, the synthesis of HPXV appears to be the first time that a whole microorganism was engineered specifically to avoid potential regulatory constraints (Stiglitz, 2008). In this example, HPXV researchers may have decided that the US$100,000 expense of synthesizing the virus was more cost effective than incurring obligations to share potential downstream benefits with the providers of physical virus samples (Stiglitz, 2008: 538).

The HPXV case is but one manifestation of how electronically stored and transmitted data are increasingly replacing tangible materials in the biosciences. In recent years, the use of "digital sequence information" (DSI) as a powerful research tool in fields such as molecular biology and genomics has coincided with the development of a series of new techniques including gene editing, synthetic biology, bio-nanotechnology, and bioinformatics (Seitz, 2020). These advancements collectively aim to find novel solutions to a number of critical global issues, ranging from human health crises through to food security and climate change mitigation. By combining approaches from classical biology, chemistry, computer sciences, and engineering with the power of informational resources, new and emerging techniques are creating novel challenges for the application of intellectual property laws to the inputs and products of scientific research (Ribeiro & Shapira, 2020).

However, aspirations to expand the use of DSI in the biosciences are currently tempered by a number of theoretical and practical issues. This chapter focuses on a particular set of enquiries, investigating how legal regimes that recognize

intellectual property and other forms of control over research inputs and products should be understood in the context of dematerialization, and how the application of these laws might affect the activities of researchers in bioscience fields.

While the chapter will attempt to distil clear lessons for policymakers and scientists alike, it is notable that at present, the meaning and scope of the DSI concept is poorly understood and inconsistently applied. For instance, if conceived narrowly DSI may refer exclusively to genetic sequence data, while broader definitions could include other related information such as annotations and interpretations of data, or even all immaterial, electronically saved information about biological materials that contain functional units of heredity (Ribeiro & Shapira, 2020: 2) Furthermore, there is uncertainty about whether the DSI concept should encompasses only DNA or RNA sequences, or whether it should also capture other genetic information such as protein sequences (Merz & Cho, 2005).

As debates over these ambiguities continue to gain traction, it is certain that questions about the use of DSI will remain at the heart of deliberations over the appropriate balance between access and exclusion in bioscience research for years to come. This chapter recounts how these debates are evolving, examining new and emerging intellectual property issues that may arise when genetic information effectively replaces genetic materials. Part I of the chapter reviews bioethical concerns that were historically expressed in relation to the use of different forms of intellectual property to claim rights in bioscience inventions, and then describes how dematerialization might affect such claims. Part II explores the implications of the increasing reliance upon data rather than tangible resources on legal frameworks that are alternately viewed as complementary to or in competition with intellectual property regimes, that is, laws that delimit how biological and genetic materials may be accessed and utilized. Part III discusses how researchers and institutions can best respond to the interaction between scientific and legal developments in the biosciences, with the aim to enable bioethical decision making.

Bioethical Concerns Arising Out of Intellectual Property for Genetic Inventions

Various intellectual property laws may apply to different activities along the research and development value chain in the biosciences. Common forms of intellectual property that allow inventors and creators to claim rights related to their works are defined in legal frameworks governing patents, copyright, plant breeders' rights, and trade secrets and confidential information, with patents being the most relevant for bioscience research. For decades, ethical concerns have been expressed about the potential impropriety of using intellectual property laws to secure private rights to inventions developed with the support of public funding and through the use of widely available biological materials, such as plants and microorganisms.

A particularly intense debate that was sustained throughout the 1990s and early 2000s centered on "gene patents," referring to patents whose claims cover one or more specific genetic sequences and/or the use of these sequences to conduct certain activities. Different categories of inventions have used gene patents as a mechanism to establish proprietary boundaries. These include diagnostics, where inventors claim rights to the characterization of an individual's genetic makeup as a means to diagnose disease; "compositions of matter," covering isolated and purified genetic materials and derivative products; and "functional use" patents that assert exclusivity based on the discovery of the role that specific genes play in disease or other bodily and cellular functions or pathways (Merz & Cho, 2005). Gene patents were also obtained in bioscience fields outside of the realm of human health. For example, in countries such as the United States, applicants filed claims to protect particular "trait genes" that were linked to agronomically valuable characteristics in crop plants (Graff et al., 2003).

Although the legal systems of some countries had established that inventions involving isolated DNA and RNA molecules were patentable as early as 1980 (Diamond & Chakrabarty, 1980) controversies over the morality of gene patenting erupted in the following decades. In medical fields, concerns emerged largely due to the impediments that diagnostic gene patents could create, where costs of genetic services could rise, the quality of genetic tests and treatments could diminish, and access to health care could be impeded (Andrews & Paradise, 2005). Other issues that were implicated when researchers claimed ownership of genetic sequences derived from human biological materials included the violation of individual rights where patients did not provide adequate informed consent for the collection and use of their materials, and the curtailment of reproductive liberty where patents effectively proscribed prenatal testing for genetic diseases (Andrews & Paradise, 2005: 409–411).

Similar ethical debates arose around the same time in relation to the use of patents to monopolize inventions containing plant and animal genetic materials. The development and commercialization of genetically modified crops in particular provoked polemical responses, with concerns that patents or other forms of intellectual property could jeopardize farmers' food security and food sovereignty by inhibiting customary agricultural practices such as seed saving and exchange (Michael & Busch, 2006). In the early 2000s, high-profile lawsuits in which agricultural corporations brought legal actions against farmers for intellectual property infringement (See, Bowman & Monsanto, 2013) incited civil society protests. Meanwhile, the patenting of higher life forms such as genetically altered mice spurred ethical concerns about the treatment of animals in scientific research, and about the harms that transgenic organisms could cause to ecosystems if they escape from laboratory environments (Morin, 1997).

Over the past ten years, several of these concerns have been at least partially tempered by scientific, economic, and legal changes. Much attention has focused on judicial decisions in countries like the United States and Australia, which have resulted in the curtailment of gene patents in these jurisdictions (Sherman, 2015). The most prominent example of this trend is found in the 2013 United States

Supreme Court verdict in the *Association for Molecular Pathology v. Myriad Genetics* case, in which a majority of the justices held that a naturally occurring DNA segment is a "product of nature" and not patent eligible merely because it has been isolated (Association for Molecular Pathology v. Myriad Genetics, Inc. 2013). An analogous outcome resulted when Myriad's sequence claims were challenged in Australia, with the High Court determining that isolated genetic sequences do not constitute a "manner of manufacture" and therefore are not patentable (D'Arcy v. Myriad Genetics Inc., 2015:35).

Although the justices in the American *Myriad* case upheld the patent eligibility of complimentary DNA (cDNA), reasoning that cDNA is a synthetic creation not normally present in nature, (Association for Molecular Pathology v. Myriad Genetics, Inc. 2013:2) by the time the decision was issued the gene patenting trend had already tapered in the United States. This change was likely driven by a variety of factors, including the introduction of new patent examination requirements in 2001 that required heightened scrutiny of the utility of claimed inventions (Graff et al., 2003). Other possible explanations for the end of the "homesteading phase" of American genetics patenting might include the diminishment of venture capital funding due to the crash of the dot-com bubble in the late 1990s, while the volume of genetic sequences that were published in scientific and patent literatures and posted to public databases during this period undermined the ability of future inventors to claim novelty for sequences that they might isolate (Graff et al., 2003:408).

In contrast to the situation in the United States and Australia, today isolated genetic sequences remain technically eligible for intellectual property protection in many jurisdictions. However, the number of gene patents that are actually granted has been moderated by the application of legal standards beyond the eligibility criterion. For example, in the European Union the 1998 Biotechnology Directive stipulates that inventions which meet the requirements of novelty, inventive step, and industrial application are patentable even if they contain biological material or a process by which biological material is produced, processed, or used (Directive 98/44/EC of the European Parliament and of the Council, 1998). Therefore, when patents similar to those at issue in the *Myriad* litigation in the United States and Australia were challenged in Europe, the scope of the rights granted was reduced not due to a determination that isolated DNA was ineligible for protection, but rather because the invention lacked novelty (Nicol et al., 2019). Similarly, although the legal framework for patents in China conceives of isolated genetic sequences as essentially chemical substances that may be claimed, the law excludes all methods for the diagnosis or treatment of diseases from patentability (Nicol et al., 2019). The application of this provision to the invention at issue in the *Myriad* litigation would have excluded it from protection, even in the absence of a blanket prohibition on gene patenting.

Due to the international fragmentation of the scope of patent protection for inventions based on biological and genetic materials, substantial uncertainty exists about whether dematerialized genetic information can be effectively claimed as intellectual property from one jurisdiction to the next. As described above, in countries such as the United States and Australia, judicial decisions in the past decade

established that the act of isolating genetic sequences should be legally understood as a discovery than an invention. Concurrently, strong advocacy for open-source governance models has emerged within bioscience networks, putting pressure on researchers to avoid making proprietary claims to their inventions. Open-source frameworks emphasize the importance of the broad disclosure, unrestricted sharing, and the free accessibility of DSI and derivative physical materials created through the use of research tools such as those which the field of synthetic biology has made available (Bagley, 2017a, b). Coupled with the rapid expansion of publicly available DSI housed in databases such as GenBank, (National Center for Biotechnology Information, 2021) the DNA Databank of Japan (DNA Databank of Japan, 2021), and the European Molecular Biology Laboratory (European Molecular Biology Laboratory, 2021) – which collectively contain over 1.5 billion sequences (Wildsi, 2020) – it is likely that concerns over the patenting of genetic sequence data will become less acute in the years to come.

Nevertheless, many questions remain unanswered about how other categories of intellectual property laws might be used to claim rights related to DSI. For instance, some scholars and researchers have advocated for the application of copyright law as a means alternative to patents to protect genetic sequences. Possible reasons to favor copyright as a form of intellectual property for DSI include the potential to invoke the "fair use" defense, which would allow for reasonable uses of claimed sequences, such as for experimentation and instruction, to proceed without authorization from the right holder (Bagley, 2017a, b). Further advantages of copyright regimes over patent systems include the limitations placed on damages for innocent infringement, while independent creation would constitute a defense to copyright infringement (Wildsi, 2020). Synthetic DNA sequences could also be analogized to computer software, in that they may meet the copyright requirements of originality and fixation, which might be more appropriate criteria than novelty and inventiveness for the evaluation of intellectual property applications (Wildsi, 2020).

However, there are significant obstacles that currently impede the use of copyright to establish ownership over genetic sequences. Some national intellectual property agencies, including in the United States, have indicated that DNA sequences do not constitute copyrightable subject matter (Holman et al., 2016). Even if such regulatory prohibitions were relaxed, important conceptual questions about the appropriateness of copyright as a vehicle for claiming rights to DSI would still need to be resolved. Significantly, genetic sequences may be better understood as representations of natural functionality than as expressions of an author's creative originality, meaning that it is difficult to apply copyright law to DSI (Seitz, 2020). These issues are further complicated by the fact that references to genomic data are entirely absent from contemporary statutory, administrative, and judicial documents that have interpreted the parameters of copyright (Seitz, 2020).

Given the challenges implicated in the application of conventional patent and copyright regimes to DSI, the form of intellectual property that currently may be best suited to encompass genomic data is subsumed under laws that protect trade secrets or confidential information. However, the principal requirement to maintain exclusive rights under such legal frameworks is the need to put in place

precautionary measures to ensure that the information claimed as proprietary is kept secret. This criterion may be extremely difficult for researchers in the biosciences to meet, given the vast amount of genetic data that has already been made publicly available in electronic databases, and the pressures that scientists may experience from their institutions, colleagues, funding agencies, and academic journals to adhere to open access standards.

Assuming that conventional intellectual property laws do not offer an appropriate means of protection for DSI, some researchers and scholars have advocated for the creation of a *sui generis* regime that would be specifically tailored to recognize exclusive rights to digitized data (Reichman & Samuelson, 1997). However, to date no government has advanced any concrete proposal to establish a specialized form of intellectual property for DSI. Due in part to the uncertainties surrounding the ability of researchers and others to make proprietary claims to genetic information, in recent years bioethical debates have shifted away from the moral implications of privatizing naturally occurring genetic material, and towards issues of equity and distributive justice that arise out of the access and use of genetic information. The following section deals with these questions.

Effects of Dematerialization on Access and Benefit Sharing for Genetic Resources

Unlike intellectual property laws, whose justifications are primarily grounded in Western moral philosophy and economics, (Drahos, 1996) legal frameworks governing the access and utilization of genetic materials were designed specifically to address global bioethical concerns. In particular, the access and benefit sharing laws that were first established in the 1990s endeavored to redress injustices caused by the misappropriation of the components of biodiversity and associated traditional knowledge worldwide. This intention was made clear during the negotiations towards the foundational international agreement in this area, the *Convention on Biological Diversity* (CBD, 1993), which were animated by the recognition that the unconstrained international circulation of biological and genetic materials was producing social, economic, and environmental harms.

Specifically, the "common heritage" approach to the governance of biodiversity, which represented the legal status quo until the adoption of the CBD, allowed anyone to freely access biological and genetic materials from any country for both commercial and non-commercial purposes, without the obligation to share any of the benefits obtained through the use of these materials with local providers (Baslar, 1996). The imbalances created by this situation were exacerbated by the expansion of intellectual property regimes throughout the 1980s, as discussed in Part I of the chapter, which enabled proprietary rights to be claimed for inventions containing or derived from organisms and their constituent parts. These legal changes meant that materials which were previously conceived as mere "natural resources" (Morgera

et al., 2014) were now being developed into innovative products that commanded significant market value.

The entry into force of the CBD effectively marked the end of the common heritage approach to the governance of the vast majority of Earth's biodiversity, as the agreement converted non-human organisms from public resources into the sovereign property of nation-states (Sand, 2004). The CBD also introduced access and benefit sharing as a mechanism that would allow prospective users of genetic materials to negotiate permission to obtain these objects from local providers, and to ensure that a portion of any benefits derived from the utilization of the materials flows back to the providers (Convention on Biological Diversity, 1993). The access and benefit sharing model aimed to simultaneously protect local ecosystems and communities from undue exploitation by outsiders, promote innovation and the transfer of technologies created through the use of genetic resources, and generate revenues that could be channeled into conservation initiatives (Laird et al., 2020).

Although evidence suggests that the aims of access and benefit sharing systems have not been fully realized,[1] over the past thirty years this model has been reproduced in a series of international legal frameworks that extend beyond the CBD. The most prominent example of this is found in the 2014 *Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization*, which is a supplementary agreement to the CBD that established minimum standards to which all access and benefit sharing agreements should adhere, while also enlarging the scope of access and benefit sharing to encompass traditional knowledge related to genetic materials obtained from local areas. Similarly, the 2004 *International Treaty on Plant Genetic Resources for Food and Agriculture*, the 2011 *Pandemic Influenza Preparedness Framework*, and the draft United Nations *Convention on the Law of the Sea* all adapted elements of the access and benefit model for specific classes of genetic materials, including crop plants, viruses, and marine biodiversity, respectively.

Despite the popularity of access and benefit sharing as a policy mechanism to achieve social and environmental justice, this model tends to presume the existence of certain tangible relations that may no longer be relevant in fields where DSI is effectively able to replace physical objects. While the CBD and subsequent access and benefit sharing laws are structured around bilateral negotiations and agreements between providers and users to enable the movement of genetic materials from one location to another, this process is disrupted where sequence information and other data may be freely and instantaneously transmitted between parties and utilized in a manner equivalent to the original sources from which they were extracted. The issue is clearly illustrated by the fact that the definitions of "genetic resources" provided in legal frameworks such as the CBD and the Nagoya Protocol focus on "materials"

[1] This is particularly the case for the conservation objective of the CBD, with evidence suggesting that to date, the access and benefit transactions that have taken place under the terms of the treaty have not generated substantial benefits for biodiversity conservation (Laird et al., 2020:1200).

rather than "information",[2] leading to questions about whether the scope of contemporary access and benefit sharing laws extends to the governance of DSI.

Doubts about whether access and benefit sharing obligations apply to DSI have reignited longstanding debates between the providers and users of genetic materials. From the perspective of providers, if DSI is not included within the scope of access and benefit sharing laws, this means that a "digital loophole" would allow users to avoid obligations such as the need to obtain prior informed consent and distribute monetary and non-monetary benefits to providers (Rourke, 2021).

In addition to allegations that "digital biopiracy" (Hammond, 2015) is occurring, proponents of the inclusion of genetic information within existing access and benefit sharing regimes highlight the possibility that technologies developed through the application of genomics and synthetic biology could further exacerbate divides between rich and poor, given the high costs associated with creating institutions that are capable of exploiting dematerialized data (Marden, 2018). In contrast to this perspective, users of genetic information complain that conceiving of DSI as the sovereign property of individual countries would jeopardize the open access principles of modern science and impede research into areas of global concern (Rourke, 2021). The discrepancy between the various contemporary conceptualizations of DSI may be driven largely by diverging understandings of what constitutes "value" in bioscience research and product development, which parties add value to resources and information, and at what point in time (Nawaz et al., 2021).

At the time of writing, the question of whether DSI should be regulated under the paradigmatic access and benefit sharing framework of the Nagoya Protocol remained unanswered. The issue only began to receive formal consideration at the 2018 Conference of the Parties to the CBD (COP 14), during which it was acknowledged that additional efforts were required to attain conceptual clarity about the meaning and scope of DSI, and to resolve the divergence of views that had emerged about whether access and benefit sharing obligations should be triggered by the use of dematerialized genetic resources (Convention on Biological Diversity, 2018).

In the context of this official uncertainty, stakeholders have discussed different options for how DSI might be regulated in the future, and on the potential outcomes that could result from each scenario. For instance, a recent report by the Centre for Genetic Resources of the Netherlands described four possible situations. The first possibility considered DSI to be outside of the scope of the CBD and Nagoya Protocol, while under the second scenario DSI would be governed by these regimes (Hiemstra et al., 2019). These outcomes represent two opposing interpretations of the question of whether dematerialized genetic information should be considered

[2] Specifically, the CBD provides definitions for "genetic material" ("any material of plant, animal, microbial or other origin containing functional units of heredity") and "genetic resources" ("genetic material of actual or potential value"). CBD, Article 2. The Nagoya Protocol defines "utilization of genetic resources" as "to conduct research and development on the genetic and/or biochemical composition of genetic resources, including through the application of biotechnology as defined in Article 2 of [the CBD]." Nagoya Protocol, Article 2. Neither instrument defines or explicitly refers to "genetic information."

equivalent to genetic materials. A third alternative proposed that DSI should not be regulated under the Nagoya Protocol, but rather based on the terms of a separate multilateral benefit sharing mechanism that the Parties to the CBD would establish and administer (Hiemstra et al., 2019). A final option speculated that if DSI were determined to be within the scope of the Nagoya Protocol, provider countries could form a voluntary "Coalition of the Willing" that would enable the free exchange of genetic information between members, while restricting access to others based on standard benefit sharing conditions (Hiemstra et al., 2019:14).

Although it is logical that stakeholders would consider solutions to the problem of how to deal with dematerialized data within the parameters of existing international legal instruments and institutions, the extent to which contemporary frameworks are equipped to administer informational resources is questionable. One issue is that the access and benefit concept has been deployed by a variety of different interest groups to consolidate diverse dialogues, including those related to ethics and equity in research, ownership and control of genetic resources and traditional knowledge, and the need for capacity building and technology transfer in different locales (Laird et al., 2020). However, the development of appropriate regulatory strategies for these multifaceted issues is hampered by the fact that the foundational access and benefit sharing instrument, the CBD, is essentially an environmental treaty whose governance body may be inadequately prepared to address social, economic, and technological questions (Laird et al., 2020).

Another weakness of the conventional access and benefit sharing model is that it is predicated on a contract ideal that assumes the existence of bilateral negotiations and agreement between parties who have complementary interests (i.e., providers and users of genetic materials) (Lawson et al., 2019) This kind of framework is cumbersome when applied to the majority of contemporary DSI transactions, where researchers need to quickly and easily access vast amounts of data from diverse sources, and where it is difficult to monitor and trace how information is used and developed (Lawson et al., 2019:114). Given these concerns, solutions have been proposed that would remove genetic information from the "access and benefit sharing transaction" and instead establish a separate arrangement that would externalize the costs associated with the access and use of dematerialized data in the form of a charge, levy, or tax (Lawson et al., 2019:115–16). Specific examples include imposing a micro-levy on the purchase of services such as DNA sequencing or synthesis, or rendering annual payments, including in the form of a subscription, to a central agency that would redistribute revenues to the appropriate providers of informational resources (Sherman & Henry, 2021a, b). Alternatively, the focus of regulatory attention could shift away from the time of access and towards a later trigger point, such as when intellectual property protection is sought or when economic benefits accrue through the use of specific sequence information (Sherman & Henry, 2021a, b:3).

Proposals to reform contemporary access and benefit sharing laws demonstrate that the phenomenon of dematerialization in the biosciences is inspiring novel regulatory approaches that transcend the assumptions embedded in the bilateral contractual model that the CBD introduced. However, it is also notable that notwithstanding

the new issues that the widespread availability and utilization of genetic sequence information raise, many of the original bioethical concerns remain acutely relevant. The question of how to ensure distributive justice where a relatively small number of actors are poised to benefit most substantially from the exploitation of certain resources is particularly pertinent. The need to obtain appropriate informed consent to use DSI also remains critical, especially where intent changes about how particular data will be utilized, for instance when the scope of a project shifts from non-commercial to commercial. When coupled with the intellectual property issues raised in Part I above, it is understandable that researchers in the biosciences might experience doubts about how to make ethical decisions in the course of their work. Part III aims to address potential concerns by providing practical considerations for researchers to enable bioethical decision making.

Dematerialization and Bioethical Decision Making

Prior to exploring options for how researchers might make bioethical decisions when their work triggers the issues described throughout this chapter, it is important to note that the onus should not be placed entirely on individual scientists to operate within appropriate moral boundaries. This is because multiple overlapping legal, cultural, and institutional infrastructures have set preexisting standards for how bioscience research should be conducted, effectively shifting the responsibility for the majority of bioethical decision making from researchers to scientific institutions. For example, in addition to the national and international legal frameworks described above, over the past several decades most scientific institutions worldwide have adopted policies that dictate norms for intellectual property protection, the circulation of biological and genetic materials, and research ethics. While the administrative infrastructure and human capital required to fully implement these policies are lacking within some institutions, others have mature systems in place to help researchers navigate bioethical questions related to their work.

In addition to research institutions themselves, extramural organizations that facilitate the practice of science, such as governmental and private funding bodies and publishers, have in some cases developed specific rules that researchers must follow to ensure compliance with bioethical norms. For example, the Nature Portfolio requires that authors who publish their work in Nature journals must make materials used in the research process available to others without undue qualifications, while also encouraging researchers to include unique identifiers of key biological resources in their manuscripts (Nature Portfolio, 2021). While it is incumbent upon scientists to familiarize themselves with the various legal and institutional norms that govern their work, the burden should not be placed on individual researchers to evaluate every decision they make based on abstract bioethical parameters. In most cases, adhering to established norms should be sufficient.

However, it is important to recognize that complications may arise when bioscience researchers work across different national and institutional contexts. This is

due to the ways in which the laws governing intellectual property and access and benefit sharing for genetic technologies diverge from one country to the next, and how particular research institutions adapt local policies to suit the legal, political, and sociocultural environments in which they are situated.

International research teams with members based in different countries may need to navigate diverse domestic juridical systems that are not always compatible with one another. For example, if a bioscience project includes researchers from Africa, Europe, Oceania, and North America, team members should be aware that if they create an invention involving isolated genetic sequences, it may be eligible for patent protection in some of these territories (e.g., the European Union), but not others (e.g., Australia). Additionally, project scientists may be required to adhere to Nagoya Protocol standards based on the national laws of some team members (e.g., those based in South Africa), but not others (e.g., those based in the United States). Confusion might be further compounded by the internal policies of each partner institution, whose terms may not align precisely with the national laws of the countries in which they are based. For instance, although the United States is not a party to the CBD or the Nagoya Protocol, certain American universities require adherence to the access and benefit sharing standards that these treaties established (Sherman & Henry, 2021a, b).

Given the discrepancies between different legal and policy regimes and the theoretical and practical problems that dematerialization introduces, there is growing recognition of an "urgent need for a global institutional and conceptual framework for ethical research and commercialization, and the environmental and social implications of scientific and technological advances" in the biosciences (Laird et al., 2020). Although researchers should not be personally saddled with the responsibility for developing such a framework, they can collectively play a crucial role in policy formation, especially in relation to the use of DSI. Contemporary governance standards for genetic data may be effectively irrelevant in the context of actual scientific practices, which have evolved significantly faster than corresponding legal regimes. To ensure that future norms are more appropriately tailored, scientists and scientific organizations could expand their participation in policy making processes, including by attending United Nations meetings, writing background documents to inform prospective global standards, (Laird et al., 2020) and contributing to national and institutional reforms, for example by submitting recommendations to inform regulatory rulemaking procedures at the national level or voicing their perspectives at events hosted by scientific societies.

While bioscience researchers will inevitably hold diverse opinions about the optimal approach to govern the use of DSI, they may consider some general guiding questions when developing their own research agendas. Foremost, scientists should reflect on the nature of their work and the kinds of information on which they rely. For example, a researcher might consider the following questions: Is the research likely to lead to commercial outcomes? Does the project rely on DSI from a single class of organism or species? Is the knowledge of Indigenous or other local peoples implicated in the work? If all three of these questions can be answered affirmatively, researchers might consider adhering to conventional intellectual property and access

and benefit sharing standards, preferring the use of physical materials over DSI where feasible.

For example, researchers working with the ARC Industrial Transformation Training Centre for Uniquely Australian Foods are aiming to develop a new agri-food sector based entirely on plants that are native to Australia (Uniquely Australian Foods, ARC Industrial Transformation Training Centre, 2021a, b, c). Some of the Training Centre's projects involve assessing the chemical composition and nutritional quality of plants such as the Burdekin plum and the Bunya nut, (Uniquely Australian Foods, ARC Industrial Transformation Training Centre, 2021a, b, c) which are processes that in theory could be conducted utilizing genetic information sourced from electronic databases rather than physical samples. However, the Training Centre has made commitments to respect the rights of Indigenous Australians, and therefore its researchers are working in collaborative partnerships with Indigenous Enterprise and Advisory groups to obtain access to plant materials and traditional knowledge, and to develop strategies for equitable benefit sharing and intellectual property ownership in relation to research results (Uniquely Australian Foods, ARC Industrial Transformation Training Centre, 2021a, b, c).

In contrast to this example, some scientists may envisage the use of DSI as a basic input to experimental (i.e., non-commercial) research, the objectives of which rely on screening the genetic compositions of numerous different species or organisms, but not on access to physical samples or the knowledge of Indigenous or other local peoples. Under such circumstances, researchers could support the development of bioethical standards alternative to the conventional intellectual property and access and benefit sharing models. These might include the broad implementation of strategies such as click-wrap license agreements, which DSI users would sign when accessing information from public databases. The terms of these contracts could stipulate that users agree to not pursue intellectual property rights for the information accessed, and to negotiate a benefit sharing agreement with the DSI provider if a specific event occurs in the future. Possible trigger points for benefit sharing in this context could include the development of a commercial product based on the genetic information obtained from a public database, or the disclosure of sequence-related information in scientific publications (Sherman & Henry, 2021a, b).

These and other proposals attempt to introduce novel approaches to ensure that researchers are able to conduct their work ethically in the context of the trend towards dematerialization in the biosciences. Although the development and expansion of new technologies create novel opportunities for the use of informational resources in areas such as genomics and synthetic biology, it is important to reiterate that many of the fundamental tensions that underlie research in the biosciences remain unaltered. Competing concerns about the importance of open access to materials and information versus the need to protect against the misappropriation of resources and knowledge are as resonant now as they were when debates over intellectual property for biological inventions and the governance of biodiversity proliferated in the 1980s and 1990s. In responding to these concerns, individual researchers should not be expected to develop their own bioethical protocols

without the support of the legal and institutional systems in which they work. Nevertheless, scientists could consider the various factors and strategies discussed throughout this chapter when making decisions at the intersection of intellectual property and the biosciences.

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See Diamond v. Chakrabarty, 447 U.S. 303. (1980). (holding that under United States patent law, protection is available for a microorganism that is understood as artificially constructed rather than naturally occurring).

See, e.g., Bowman v. Monsanto, 569 U.S. 278. (2013). (holding that the doctrine of patent exhaustion does not permit a farmer to plant and grow saved, patented seeds without the patent owner's permission).

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Specifically, the CBD provides definitions for "genetic material" ("any material of plant, animal, microbial or other origin containing functional units of heredity") and "genetic resources" ("genetic material of actual or potential value"). CBD, Article 2. The Nagoya Protocol defines "utilization of genetic resources" as "to conduct research and development on the genetic and/or biochemical composition of genetic resources, including through the application of biotechnology as defined in Article 2 of [the CBD]." Nagoya Protocol, Article 2. Neither instrument defines or explicitly refers to "genetic information."

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This is particularly the case for the conservation objective of the CBD, with evidence suggesting that to date, the access and benefit transactions that have taken place under the terms of the treaty have not generated substantial benefits for biodiversity conservation. Laird, et al, ibid,1200.

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Part III
Institutional Ethics and Bioethics Committees: *Principles, Roles and Perspectives*

Chapter 13
The Ethics of Biomedical Practitioners: A Brief Historical Introduction

Robert Baker

Abstract This chapter provides a brief introductory history of biomedical practitioners' efforts at self-regulation though oaths, codes, and statements of ethical principle, tracing them from ancient oaths through the nineteenth-century transition to codes of medical ethics. The more recent foundation for modern biomedical ethics was laid in post-World-War II oaths and codes written in the aftermath of the Holocaust, and later modified in response to animal rights and patients' rights movements that promoted principles and practices enforced by semi-self-regulatory acronym-laden ethics committees— HECs, IACUCs, IRBs/REBs/RECs. The last section of this chapter discusses the modern origins of self-regulatory ethical principles for benchside biomedicine and biomedical publications.

Keywords Animal rights · Ethics declarations, oaths, codes, and principles · History of healthcare professions ethics · Nazi medical ethics · Patients' rights · Research ethics

Physicians' Oaths: Ancient to Eighteenth Century

The Hippocratic Oath was written after Hippocrates, or his sons, permitted non-family members to train as apprentices. No oath had been necessary when Hippocratic medicine was a family trade since sons and nephews assimilated norms and practices by assisting their fathers and uncles. Admitting outsiders, however, forced the family to formulate an oath binding apprentices to abide by family practices (Jouanna, 1992, 46–48). The version of the oath that survives is written in a

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style and uses terms current about a century after Hippocrates died and thus appears to be a later version of an earlier oath. It opens with the affirmation (1.i) "I swear… (1.iii) to bring the following oath and written covenant to fulfillment."[1] By virtue of this pronouncement and by signing the contract, apprentices accepted the obligation to teaching, "without fee and written covenant… rules… lectures…and all the rest of learning [to family members and to others] who have [sworn the Oath]," but to no one else. Apprentices also agreed to "(3.i) use regimens for the benefit of the ill in accordance with [their] ability and judgment, (ii) from [what is] to their harm or injustice [apprentices] will keep [the sick]." And, (7.i) "Into as many houses as [apprentices they] may enter, [they] will go for the benefit of the ill, (ii) while being far from all voluntary and destructive injustice especially from sexual acts both upon women's bodies and men's, both of the free and of the slaves. (8.i) And about whatever [they] may see or hear in treatment, or even without treatment, in the life of human beings—things that should not ever be blurted out outside (ii) [they] will remain silent, holding such things to be unutterable, [sacred, not to be divulged]." By virtue of this oath and contract apprentices were obligated to share medical knowledge and techniques with other Hippocratics, to use their medical knowledge and techniques to benefit the sick, not to harm the sick or anyone else in the households they visited, and not to treat anyone unjustly or sexually exploit them, irrespective of their social status (free or slave), or gender (male or female). They were also to respect confidentiality and, as apprentices, were forbidden to prescribe or use dangerous medicines such as destructive pessaries (to expel a retained placenta).

Later Hippocratic Influence

For centuries after the Hippocratics left the stage, their writings attracted the attention of later generations of practitioners. Thus, some 500 years later, Scribonius Largus, a Greek physician practicing in first century Rome, claimed that the oath forbade Hippocrates' disciples to harm anyone in their care, not "even enemies, …for medicine does not evaluate people by [their] fortune or character but promises to bring help to all equally and vows never to harm them" (Tempkin, 1991, 61). Centuries later, as Europe Christianized, the oath was transformed into an "Oath According to Hippocrates Insofar as a Christian May Swear It" (MacKinney, 1977; Welborn, 1977). This oath opened with invocations to Christ and prohibitions against harming patients were interpreted as forbidding the use of poisons and the prohibition against apprentices use of destructive pessaries was interpreted as forbidding (post-quickening) abortions (Verhey, 1984, 140).

[1] Numbers in parentheses refer to lines in Heinrich von Staden's translation (von Staden, 1996, 407).

By the seventeenth the oath had been translated into English and other vernacular languages (Larkey, 1977) and in the 1730s faculty at the Edinburgh Medical College replaced a loyalty oath to the English church and crown with a version of the Hippocratic Oath, suitable to gentlemen of any religion. Thus, entering students pledged to act cautiously, purely, and honorably, "to take care faithfully that all [my actions] are conducive to [effecting] health in sick bodies. And…to keep silent on all matters seen and heard during the course of healing…. Thus, may the divine presence be favorable to me as I make this pledge" (Baker, 2013, 44). The invocation of a divine presence, rather than a particular version of the deity, opened the medical school to students of all religions including Roman Catholics, and later, to Jews and Quakers. As Catholic alumnus Michael Ryan, the first professor of medical ethics, explained to his students, the oath's duty "of *caution* means taking 'care not to expose the sick to any unnecessary danger.' The best rule of conduct on this important point is the simple and comprehensive, religious and moral precept 'do unto others as you would they should do unto you" (Baker 2013, 44, 49, 73.).

Midwives Oaths and Nurses Pledges

In the 1550s midwifery and nursing transitioned from household tasks to become separate occupations. In an effort to ensure that newborns would be baptized into the dominant religion, religious authorities had midwives swear an oath. The Catholic Bishop of London, for example, required midwives to sign and swear an oath pledging that newborns would be baptized as Catholics. His oath also required midwives to prevent infanticide, and to ensure that stillborn babies received a religious burial rather than being "cast into an outhouse" (Baker, 2013, 20–23). Later Protestant oaths were similar except that they introduced a measure of social justice by requiring midwives to "be ready to help aid, as well, the poor as the rich woman being in labor" (Baker, 2013, 23–26). In 1716 New York City adopted a secular version of this oath, with the new requirement that, should a midwife "see any peril or jeopardy, either in the mother or child, she will call other midwives for council," (Baker, 2013, 19).

The earliest self-imposed nursing or midwife's oath returned to the Hippocratic tradition. Called the "Nightingale Pledge" to honor the founder of professional nursing, the pledge was written for a Detroit nurse training school in1893. It commits nurses to living purely, to abstaining "from whatever is deleterious and mischievous," to never knowingly administer harmful drugs, and to respect patient confidentiality (Cratherm, 1953, 80–81). It was the primary ethics statement for nurses until 1926, when the American Nursing Association (ANA founded 1896) suggested a tentative ethics code (revised1940) and The International Council of Nurses (ICN founded 1899) issued a code of ethics in 1953, that was revised in 2021 (International Council of Nurses, 2021).

Codes of Physicians Ethics 1647–1957

Percival's Innovation

Codes of Professional Ethics: Unlike medical oaths and pledges, codes are not first-person commitments made by publicly utterances. They are presumed binding on practitioners simply by virtue of their occupations. Initially, however, they were imposed as a condition of organizational membership. Thus, a 1663 Royal Charter for London Physicians had a "Moral or Penal Decree." However, these organizational rules were inadequate to prevent physicians' public quarrels between or with unaffiliated practitioners. Recognizing this limitation in 1803 English physician Thomas Percival published *Medical Ethics*, an innovative code of "moral duties" governing "the relations in which a physician stands to his patients, to [fellow practitioners], and to the public," that was binding on physicians and surgeons simply by virtue of their professions (Percival, 1803, viii). This "tacit compact" (Chap. II, Art. XXIII) obligated them to minister to the sick with "attention, steadiness, and humanity," irrespective of whether the sick person was rich or poor (Chap II, Art. I). It also bound practitioners to submit their quarrels to arbitration by peers (Chap. II, Art. XXIV), and to submit proposed "*new remedies* and *new methods of chirurgical* [surgical] *treatment"* to peer to review to ensure that they are based on "sound reason, just analogy, or well authenticated facts" (Chap. I, Art. XII).

The AMA's Professional Codes of Ethics

Percival's medical ethics had little initial appeal in Britain, but it was readily accepted in nineteenth century America where newly founded allopathic medical societies adopted parts of it, in 1847 when these physicians founded a national society, the American Medical Association (AMA). At their initial meeting they adopted a code of medical ethics that reconstructed Percival's tacit compact as an explicit social contract between physicians, patients, the medical profession, and the public. Among the duties stipulated in this compact was recognizing "poverty...as presenting valid claims for gratuitous services… [that] should always be cheerfully and freely accorded" (AMA 1847, Chap. III, Art I, Sec. III, Baker et al., 1999); and being "ever ready to obey the calls of the sick" (AMA 1847, Chap. III, Art. I); and thus, "when pestilence prevails, it is their duty to face the danger and to continue their labors for the alleviation of the suffering, even at jeopardy of their lives" (AMA 1847, Chap. III, Art I, Sec. III.). The American Institute of Homeopathy (1884), and American Osteopathic Association (1904) adopted codes modeled on the AMA's 1847 code, that include the same duties.

Replacing Social Compacts with Professional Principles

In 1903 the AMA reformulated its professional ethics as a collection of principles. In a 1912 revision the AMA valorized the racially segregationist medical practices of the American South by introducing the principle of physicians' freedom "to choose whom he will serve," except in emergencies (AMA 1912, Chap. I, Sec 4). But it retained the principle that "The poverty of a patient…should command the gratuitous services of a physician" (AMA, 1912, Chap. 2 Art. VI, Sec. I) and reiterated the duty tend to the epidemic stricken "without regard to the risk to his own health or life or to financial return" (AMA 1912, Chap 2, Sec. 2, Baker et al., 1999 347, 353, 354). Consequently, during "Spanish Flu" (H1N1) pandemic of 1918–1919 the AMA leadership modeled ethical conduct by treating influenza patients and most physicians followed their example (Baker, 2013, 309).

In 1957 the AMA demoted its principles to mere advisory pronouncements by "which a physician may determine the propriety of his conduct" (Baker et al., 1999 355, 356), but it still proclaimed physicians' right to choose whom they may serve. Consequently, the duty of attending to the epidemic stricken became secondary annotation—that was deleted in a 1976 revision. Thus, during the 1980s HIV/AIDS epidemic, the AMA's ethics principles offered physicians no guidance for ethical conduct during an epidemic. Not surprisingly, therefore, a survey of primary care physicians found that half stated that they had no ethical obligation to treat HIV/AIDS patients (Gert; Link et al., 1988). As one surgeon put this point, "I've got to be selfish. It's an incurable disease that's uniformly fatal, and I'm constantly at risk for getting it. I've got to think about myself. I've got to think about my family. That responsibility is greater than to the patient" (Bayer, 2000, 4–5). Reviewing the incident, one historian concluded, "the American medical profession… [was] conceptually ill prepared for [the HIV-AIDS] epidemic that threatened practitioners as well as patients [because] the American Medical Association's Code allowed physicians to choose their patients (Wallis, 2011, 623, 624.) Skeptics often dismiss professional ethics as high-toned public relations pronouncements that have little impact on practitioners' conduct. Yet in 1918, when the AMA code obligated physicians to provide care during epidemics and the AMA leadership modeled this conduct, American physicians uncomplainingly offered care to those stricken. In contrast, during the AIDS epidemic of the 1980s about half of all American physicians complained about and/or abstained from providing such care. Absences have consequences: *Res Ipsa Loquitur*: Some things speak for themselves!

Research Ethics Before, During, and in the Aftermath of the Nazi Period

Prewar and Interwar Period Research Ethics

During the pre-war and interwar periods clinicians in major research centers in Europe and the US saw themselves as "absolute rulers over 'clinical material' [i.e., patients, and used them] as needed for their research interests. The question of consent was viewed to be for the most part irrelevant" (Elkeles, 2004, 26). In 1902, for example, German physician and ethics reformer Albert Moll amassed "a collection of approximately six hundred [experiments] from… [the] international professional literature." He found that, despite a few regulations that might constrain conduct. "Some medics obsessed by a kind of research mania, have ignored the areas of law and morality in a most problematic manner. For them, the freedom of research goes so far that it destroys any consideration for others. The borderline between human beings and animals is blurred for them. The unfortunate sick person who has entrusted herself to their treatment is shamefully betrayed by them, her trust is betrayed, and the human being is degraded to a guinea pig. …There seem to be no national or political borders for this aberration" (Vollmann & Winau, 1996, 11; Grodin, 1992, 131–132; Mahhle, 2012, 227).

Nazi Medical Ethics

When the National Socialist German Workers Party (NAZI) assumed control of the German state in 1933 they inherited the medical practices of the pre-war era. They then leveraged governmental power to introduce a new biomedical ethics, *Rassenhygiene* (Racial Hygiene), that made physicians "Guardians of the Health of the *Volk* "(Proctor, 2000, 15, 40). This new ethics required, physicians to discourage tobacco use and eating foods with petrochemical dyes as carcinogenic (Proctor 1999, 5) and not to "weaken the *Volk* community through the abortion of a fetus" (Ramm, 1943, 92), or euthanasia (Ramm, 1943, 94, 95). Non-*Volk* (Jews, Roma) and "dysgenic" *Volk* (gays, people with mental or physical disabilities), however, were seen as threats to the gene pool, and so physicians were to cooperate with eugenic initiatives like *Aktion T4* by reporting children with disabilities to authorities (Ramm, 1943, 97), and encouraging parents to bring such children to clinics (such as Hadamar psychiatric hospital) to be surreptitiously "euthanized." (*Aktion T4* later served as a model for the Holocaust.)

Postwar Medical Ethics

The Nuremberg Code

In 1947 German physicians accused of participating in *Aktion T4*, the Holocaust, or of conducting unethical medical experiments were tried for war crimes and crimes against humanity at Nuremberg (*US vs. Karl Brandt,* et al.). Necessity, mother of inventiveness, led Brigadier General Telford Taylor to open the trial with a fib: this is "'no mere murder trial' because the defendants were physicians who had sworn to 'do no harm' and 'abide by the Hippocratic Oath'" (Shuster, 1997, 1437). However during the interwar period Hippocratic oaths had been replaced by oaths to a party, a people (*Volk*), or to leaders, like Hitler (Lifton, 1986 207, 435; Weindling 2004,151, 282; Shuster, 1997, 1437). Nonetheless, the Hippocratic Oath was invoked throughout the trial. Andrew Ivy, the AMA's representative, testified that "the Hippocratic Oath represents the Golden Rule of the medical profession…throughout the world," thus the researcher should "have respect for life and the human rights of his experimental patient" (Schuster, 1997, 1439). The fictive universality of the oath was adopted as a fib of necessity because, whereas *Aktion T4* and "thanatological" experiments (designed to improve mass killing or sterilization) were war crimes, therapeutic experiments were not condemnable on these grounds. Scientists serving armies facing each other on the same battlefields, encountered the same biomedical challenges, and naturally conducted similar experiments. Thus, to condemn German anti-malaria drug experiments at Dachau concentration camp prosecutors had to differentiate them from American anti-malaria drug experiments conducted at Jolliet-Stateville prison (Alving et al., 1948; Miller, 2013). At Dachau, however, subjects were not volunteers, and most died (Blaha, 1946); whereas, at Jolliet-Stateville, subjects signed written informed consent forms, and none died (Green, 1948, 457). Given these differences the Nuremberg Tribunal dismissed claims of similarity and in its summation the Nuremberg court replaced the fictively universality Hippocratic Oath with the ten fictively universal principles for ethical research on humans, later called, "the Nuremberg Code." The first principle states, "The voluntary consent of the human subject is absolutely essential." (Brody, 1998, 213).

The 1948 Declarations of Geneva

Post Nuremberg, the Hippocratic Oath and Nuremberg code became talismans of ethical research on humans even though neither was a workable code for researchers because the oath's "do no harm" provisions prohibited potentially harmful non-therapeutic research and the Code's requirement of informed voluntary consent ruled out research on anyone incapable of consenting, such as children, or the physically or mentally incapacitated. Recognizing these limitations, the World Medical Association (WMA, founded 1947) sought to develop workable ethics standards

for experimenting on humans. Moreover, noting that the absence of Hippocratic oath-swearing ceremonies created social spaces filled by oaths to Adolf Hitler, the WMA sought to reclaim this space with a modernized Hippocratic oath to prevent future physicians from placing obedience to a leader or a *Volk*, above their commitments to patients (Baker, 2020; Lifton, 1986, 207, 435). Thus, when the it issued a new version of a Hippocratic oath in Geneva, that oath opened with "THE HEALTH OF MY PATIENT [is] my first consideration; ... [and I will] NOT PERMIT considerations of religion, nationality, race, party politics or social standing to intervene between my duty and my patient (original capitalization, World Medical Association, 1949, 12). Versions of the Geneva Declaration or other "Hippocratic" oaths are sworn at medical and veterinary schools in Canada, the US, and worldwide. (American Veterinary Association, 2021; Dossabhoy et al., 2018; Kao & Parsi, 2004; Orr et al. 1997).

The 1964 Declaration of Helsinki

The WMA's Committee on Ethics next objective was developing workable ethics standards for clinical research. However, this initiative became so entangled with careerist and pocketbook concerns that a consensus draft was first circulated in 1962 (Lederer, 2004). That draft reminded physicians that even when conducting research, they remained protectors of patients' life and health and that research required the informed voluntary consent of subjects or their surrogates. At a 1964 meeting in Helsinki written documentation of consent was added and researchers were reminded that medical students and laboratory assistants are in a dependent relationship. The 1964 version also gave subjects the right to withdraw from research at any time and obligated investigators to discontinue research that could prove harmful. This revised Helsinki declaration passed unanimously and immediately became an authoritative statement of the ethics of clinical research on humans. As research ethics reformer Henry Beecher observed. "Until recently the Western World was threatened with the imposition of the Nuremberg Code as a Western Credo. With the wide adoption of the Declaration of Helsinki, this danger is now past" (Beecher, 1970 279). Depending on when one starts the clock—1947, 1949, 1962—it took between 2 and 17 years to fashion a practical alternative to the Nuremberg Code.

The 1970–1980s: Rights Revolutions to the Birth of Bioethics

The 1972 Patients' Bill of Right

From 1847 to 1979 the AMA's codes of ethics presumed that clinical encounters involve benign scientifically trained physicians paternalistically caring for patients who gratefully complied with their doctors' order—and paid their bills. Reflecting

this paradigm hospitals admitted paying patients through the front door, while directing the indigent elderly, unmarried mothers, and other poor folks to the rear—or, in the American South, to Colored or Negro entryways. In the 1960s civil rights, Medicaid, and Medicare legislation obsolesced these practices. Yet these newly entitled patients were still directed to the same entrances and equitable access and treatment remained elusive, stymied by architecturally reinforced lingering ageist, classist, racist, and sexist practices. Reacting to this systemic discrimination, the Boston Women's Health Book Collective (BWHBC), the National Welfare Rights Organization (NWRO) and various African American civil rights groups lobbied the American Hospital Association (AHA) "to do something about doctors who were: condescending, paternalistic, judgmental and non-informative" (BWHBC, *Preface*), and who refused offering prior appointments to patients treated in former charity, Colored/Negro, and welfare clinics: thereby frittering away their time in overcrowded waiting rooms as if it—or they—were of little value. Consolidating their demands as A Patient's Bill of Rights, the protesters publicized them in a bestselling 1970 feminist women's handbook, *Our Bodies, Our Selves* (Boston Women's Health Book Collective, 1973, Preface; Jonsen, 1998, 368–371). Embarrassed by the negative publicity in 1972 the AHA placated the protesters by endorsing "A Patient's Bill of Rights." Among the rights endorsed were having advance appointments; having diagnoses, prognoses, and treatment options explained; being told whether a treatment was experimental; and the right to refuse treatment and to be informed of physicians' conflicts of interest. Yet, inactions speaking louder than words, the AHA never enforced the announced rights and hospitals' treatment of these patients remained unchanged. Nonetheless, the ideal of patients' rights was disseminated, and charters or bills of patients' rights were ultimately recognized in European and American healthcare. In 1998 the US congress enacted a patients' bill rights.

The 1976 Belmont Report and the Creation of Acronym Committees (e.g., IRBs)

On July 26, 1972 a *New York Times* headline screamed, "Syphilis Victims in U.S. Study Went Untreated for 40 Years." Peter Buxtun, the son of Holocaust refugees who worked as a United States Public Health Service (USPHS) contact tracer for sexually transmitted diseases had reported to the USPHS that one of its experiments was comparable to Nazi experiments condemned at Nuremberg. After the USPHS refused to terminate the experiment, Buxtun informed the press. The consequent scandal led to a congressional investigation which, in turn, led to the formation of a National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1974–1978). The commission ultimately recommended new regulations whose enforcement was to be outsourced to semi-self-regulatory Institutional Review Boards (IRBs), and the Commission promulgated three ethical principles designed to guide researchers and IRBs. These principles responded

directly to the USPHS study that inspired Buxton's protest. In that study physicians gulled about four hundred African American men into consenting to *treatment* for "bad blood," although the researchers were actually studying the progress of *untreated* syphilis. The USPHS contended that this did not violate the Nuremberg Code or the Helsinki Declaration because, harmlessly monitoring the progress of a disease did not require informed consent. The National Commission concluded, however, that consent involved more than mitigating researchers' legal liability for harm; it affirms respect for subjects as persons, as autonomous agents with a right to understand the implications of volunteering. The Commission also recommended two other principles in addition to respect for persons: a principle of beneficence to ensure that the benefits to be attained from an experiment outweighed the risk or harm to subjects, and a principle of justice to guide the equitable selection of research subjects (Department of Health, Education, and Welfare, 1979).

The formulation of principle-based biomedical ethics proved foundational as a transition from a paternalistic medical ethics of "doctor/researcher knows best" to a bioethical paradigm based on respect for patients' and subjects' rights that became the dominant form of clinical and research ethics in the 1980s. Thus, a 1980 revision of the AMA's principles accepted the idea of patients' rights fleshing it out in a 1990 statement, "Fundamental Elements of the Patient-Physician Relationship" (Baker et al., 1999, 358–361). To enforce these rights medical centers began to form hospital ethics committees (HECs), to recruit "ethicists," or to train clinicians as ethicists. A 1983 survey found that 4.3% of hospitals had HECs, which proved helpful in clarifying ethical issues (73.3%), in providing legal protection (60%), in "shap[ing] consistent policies with respect to life support (56.3%); [and in] provid[ing] opportunities for professionals to air disagreements (46.7%)" (Youngner et al., 1983). By 2006 4 out of 5 hospitals in the US had HECs as did in virtually all US hospitals with over 400 beds (Fox et al., 2007).

Ethics Codes for Bioethicists

As ethics consultation became commonplace in the 1990s and 2000s, the emerging field faced a chorus of criticism. Ethicists were disparaged as a secular priesthood trespassing on the authority of medicine and religion (Shalit, 1997; Siegler, 1999; Smith, 2000) who were easily corrupted by money, prestige, and power (Elliott, 2001a, b; Sharpe, 2002). Critics also singled out ethicists advising biotech and pharmaceutical companies as "sellouts" (Boyce, 2001, Stolberg, 2001). "The problem with ethics consultants" one critic wrote, "is that they look like watchdogs but can be used like show dogs" (Elliott, 2001a). Anticipating such a critique, Canadian bioethicist Benjamin Freedman had warned colleagues in the emerging field that "clinical ethics is [not] so complicated...that it alone among [healthcare] professions should be without a shared and public understanding of the moral dimensions of its practice" (Freedman, 1989, 137–8). Yet the nascent profession had no official ethics standards and so its members could only feebly protest their personal integrity (Perlman, 2005).

Responding to this criticism the American Society for Bioethics and the Humanities, (ASBH founded 1998) and the American Society for Law, Medicine and Ethics (ASLME founded 1911) jointly published guidelines for bioethicists advising biotech and pharmaceutical companies (Brody et al. 2002). After 12 years of debate, the ASBH issued a Code of Ethics and Professional Responsibilities for Healthcare Ethics Consultants (ASBH, 2014). This code addresses a range of subjects including professional competency, integrity, transparency, managing conflicts of interest and obligation, respecting privacy and confidentiality, the ethics of communicating though mass media and social media, and the responsibility of reducing discrimination, disparities, and inequities in healthcare.

Anti-Vivisectionism and Animal Rights: Nineteenth and Twentieth Centuries

Rules Regarding Animals and the 3Rs

Humanity has used and abused non-human animals as food sources and slave labor since before recorded history. However, as European and American societies urbanized, and as the meat-eating public outsourced butchering, petkeeping, once the prerogative of rulers and elites, democratization downwards. Thus, utilitarian animals once used as hunters and mousers became lapdogs and pussycats, and the middle class, now mindful of animal welfare, joined with aristocrats to pass such laws as the 1890 British Vivisection Act, which regulated the treatment of animals in agriculture and science. Around this time antivivisectionist in the US began to agitate for laws regulating experiments on animals. In response the AMA formed the aptly named, Council for the Defense of Medical Research (CDMR 1908–1926). When CDMR's director, Harvard physiologist Walter Cannon, discovered that some laboratories had standards for animal welfare he encouraged all laboratories to adopt such "Rules Regarding Animals." These rules require anesthetizing animals at risk for pain, painlessly killing animals to prevent their suffering, and creating holding areas for purchased animals to allow repatriation with owners.

In 1916 Cannon lobbied the AMA for rules requiring the informed voluntary consent of human research subjects and forbidding publication of unconsented research. The AMA rejected his proposal. Thus, until the Nuremberg trials embarrassed it into acting in 1946, the AMA supported ethics standards regulating research on animals, but not for experiments on humans (Baker, 2013, 263–273, Lederer, 1995, 97–100). In the 1930s the emerging Nazi party championed antivivisectionism (Lisner, 2009; Proctor, 1999, 5; Sax, 2000, 41) and one of the Nazi government's first acts was a 1933 law on animal protection that restricted animal experimentation to painless experiments (German State Law on Animal Protection (1933), Sec. III Articles 5–8). In the immediate postwar era, however, enthusiasm for antivivisectionism waned. Defying this trend, Oxford University polymath William Russell, together with microbiologist Rex Burch, wrote a 1956 report for

the Universities Federation for Animal Welfare (UFAW, founded 1926) setting out a 3R program for ethical research animals by: (1) *Replacing* experiments on animals with experiments without animals; (2) *Reducing* the number of animals used in experiments; (3) *Refining* experiments to minimize potential pain and to enhance the welfare of the animals used (Russell & Burch, 1959).

The AWA, Inventing Speciesism and Animal Rights

American antivivisectionism was resurrected by a February 4, 1966 cover of *Life* magazine that warned, "YOUR DOG IS IN CRUEL DANGER." The accompanying photo essay, "Concentration Camps for Dogs," illustrated dealers' cruel treatment of the animals they sold to medical laboratories (Wayman, 1966). This story reinforced concerns sparked by an earlier article in *Sports Illustrated*, "*T*he Lost Pets That Stray to The Labs: Science's Need for Experimental Animals is Very Real but is Often Filled by Unscrupulous and Cruel Professional Dognappers" (Phinizy, 1965; Unti, 2007). Stirred by public outrage, in 1966 the US congress passed the Animal Welfare Act (AWA) setting standards for the handling, sale, and transport of animals. Laboratory practices, however, remained self-regulated by Cannon's Rules Regarding Animals and the 3Rs. Meanwhile, in Britain, Richard Ryder realized that, "The 1960s revolutions against racism, sexism and classicism nearly missed out on animals…. We need to draw the parallel between the plight of other species and our own….It suddenly came to me: Speciesism!" Soon Australian philosopher Peter Singer, a proponent of utilitarianism, took up the battle cry and in 1974 one of Singers' students, Belgian-American public-school teacher, Henry Spyra, founded Animal Rights International (ARI). The ARI's tactics varied from non-public to public shaming designed to embarrass organizations to discontinue abusive experiments. In 1971 the US congress responded to the resurgent animal rights movements by establishing committees to monitor and enforce AWA rules. A 1986 revision reconstituted these committees as Institutional Animal Care and Use Committees (IACUCs): a hybrid between an IRB, monitoring compliance and reviewing research proposals, and a HEC, resolving ethical issues and recommending policy.

In 1975 Peter Singer published *Animal Liberation*, providing a utilitarian ethical foundational for the animal rights movement (Singer, 1975). In 1983 American philosopher Tom Regan proposed the non-utilitarian ethical theory that animals, as "subjects of a life," have inherent rights (Regan, 1983). In 1997 the European Union adopted Regan's conception in its Protocol on Animal Protection which recognizes animals as "sentient beings" and requires countries to pay "full regard to the welfare requirements of animals" when making laws regarding their use (EU Directive, 1998/58, Pederson, 2003). Regan's conception of animal rights was reinforced on July 7, 2012 when an international group of neuroscientists issued *The Cambridge Declaration of Consciousness*, a neuroethical statement on the unity of conscious

life which states, "the weight of evidence indicates that humans are not unique in possessing the neurological substrates that generate consciousness. Non-human animals, including all mammals and birds, and many other creatures, including octopuses, also possess these neurological substrates" (Low et al., 2012). As Regan argued, since non-human animals are conscious, they have rights—specifically, those codified in the EU's Protocol on Animal Protection.

Self-Imposed Ethical Principles for Benchside Biomedical Sciences

The Gordon Moratorium and the Asilomar Principles, 1973–1975

Microbiologists initiated a moratorium on recombinant DNA (rDNA) research at the 1973 Gordon Conference upon learning that some researchers planned to transplant a tumor virus "into [e. coli] a bug that grows in the human gut" (Wade, 1973, 566; Wade, 1977, 33). They also called upon the National Academy of Science (NAS) "to establish a committee…[to] recommend specific actions or guidelines" on rDNA research (Committee). At a 1975 conference at Asilomar California the microbiologists settled on "Reasonable principles for dealing with… potential [rDNA] risks: (i) that containment be made an essential consideration in the experimental design and, (ii) that the effectiveness of the containment should match, as closely as possible, the estimated risk. Consequently, whatever scale of risks is agreed upon, there should be a commensurate scale of containment." (Berg et al., 1975) These principles also "forbade… cloning of recombinant DNAs derived from highly pathogenic organisms [or] DNA containing toxin genes, or largescale experiments using recombinant DNAs that were able to make products that were potentially harmful to humans, animals or plants (Berg et al., 1975). On the basis of these principles the moratorium was rescinded (Committee to Study Decision Making, Institute of Medicine (US) (1991), Gerbert (1991)).

Guidelines for Good Publication Practice

In 1997 an ad hoc network of medical journal editors, the World Association of Medical Editors (WAM, founded1995), realized that the most vexing questions facing editors were "ethical…issues…plagiarism, fraud, peer review, duplicate publication," and it formed a Committee on Publication Ethics (COPE) to address these problems. COPE issued a *Consensus Statement of Guidelines on Good Publication Practice* in 1999 (Committee on Publication Ethics (COPE), 1999), and has been regularly updating its standards, identifying ethically problematic papers, and

sometimes naming and publicly shaming their authors. Since journal editors can only police their own publications, governmental agencies were founded in the 1980s and 1990s to develop and enforce standards for the responsible conduct of research.

Conclusion

From ancient times to the present, bedside and benchside biomedical practitioners recognized both the inherent nobility of their occupations—preventing, ameliorating, and curing disease, disability, pain, and suffering—and the inherent dangers of practitioners' abuse of their knowledge or their role. Recognizing this, from ancient times to the present they have repeatedly developed and accepted oaths, codes, and principles that express these ideals and sought to prevent their abuse. Some of these were succinctly described in this brief introductory history, more are discussed in detail in this Handbook. Although, to paraphrase Unitarian minister Thomas Marker, we should not pretend to understand the arc of the moral universe, we can appreciate that it is long, and that despite anomalies like *Rassenhygiene* and pervasive tolerance of classism, racism, sexism, and speciesism, from the Hippocratic Oath to the present day the arc of biomedical ethics has bent towards social justice.

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Chapter 14
Principles of Institutional Ethics

Christian Byk

Abstract Ethics committees are now part of the landscape of biomedicine but also of the public debate on questions of bioethics. This evidence is however the heir of a story. In the first place, it is about the history of science and scientific responsibility which is perceived differently according to the times because of the influence of the religions or of a primacy of scientific rationality, today contested. But this role assumed by the ethics committees at the heart of our societies goes in many ways beyond the sole question of responsibility and touches on the question of governance. Indeed, with the institutionalization of bioethics, it is less an ethics of reflection than an ethics of procedure that is developing and questions us about the standardization and globalization of ethics.

Keywords Ethics committees · Scientific responsibility · Governance · Procedural ethics · Institutionalization · Globalization

Introduction

At the beginning of the twenty-first century, the development of biomedicine is no more a question of individual research and personal involvement. It relies on the essential role played by different institutions at all the stages concerned with the progress of biological knowledge and practice. I mean universities, research centers, regulatory and financing agencies, academic bodies…

Scientific rationality justifies this organization but the social impact of biomedicine today on our health, way of life, economy and social transformations are also good reasons to question the role of the concerned institutions in the field of bioethics.

The idea is that they participate in a process which raise many sensitive societal issues and, consequently, they have to take such issues into account in performing a

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role which makes them stakeholders in the elaboration of public policy or in taking decisions which can affect a part of the community.

In the reality, the intervention of institutions in the field of biomedical sciences may reply to different objectives which derived all from the idea that those institutions have a social-no to say moral-responsibility towards the scientific community and the Society (I).

Therefore, the principles and the means by which the institutions try to fulfil these missions are particularly important because science, as the French biologist Jacques Testart explained, is "an activity under influence: every institutionalized power is trying to instrumentalize it because science models the life of individuals and societies" (Testart, 2009) (II).

The Moral Responsibility of Institutions and Its Objectives

Since the Second World War we are now accustomed to the fact that medicine and science in general may pose ethical issues when concretely applied in certain circumstances: eugenics, experimenting on human beings, controlling procreation, the use of nuclear energy or artificial intelligence for military purposes, the potential effects on man and the environment of genetic manipulations or the respect of privacy in collecting mega data for the advancement of medicine and science. This has created an awareness about the need of some social and moral responsibility for those institutions which contribute to this advancement and about the main objectives they should fulfil.

The Concept of Moral Responsibility

The famous writer and physician of the Renaissance, François Rabelais thought that "science without conscience is only the ruin of the soul". However, a modern scientific approach has long considered that science did not care about morality. It is the twentieth century which brought back ethics at the forefront of science and its applications.

From the "Amorality" of Science…

What means the concept of "amorality" of science and how does it apply to scientific institutions?

(a) **Objectivity and science**

Objectivity as a notion which designates not a real object but a known object dates back to the Middle Age (Daston & Galison, 2007: 29). For Descartes, objective

reality is the power that an idea has to represent what is being. For him, "to be objectively" is not to be outside the mind but on the contrary corresponds to the abstract idea that the mind has of external things (Descartes, 1979: 107). What is known is therefore not the object in itself but the object that it is represented by the mind. "Finally, Descartes and then Kant's use of the notion of objectivity not only accommodates the intervention of the knowing subject but is defined by it" (Devictor, 2020: 7).

– During the nineteenth century, the meaning of the concept of objectivity changed to cover all the phenomena whose existence manifests itself to us (Daston & Galison, 2007: 30). It then becomes a matter of getting rid of all human intervention to develop a scientific method that quantifies the objects of nature.

(b) **Objectivity and amorality**

Therefore, the objectivity of a thing is independent from the subject who observes it. And as science is observing and measuring the reality as it is and not the reality as viewed by the observer, science does not care about moral values which are outside the scope of its activities because values are not absolute realities and cannot therefore be quantified. This was also the view of the biologist Jacques Monod for whom the true knowledge is synonymous with "objective" knowledge, that is to say governed by the "postulate of objectivity", defined at the beginning of his book "Chance and Necessity" as "the cornerstone of the scientific method" (Monod, 1997).

However, if for him, "science ignores values; the conception of the universe that it imposes on us today is empty of any ethics, (nevertheless) ...research constitutes by itself an asceticism; it necessarily implies a system of values, an " ethics of knowledge " of which it cannot however objectively demonstrate the validity" (Monod, 1967: 16).

To the "Morality" of Scientific Institutions

Can giving the twenty-first century a fully ethical dimension to scientific institutions reintroduces into scientific practice the outdated moral dimension that Monod called to reject or does this movement open the way to replacing it with the ethics of science?

To admit that those who do a work of science can produce an ethics commensurate with the questions that their scientific approach and the applications which result from it, implies to recognize that there is a scientific community of which institutions today constitute a key element of this ethical and normative activity.

(a) **The idea of the scientific community**

We have known for a long time that there is a scientific community as a working community in the field of the production and dissemination of knowledge (Morgan & Molyneux-Hodgson, 2011: 141–154). This is particularly the role of universities which bring together universality of knowledge.

But the scientific community is aware that between science and ethics, there is an old and lasting relationship, in particular with regard to two questions: the scientific foundations of ethics and the moral responsibility of the scientist in the applications of science knowledge (Latouche, 1987: 7–16). Unless rationalized ethics boil down to "a simple adjustment variable leading to the implementation of certified ethical recommendations or opinions» (Dekeuwer et al., 2011: 125–131).

However, this community's awareness of ethical issues has long been dependent on the action of some of its illustrious members (Toulouse, 2016). It is also dispersed insofar as the notion of the scientific community must be understood more in the plural than in the singular. Medical ethics are very different from that of computer scientists or even that of physicists. Finally, a scientific community constitutes a vague sociological subject, not very homogeneous and evolving, which hardly allows the establishment of a readable and lasting normative system (Vergès, 2008: 131–149).

This is why it is necessary to turn to scientific institutions to try to better understand what are today the role of normative production in the field of ethics of science.

(b) **Scientific institutions: a place of normative production in science ethics - In the days of "pure science" ...**

If the idea of scientific objectivity led some to think of science as a "pure science", preserving its autonomy and epistemic purity, a less radical approach nevertheless admitted that science could be influenced by the social values of the moment but nevertheless believed that "the hard core of science remains characterized by neutrality and objectivity. Consequently, the organization of the scientific community depends on tacit values, but, in return, it guarantees standards (ethical and technical) necessary and specific to science" (Carvallo, 2019a, b: 299–326).

However, in the twenty-first century, the ethical questions posed by science are no longer limited to certain applications in some disciplines (research on humans, the use of nuclear energy for military purposes, genetic "manipulations"...). They are generalized and transversal, either by convergence of technologies (NBIC), or by questioning the organization and functioning of research through the institutions that regulate it.

In the Days of "Piloted Science"

This turning point will take off from the 1980s, which saw above all, with the techniques of assisted reproduction and the rise of human genetics, the emergence of an ethics of life sciences, "bioethics". But it continued by taking into account the environment and sustainable development, suggesting that the world and science can be governed by principles, such as "the precautionary principle" which can ensure us a better mastery of technology without irreversibly damage the environment and the biosphere.

Little by little, a new model of research "governance" was thus imposed, which required it to integrate an ethical dimension into its institutional practice, combining new standards and bodies, mainly ethics committees.

The interest of institutions in occupying the field of science ethics should lead us to reflect on the foundations and objectives of this integration of ethics into the very organization and functioning of research.

The Origins and Objectives of Institutional Ethics

The objectives which guide the establishment of an institutional ethics are intrinsically linked to what has become of science for our contemporary societies: the motor of their development, even of their existence, as much from a physical point of view as with regard to the meaning given to this existence.

(a) **A paradigm shifts (The origins)**

To put it simply: today we are experiencing a new revolution, both industrial and socio-cultural, that of a society that develops through technoscience - innovation through the applications of science - to the point of leading us to be at a rupture, a radical discontinuity of culture and civilization. (Bensaude-Vincent, 2009).

This observation leads to underline two essential keys necessary to understand which are the logics of influence which weigh on the institutional ethics and determine where their balance or their imbalance can lead us.

(b) **Various and even opposing foundations**

- The first of these foundations resides in the idea that since progress and catastrophe are "the obverse and the reverse of the same coin" (Ombrosi, 2006: 263–284), it is advisable to supervise research in order to maximize its advantages and minimize the risks.

The break certainly appears less radical with the idea of progress and its "deviations" (consumer society and a "philosophy" of "materialist hedonism"), but, in terms of the relationship between science and society, it does not. It is not less because it puts forward the question of sovereignties. Who of the States, which have often failed to make their citizens happy by controlling the economy and limiting liberties or emerging powers, such as GAFAM, nourished by a libertarian philosophy, will dominate the world of tomorrow? Certainly, technoscience questions who will be the new empires.

With regard to research institutions, this new logic places them in a situation where they are expected to « participate in a knowledge-based economy in which it plays a crucial role as a driver of innovation. It embodies epistemic values, such as consistency, simplicity, impartiality, etc., but also, henceforth, performance, efficiency and acceleration, which are reflected in the evaluation indicators of research » of which ethics is now an important dimension (Carvallo 2019a, b: 299–326).

> Ethics is therefore often conceived as a neutral instrument capable of rationalizing collective decisions in connection with an awareness by individuals of their responsibilities as actors in collective systems (Carvallo 2019a, b: 299).

– The second is the questioning, even the mistrust, which gives rise to what some analyze as a deviation of scientific practices and which, for them, would require giving the floor to citizens more widely. This movement, which developed during the 1980s in the field of bioethics, seems to find its voice at the beginning of the twenty-first century with the issue of climate change. Let us recall in this regard the doubts developed by certain theorists on the capacity of the democratic system to meet this expectation. Heidegger said: "It is for me today a decisive question of how one can in general correspond a political system to the age of technology and what system it could be. I don't know the answer to this question. I am not convinced that it is democracy" (Ferry, 2001: 68).
– The third foundation is the way in which scientists and their institutions welcome this appropriation of science through ethics and its institutionalization.

However, as Carvallo underlines (Carvallo 2019a, b: 318) "This new alliance between science and value is reflected in the facts: the evaluations of the ethics committees - for example in the biomedical fields - do not confine themselves not to ethical issues (consent, non-maleficence, confidentiality, etc.) but inextricably combine scientific and ethical considerations. Some criticize it in the name of an autonomy of science, others justify it by contesting the demarcation between science and ethics ".

This is why Toulouse (2000) is not afraid to say that the institutionalization of ethics is in fact essentially an alibi for scientists to maintain their hold on the regulation of research.

The question of the choice of the objectives given to the institutionalization of ethics then assumes all its interest.

The Objectives

Since the institutionalization of ethics is expected to facilitate the consecration of technoscience as a motor of innovation, this mode of governance aims at both internal objectives and management of research and development as well as its social impact because institutionalized ethics seem above all to be perceived by those responsible for public policies as a way of (r) establishing the relation of trust between society and public policies (Boisvert, 2011).

(a) **Internal objectives**

The internal objectives aim to ensure that, in addition to their professional capacities, researchers are able to meet the obligations of an ethical nature incumbent on them. The institution therefore supports the researcher so that he/she does not remain isolated and provides him/her with training to make him/her aware of how to articulate his/her practice in an ethical dimension.

Assist Professionals in Fulfilling Their Ethical Obligations

The diversity of the principles and standards which cover the field of professional practices constitutes the first enlightening element on the orientations that the institution wishes to give to the ethical process.

Scientific integrity being defined as "the set of rules and values that must govern research activity to guarantee its honest and scientifically rigorous character" will rather be seen as a normative process because "it is a code of professional conduct which must not be infringed" (Corvol & Maisonneuve, 2016: 8).

Conversely, the "stricto sensu" research ethics refers to a reflective approach on the values and purposes of research.

Another approach consists in emphasizing operational ethics, that of the field, as opposed to the ethics of social responsibility which would be more oriented towards societal questions.

Thus implemented, ethics, even internal, can have an approach more oriented towards the scientific community or, on the contrary, oriented towards society.

Training and Pedagogy

Ethics training and its pedagogy will then be essential vectors for integrating ethics into the professional process. They will make it either a method aimed at ensuring an inseparable link between research ethics and scientific integrity, or a formal constraint that must be fulfilled in order to preserve the image of the institution.

The objective is not illegitimate if it is not limited to making institutional ethics a quality certification process but emphasizes the importance of the link between internal objectives and external ones (Coutellec, 2019: 381–398).

(a) **External objectives**

These are of course those which concern people outside the scientific community, but it is also, indirectly, the very interest of this community that is involved.

Respect for Ethical Rules for the Benefit of Research Subjects and Patients

Ensuring the ethical interest of research protocols and the protection of the people who participate in them, as well as the discussion of ethical questions raised in clinical practice are undoubtedly for the general public the most telling aspects of everyday ethics. These examples show, moreover, how much the health system and social concerns are linked.

Integrate Social Values into the Development of Public Policies and Involve Citizens

The speed with which technoscience is radically transforming the way we live makes it necessary to find the means for a transition that is not too chaotic. For a long time, it was thought that this was only a matter of explanation, even of educating public opinion. But faced with the recent catastrophes of which man is, at least in part at the origin (the "mad cow" crisis, greenhouse gases, climate change), oppositions, sometimes violent, sometimes irrational, have developed and have led governments to take better account, for the elaboration of policies, of social values and modes of citizen participation in the process of their elaboration.

Preserve the Image and Credibility of Scientific Institutions

Science needs trust, but it must be reciprocal for the benefit of citizens as individuals and as a community. This is why the institutionalization of ethics cannot be only a question of image because ethics is not an advertising slogan, an alibi to continue to act as before.

It is also a reflection on how to organize scientific research institutionally: between what is private and what is public, in its management and financing methods ...

All these objectives have an undeniable legitimacy and have developed a dynamic conducive to the dissemination of ethics, in the form of certain models, in research organizations. However, as they are also part of public policies of an economic nature, won't these objectives make ethics lose its capacity for questioning, for "transgression"? The tension between these two approaches to ethics is real, but it is questionable whether an empirical analysis of the way in which the institutions in charge of ethics accomplish their mission is not likely to provide a more nuanced view on this question (Jolivet, 2018: 189).

How Do the Institutions Fulfill Their Ethical Mission?

The institutionalization of ethics is now one of the essential features of the ethical process. Developed from the 1980s in limited areas such as the use of new medical techniques and biomedical research in humans, it has since been extended to other sectors (genetics and biotechnology, health safety, environment, etc.). It is as much a legal requirement for certain scientific practices (biomedical research in humans) as it is a rule of good professional practice, which is reflected in the diversity, even the complexity of the network of institutions concerned. But above all, it integrates practitioners and researchers into a logic of procedural ethics at the expense of the ethics of reflection.

A Common Requirement Set Out by a Variety of Institutions

A Common Requirement

Although born from an ancient tradition, this requirement now seems to be based on a different logic.

(a) **A deeply rooted tradition**

This is the "old model" of a "scientific community (which) functions autonomously and (of) researchers (who) themselves determine their research subjects. An invisible hand guides the coordination of the activities of each scientist through mutual adjustments "(Bernatchez, 2010: 55–78). It is essentially through peer review that access to publication, resources and academic recognition is achieved (Polany, 1962: 54–73.).

An intellectual community rather than an institutional one, the world of science is perceived, except perhaps in medicine, as detached from the daily concerns of our societies and, so to speak, locked in its ivory tower.

As we have mentioned, the twentieth century upset this perception and subjected science to external influences for the benefit of States and their policies (Nazi Germany and the Soviet Union, for examples), in particular for purposes of war.

This common requirement now follows a different logic, that of globalization.

(b) **Another logic: globalization**

If the movement of May 1968 raised the question of knowing whether to destroy or rebuild the university (Bernard, 2003: 205–256; Bock, 1982), it is without doubt "the phenomenon of globalization, which reflects the emergence of a world market characterized by the planetary integration of trade and production" (Bernatchez, 2010), which has imposed the model of the economy of knowledge (Organization for Economic Co-Operation and Development (1982), New Forms of Cooperation and Communication Between Industry and the University, Paris, OECD).

The oil crisis of the 1970s also played its part in this change by encouraging developed States, whose traditional industries were in decline, to embark on a new industrial revolution aimed at giving economic applications to scientific research work.

Placing this transformation in a historical perspective, D. Pestre shows us that it highlights two radical evolutions. On the one hand, it is no longer, since the 1970s "physics which shapes the standards of " good science ". (It is) the bio-technosciences which have taken this place - sciences capable of recombining and to optimize the biological material, and therefore to remodel the human and nature" (Pestre 2013: 34–44).

On the other hand, "a new political and moral economy of knowledge has appeared in the last decades ... Politically, we have moved from a regulated universe within the framework of nations in Westphalian equilibrium by elected (or joint) bodies defining priorities - global, if not planetary, systems regulated in multiple

"governance" spaces by numerous actors and with varying democratic legitimacy" (Pestre 2013: 34–44).

Thus, "industrial research has freed itself from the territorial framework which remains, by definition, that of universities, and the location of this research is now defined on a world scale, according to potentialities and opportunities" (Pestre 2013: 34–44).

It is this diversity of governance spaces that reflects the organization of institutional ethics in the field of life sciences.

A Variety of Institutions

If the role of experts is dominant there, however, it is necessary to distinguish from the outset the institutions which develop macro ethics from those which contribute to case ethics. But it is also important to pay attention to the degree of autonomy of the ethical institution concerned.

(a) **Macro-ethics and case ethics (macro-ethics)**

As soon as the nature of the problems calls into question choices relating to human identity, our economic model (consumer society versus taking sustainable development into account), health or food security or other questions relating to social organization, "macro-ethics" interferes with "governance" and therefore poses a double question: that of the legitimacy of the institutions which formulate these policies, particularly in terms of democratic government, and that of their efficiency to produce an ethics of governance that each actor can appropriate.

At a time when there is a mistrust of science and experts, which is not always rational, how can we put in place a process of developing ethics that combines what is called "the civil society"?

Can education, debate, recourse to consensus or mediation be successful? Does the multiplicity of competing interests allow it?

At another level, that of globalization, which institutions are capable of assuming an international ethical function? Do the intergovernmental institutions (Council of Europe, European Union, OECD, WHO, UNESCO), whose adoption of programs and recommendations depend on the States, have all the necessary legitimacy? Should we create new committees with no direct link to interstate governance, such as the IPCC when it comes to climate change? Should we prefer judicial bodies like the European Court of Human Rights?

But then are we still in the field of ethics?

Micro-ethics

It appears more concrete and concerns us more directly when we or a parent requests the benefit of a new technology (ART, pre-implantation genetic screening), better protection of their rights (biomedical research)…

However, is it a means of creating a more human relationship in care or research, devoid of the need to provide evidence, to be better listened to?

And for the practitioner or the researcher does not this ethics place them under the influence of the ethics committees (Felices-Luna, 2016: 3–23) which lead them to abandon an ethics of reflection in favor of procedural ethics, the source of management based on the search for labeled, standardized quality?

But, the ethics committee, to the extent that it is the one belonging to the institution that requests it, that appoints its members and provides it with the means to operate, can it really operate in complete independence?

(a) **The degree of autonomy of the institutions in charge of ethics**

It is generally accepted that ethical comitology must meet a certain number of criteria in both its composition and its functioning. Thus, the independence of the members and the autonomy of the institution constitute, along with multidisciplinarity and pluralism, one of the important criteria for the credibility of these new bodies.

The Independence of Members

Independence has two aspects: the moral independence of each member who, in his analysis, reasoning and opinions, must reject all external influence and guard against influences created by habits. But there is also independence from institutional ties that can put him/her in a situation of conflict of interest. As with the judge, the member of an ethics committee must be impartial and appear so.

The method of appointing committee members is thus a good indicator of the independence of members; thus, a diversity of appointing authorities is a better guarantee of independence than an appointment by a single authority. But we must not neglect the strength of professional solidarity - many committees are still composed of peers - or the way of reasoning - an expert approaches questions in a different way from a layman or a politician, for example.

These logics of belonging thus lead to the question of the autonomy of the committees.

The Autonomy of the Committees

In this regard, there is an essential difference between committees constituted as truly independent authorities (this is the case for many national ethics committees) and committees which are internal to medical, scientific, academic, or even industrial, institutions. In this situation, it is not only the general interest that these committees must take into account, but they must also ensure that the institutions which mandated them can exercise their mission.

Moreover, the notion of autonomy does not have the same meaning depending on the powers available to the committee. In an advisory capacity, autonomy guarantees the committee's freedom of expression and the moral force of its opinions. If the committee participates in the decision-making process, it confers on it a responsibility, for which it must be accountable and procedures must exist for this purpose.

But, in either of these situations and undoubtedly with more force in the second, one must wonder whether the increasingly imperative need to seize an ethics committee will not reduce the ethical reflection. to a purely procedural question.

(a) **Towards ethical reductionism and its consequences?**

In rapid evolution, can bioethics be defined as a discipline like any other when the ethical questions posed by technical innovations in the field of life sciences require taking into account this context but also the diversity of social values that confront each other?

So, is bioethics just a relativism sacrificing reasoning and ethical values for the benefit of biomedicine by making procedural ethics prevail? Bioethics would then only be the observation of an impossible universal ethics in the face of the force of the pluralism of values! What would then be the consequences, in particular for the institutions responsible for putting bioethics into practice?

Is Procedural Ethics the Main Feature of Bioethics?

Ethics is the practical science of responsible behavior, good and evil would have said the classics. It deals with choices and decisions and the actions that result from them, especially when human values are either ignored or threatened.

But, what to do with the failure of ideologies and the rejection of imposed beliefs? Do the ethical pluralism and individualism of Western societies leave us any other choice than to organize a debate where the diversity of points of view can be expressed and be the subject of a critical analysis in broad daylight, where these points of view and their supporters will learn to coexist because in a democracy, which allows everyone the freedom to determine their way of life, it cannot be otherwise?

Questioning this observation of the impossibility for philosophy to fulfill its mission of founding a universal ethics, the philosopher Anne Fagot provides the

beginning of an answer: “our societies have accepted the pluralism of ethical opinions, ... they have made it into a value, under the title of “respect for differences“ and the development of a public space for critical discussion ... has created a gap between what is a matter of objective truth (the scientific data on which a rational consensus can be established) and this which is a matter of individual preferences” .

Thus emerges the path of procedural ethics which “postulates that in our morally plural societies, the only legitimate way to build common just standards is argued and egalitarian discussion between all interested parties leading to consensus” (Lazare Poamé, 2001: 409).

Procedural ethics emphasizes the method to be used to define the content of the standard rather than the standard itself. Nevertheless, understood as a mode of management of (good) practices in clinical biomedicine and in research, does not procedural ethics become an alibi which eludes ethical reflection?

The Reductionism of Procedural Ethics and Its Consequences

(a) **Ethics as a managerial way to integrate biomedicine into the new economy?**

The 1980s, by making technological development the new motor of the economy, brought the world of scientific research into a new era of market valuation (Bernatchez, 2010).

Biomedicine and biotechnologies have played an identical role, accentuating the economic dimension of the health market, especially since the doctor-patient relationship has been rebalanced in favor of the latter (Batifoulier, 2012: 155–174).

We are therefore entitled to wonder if ethics, in particular that implemented by the committees responsible for giving an opinion to this end on practices or research, has not become the guarantee that such and such a practice or research is compliant not only to the rules of the art but also to the legal standards and to the guidelines consensually adopted by the professionals concerned.

(b) **What remains of ethical reflection?**

Professor Didier Sicard, Honorary President of the French National Ethics Committee, goes in this direction when he writes: ““Is bioethics the new conformism of a rich society that likes to give itself shivers? “(Sicard, 2006). With regard more particularly to research ethics committees, Bernatchez (2010) observes that “Paradoxically, institutional research ethics committees scrutinize projects which request the contribution of human subjects in a perspective which most often falls short of any minimal risk, but evacuates those which lead to the production of death devices, if no human subject takes part in the experiment” .

Likewise, is it a coincidence that French researchers have obtained in 2012 to incorporate in the Human Experimentation Act a new mission for research ethics committees: that of giving an opinion for the publication of research work, with regard to observational research which are of non invasive for the human being?

This is why some authors ask the question: “Ethics becomes obligatory and the logic of the quality approach is applied to it. Is this compatible with the requirements of ethical reflection? As the quality approach imposes rationalization imperatives for better organizational efficiency, does not the ethical approach run the risk of being reduced to a simple adjustment value leading to the implementation of recommendations or certified ethical opinions? “ (Dekeuwer et al., 2011: 125–131).

For these authors, five effects of current procedures run counter to ethical reflection:

- ethics are more a matter of usual practice than of reflection;
- ethics are reduced to obedience to civil law;
- ethics are reduced to the application of a procedure;
- ethics are entrusted to experts or ethics professionals;
- By dint of being confronted with collective problems, ethics are reduced to misguided utilitarianism.

However, despite the problems it raises (the approach of Apel and Habermas, which favors a proceduralism with a universal aim, seems ill suited to providing solutions to concrete situations while the approach of Engelhardt, by insisting on the practice of peaceful negotiation, opens the way to modes of discussion that are not exclusively rational), procedural bioethics is a useful methodology for the functioning of ethics committees and can also make its contribution to finding solutions, at the very least. Less common values or references (Appel, 1994; Engelhardt, 1991; Habermas, 1992; Rawls, 1971).

Is it not then appropriate to “go beyond the semantic point of view to reach the pragmatic point of view, specific to procedural ethics? We can then understand how taking into account the pragmatic aspects of discursive interaction profoundly transforms the way we must think about the foundations and the meaning of ethics today. A procedural ethics is a discursive ethics because it is an ethics which takes note of the pragmatic constraints of the development of standards “ (Berten, 1994: 537–551).

Conclusion

Institutionalized bioethics is a reality that is already half a century old. Its development, even if it comes from different theoretical approaches, is mainly a pragmatic and empirical construction that responds to the needs of a society in transformation whose institutions and functioning are today largely based on the use of technoscience, especially in the biomedical field.

Characteristics specific to institutional bioethics were thus formed in connection with this context; it is:

– the multidimensional aspect: institutionalization now concerns all sectors of technoscience, micro-ethics and macro-ethics;

– the recourse to experts and to multidisciplinarity to affirm that what science and technology have given rise to as an ethical question, they can, through the play of knowledge, find ethical answers to them;
– the search for common objectives making it possible to recognize the pluralism of the values on which they are based;
– the international dimension because the global nature of certain bioethical questions deserves to provide answers by setting up bodies which are themselves international.

We could be satisfied with this situation by observing that "all are at least on a few common convictions close to Kant's morality, refusing in particular to treat man as a means. This leaves it to personal religions to give life to values which without them risk losing strength and depth. Finally, the institutionalization of bioethics took place in the context of multicultural societies in search of a secular ethics of consensus, but neither in the countries of North America nor in European countries has this led to want "to build a corpus of national morality immediately transportable in the terms of positive law", nor to set up the ethics committees in moral magisterium".

However, this history and consecration of institutional ethics still leaves unanswered questions that affect the capacity of our societies and their institutions to establish secular ethics. How to strike a balance between a procedural ethics of consensus and the risk of binding moral dogmas? How to establish democratic institutions adapted to technoscience without confusing what concerns public policies and what concerns moral choices? "Does such ethics applied from within institutions by 'experts' constitute a threat to democracy? Does it boil down to the instrumentalizations that can be made of it by the political powers? Does it risk being distorted by its recourse to a principist approach if the latter opens up to an ethics of discussion? Does it lead to the disqualification of other critical speeches, in particular political critics? "(Massé, 2019: 43–55).

Here are some of the questions that we must keep in mind if we do not want institutionalized bioethics to become the field of dead reflection on the future of humanity.

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Chapter 15
Institutional Review Board (IRB): US Perspectives

Maria I. Lapid, Yves Ouellette, Matthew T. Drake, and Bart L. Clarke

Abstract The institutional review board (IRB) is a federally mandated group instituted by the U.S. government to protect the rights and welfare of human subjects engaged in clinical research. Research involving human subjects, whether living individuals, data, or specimens, requires IRB approval and oversight prior to implementation. Investigators must conduct research in accordance with federal regulations, state and local laws, relevant policies and procedures, and ethical principles. IRBs provide oversight by reviewing and monitoring research to ensure research is conducted in a scientific, safe, and ethical manner and in compliance with research regulations. This chapter describes the role and purpose of the IRB in protecting the rights and welfare of human subjects in research in the United States, reviews federal regulatory standards relevant to IRB oversight, discusses research involving special populations, and comments on the non-research functions of the IRB.

Keywords Research ethics · Human subjects · Informed consent · Confidentiality · Research compliance · Participant rights

Introduction

Institutional Review Boards (IRBs) are an integral component of all regulated research performed with human subjects. IRBs oversee subject safety and ensure that research efforts are conducted within an ethical framework. As guidelines, rules and regulations have continued to evolve regarding human subjects research, the central role that IRBs play in providing oversight for increasingly complex studies has likewise continued to change and expand (Stark & Greene, 2016). In light of both regulatory changes and evolving societal expectations surrounding

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optimization and transparency of the consent process, investigative teams performing research involving human subjects have noted increasing confusion and frustration with what is frequently characterized as an ever-increasing regulatory burden associated with such studies (Breault, 2006; Lapid et al., 2019). In the face of such challenges, a solid understanding of the role for IRBs in both approving and providing continued oversight is needed by clinicians and scientists alike who engage in research involving human subjects.

Defining the Role and Purpose of Irbs

As defined by United States Food and Drug Administration (US FDA) regulations, an IRB is a group formally designated to both review and monitor biomedical research that involves human subjects (U.S. Food & Drug Administration, 2019b). In this role, an IRB is tasked with the authority to approve, disapprove, and require modification of human subjects research in order to protect the rights and welfare of research subjects. In assuming this role, an IRB is purposed with assuring both prior to the initiation of any research, and via periodic review of research studies that have already received IRB approval, that all appropriate safeguards are in place to adequately protect the rights and welfare of subjects involved in the research.

To understand the current role of IRBs in the regulatory oversight of human subjects research, it is useful to recognize the historical context that led to the current regulatory structure. The Tuskegee study included vulnerable African-American males afflicted by syphilis who were studied between 1932 and 1972 by the US Public Health Service and the Centers for Disease Control. Although treatment with penicillin was established as the standard of care for syphilis from 1947 onwards, subjects were misled into thinking that they were receiving medical care for their syphilis. Instead, subjects were simply followed in order for the researchers to document the natural history of the syphilitic infection (Gamble, 1997). The subsequent reporting and resultant outrage from this study ultimately resulted in congressional passage of the National Research Act of 1974. This legislation delineated US Health and Human Services polices for the provision of protection for all subjects of human research and resulted in the requirement for IRBs to review and approve all human subjects research conducted within the US.

IRB Composition and Performance of Administrative Tasks

The specific composition of an IRB is defined in US federal regulation 21 CFR 56.107 (U.S. Food & Drug Administration, 2020b). This regulation stipulates that each IRB must have a minimum of five members whose backgrounds must vary so

as to permit the complete and adequate review of research activities performed at the institution. It is expected that IRBs are composed of scientific reviewers from a variety of biomedical and behavioral backgrounds. In addition, each IRB must include at least one non-scientific member with limited or absent medical expertise, as well as at least one member who is not otherwise affiliated with the institution where the IRB is convened. Each IRB must also include staff who are appropriately trained to perform the activities of the IRB. Finally, US governmental statute notes that if an IRB routinely reviews research which includes vulnerable or protected subjects such as pregnant persons, children, prisoners, or subjects who are mentally or physical handicapped, specific efforts should be made to include within the IRB membership individuals who are knowledgeable of, and have experience working with, such subjects.

Diversity is an integral component of IRB composition, with numerous factors including gender, race, cultural backgrounds, and community attitudes which must be taken into consideration within the IRB membership. Such diversity is of fundamental importance for providing a wide range of expertise and experiences which extend beyond the scientific merits of each study. This diversity of disciplines and capacities is critical to ensuring human subjects research acceptability when viewed from societal, legal, and institutional perspectives.

From a practical perspective, IRBs are most commonly locally administered, although research that is conducted at multiple sites can sometimes utilize a single central IRB to provide either complete or partial regulatory study oversight. Given the complexity of human subjects research protections, local IRBs are most commonly housed within larger institutional human research subject protection programs, which function to coordinate the work of interrelated entities (see Fig. 15.1).

Although locally administered IRBs function within the larger institutional frameworks in which they are situated, from an administrative perspective they are by necessity independent of review from those same institutions. Accordingly, their decisions are final and independent of reversal by those institutions at which they are convened. In their review of research, IRBs must evaluate each study's compliance with ethical principles as described in US federal regulations, as well with as international guidelines regarding quality, safety, efficacy, and cross-cutting topics as categorized by the International Council for Harmonisation for Good Clinical Practice for studies which evaluate pharmaceuticals (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 2020). Individual IRBs can also receive voluntary accreditation from the Association for the Accreditation of Human Research Protection Programs (AAHRPP), which uses a set of pre-defined objective standards to independently evaluate the quality and level of protection provided to research subjects at an individual institution. Lastly, the US Department of Defense requires its own accreditation requirements when it provides funding for human subjects research.

Fig. 15.1 Human research protection program

Defining Human Subjects Research, Levels of Risk, and Levels of IRB Review

As defined, research is a systematic investigation, including research development, testing, and evaluation, that is designed to develop or contribute to generalizable knowledge (National Archives and Records Administration's Office of the Federal Register & Government Publishing Office, 2017). It is noteworthy that not all studies that involve humans are considered research. Thus, case reports that describe a single individual, public health surveillance activities conducted or authorized by a public health authority, the collection and analysis of information or biospecimens for a criminal justice agency as authorized for criminal investigative purposes, or activities to support intelligence, national security, or homeland defense are all collectively not considered to be research. Likewise, activities which are deemed to reflect 'quality improvement' that do not meet the definition of research as defined above are exempt from IRB review, even if the ultimate intention is to publish the results. However, quality improvement projects do require IRB review when the conducted work is considered to be human subjects research (Office for Human Research Protections, 2021e).

As delineated by the US Code of Federal Regulations, a human subject is defined as a living individual about whom an investigator conducting research obtains

information or biospecimens through intervention or interaction and uses, studies, or analyzes the information or biospecimens; or alternatively obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens (National Archives and Records Administration's Office of the Federal Register & Government Publishing Office, 2017). Human subjects research, therefore, is a systematic investigation of human subjects, be they living persons, data, or specimens. In their regulatory role, IRBs have the authority to determine whether a proposed activity is considered to be human subjects research.

Three levels of IRB review exist. They are primarily distinguished from one another based on the perceived level of potential risk to, and associated vulnerability of, the human subjects intended for study. These levels are: (1) exempt from IRB review; (2) expedited IRB review; and (3) fully convened IRB review.

Exempt from IRB review reflects that the proposed research meets the requirement for IRB exemption as specified in US federal regulation 45 CFR 46.101. Collectively, research categorized as exempt must involve either no risk or risk that is considered to be less than minimal risk to human subjects. It is notable that studies deemed to be exempt from IRB review do not require continued oversight unless the risk to subjects' changes as a result of changes in the research procedures. Both institutions and IRBs are required to have clear policies and procedures to identify the mechanism for making exemption decisions, with specific exemption categorization recorded and available for oversight and future auditing purposes as necessary (Office for Human Research Protections, 2021b).

Expedited IRB review is used when the proposed research involves no more than minimal risk to human subjects and is therefore eligible for IRB review via expedited procedures. The expedited review categorization is also appropriate when minor changes to research which has already received IRB approval is proposed, if the proposed changes do not alter the level of risk to subjects. Expedited review procedures may be performed by an IRB chairperson, or alternatively by an experienced IRB reviewer as designated by the IRB chairperson, with application of the same standards used for studies which receive full IRB review (Office for Human Research Protections, 2021d). As with all IRB decisions, clear documentation of the specific permissible categorization justifying the expedited review and evidence of the completed review are requisite. Collectively, judicious use of both the exempt and expedited IRB review categories can be helpful for streamlining IRB procedures without sacrificing any protection afforded to human research subjects.

Full IRB review is used when the proposed research is determined to involve greater than minimal risk to subjects, or involves research subjects from vulnerable or protected populations, and is therefore ineligible for other categorization (National Archives and Records Administration's Office of the Federal Register & Government Publishing Office, 2017). Such research is reviewed at a fully convened IRB meeting with appropriate member composition as detailed previously. It is noteworthy that the categorizations of *minimal risk* and *greater than minimal risk* are not always obvious to researchers. As defined, minimal risk generally means that the probability and magnitude of physical or psychological harm reasonably anticipated in the research are not greater than that ordinarily encountered in daily

life, or in routine medical or psychological examinations (National Archives and Records Administration's Office of the Federal Register & Government Publishing Office, 2017). Research that does not meet this definition, as well as any study that anticipates including either vulnerable or protected populations, is considered to be *greater than minimal risk* and must be reviewed by a fully convened IRB.

U.S. Federal Regulations and Human Subject Research

The U.S. Code of Federal Regulations (CFR) describes regulations for protection of human subjects during conduct of research in titles 21 (Food and Drugs) and 45 (Public Welfare) (Office for Human Research Protections, 2016a). Human subject protection regulations were first issued by the U.S. Department of Health, Education, and Welfare (DHEW) in the late 1970s based on the Belmont Report (Department of Health Education and Welfare, 1979), which described respect of persons, beneficence, and justice in the conduct of human research. The Belmont report was first published on September 30, 1978. In 1979 the DHEW was restructured to form the Department of Health and Human Services (DHHS) (U.S. Department of Health & Human Services, 2021) and Department of Education.

The U.S. Food and Drug Administration (FDA) is a federal agency of the DHHS charged with implementing the Federal Food, Drug, and Cosmetic Act passed by Congress in 1938 (U.S. Food & Drug Administration, 2018c). The FDA is responsible for protecting and promoting public health through control and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED), cosmetics, animal foods & feed, and veterinary products. Because local Institutional Review Boards (IRBs) frequently contacted the FDA for advice on how best to achieve comply with DHHS rules in the context of pharmaceutical research, the FDA consolidated the informal guidances it had given beginning in the late 1970s into a series of guidance documents including FDA "Information Sheets for Institutional Review Boards and Clinical Investigators" in 1984 (U.S. Food and Drug Administration, 2006). These information sheets were revised in 1995 and updated in 1998. In 2006, the FDA began an Information Sheet Guidance Initiative to rescind obsolete guidance, revise and reissue guidance that is current, and develop new guidance as needed.

The most recent FDA information sheets dated August 19, 2020, are intended to provide answers to frequently asked questions about human subject protection, informed consent, review of research, and related topics in an effort to help IRBs, clinical investigators, and sponsors ensure that the rights and welfare of human research subjects are protected (U.S. Food & Drug Admnistration, 1996). The information sheets describe IRB continuing review of research, sponsor-investigator-IRB interrelationships, subject recruitment, payments to study subjects, subject screening tests, and treatment use of investigational drugs.

The role of the FDA in regulating food and drug research is described in title 21 CFR1 parts 11 (Electronic Records and Electronic Signatures), 50 (Protection of Human Subjects), 54 (Financial Disclosure by Clinical Investigators), and 56 (Institutional Review Boards). Protection of Human Subjects, including the Common Rule, is described in title 45 CFR part 46. Title 45 CFR1 part 164 subpart E describes Health Information Portability and Accountability Act (HIPAA) enacted in 1996 and research. In addition, the FDA gives specific guidance on investigator and IRB responsibilities, and has a Bioresearch Monitoring Compliance Program.

The U.S. Office of Human Research Protections (OHRP) was created by the Secretary of Health and Human Services in 2000, and provides leadership in protecting the rights, welfare, and wellbeing of human subjects involved in research conducted or supported by the U.S. Department of Health and Human Services (DHHS), mostly through the National Institutes of Health (NIH). The U.S. OHRP is located within the Office of the Assistant Secretary of Health, within the Office of the Secretary of Health, and its main role is to implement the regulations given in 45 CFR 46. Institutions conducting research under DHHS regulations must obtain a Federal Wide Assurance (FWA) (Office for Human Research Protections, 2017a) that indicates they agree to ethical oversite by OHRP. OHRP gives guidance regarding unanticipated problems involving risks to subjects or others and adverse events, and the U.S. DHHS gives guidance on HIPAA privacy in research.

In most cases the U.S. FDA and OHRP guidances are in keeping with the 37 principles established by the World Medical Association Helsinki Declaration (World Medical Association, 2018) in 1964, and subsequently amended seven times through 2013. The Helsinki Declaration is a cornerstone document on human research ethics, yet not legally binding under international law. It draws its authority from the degree to which it has been codified in or influenced national or regional legislation and regulations. The fundamental principle is respect for the individual (Article 8), and the right to self-determination and right to make informed decisions (Articles 20–22), before and during the research. The investigator's duty is solely to the patient (Articles 2, 3 and 10) or volunteer (Articles 16, 18), and while there is always a need for research (Article 6), the subject's welfare must always take precedence over the interests of science and society (Article 5), and ethical considerations must always take precedence over laws and regulations (Article 9).

FDA-Regulated Drugs or Devices

FDA requires review and approval of all clinical research involving new or non-FDA-approved drugs or biologics. This requires submission of an Investigational New Drug (IND) application (U.S. Food & Drug Administration, 2021). Because some types of clinical investigations may be exempt from IND application requirements, this requirement may not apply to all new investigational products (U.S. Food & Drug Administration, 2015].

There are three types of Investigational New Drug application. These include the (1) Investigator IND submitted by a clinician investigator physician for use of a new investigational product, the (2) Emergency Use IND submitted for emergency use of an investigational agent in life-threatening situations without adequate time to file a full application, and the (3) Treatment IND for use of experimental drugs in the clinical setting and not in research. When submitting these applications, investigators commit to complying with all FDA regulations by signing an FDA Statement of Investigator Form 1572. This form states that the investigator acknowledges that non-compliance with FDA regulations will have serious consequences both for the investigator and the institution (U.S. Department of Health and Human Services, Food and Drug Administration, Office of Good Clinical Practice, Center for Drug Evaluation and Research (CDER), & Center fo Biologics Evaluation and Research (CBER), 2010).

A medical device is defined by the FDA as (1) an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes (U.S. Food & Drug Administration, 2018d). Significant risk devices have the potential to expose research subjects to serious risk when used as proposed in the research study. Investigational use of significant risk devices requires approval of an Investigational Device Exemption by the FDA before beginning the research. Non-significant risk devices do not require FDA Investigational Device Exemption approval, but the IRB giving oversight to the research must give a non-significant risk determination. Humanitarian Use Devices are unapproved medical devices used clinically for the benefit of patients with rare conditions with not more than 8000 patients affected in the U.S. each year. Use of Humanitarian Use Devices requires the manufacturer to request a Humanitarian Device Exemption from the FDA that allows the device to be marketed as a Humanitarian Use Device (U.S. Food & Drug Administration, 2017). Physicians using these devices must submit annual clinical progress reports to the local IRB giving oversight.

Compliance

Investigators must comply with research protocols as written to both minimize risk to subjects and protect their safety, and to adequately answer the research question(s) being asked. The investigational plan must be followed accurately, and deviations from the protocol, or reportable adverse events, must be reported in a timely manner

to the IRB and/or FDA. The report must include the investigator's determination of increased or decreased risk for subjects, as well as need for revisions to the consent form, requirement for subject reconsent, and any changes to the protocol to correct or prevent future adverse events.

Research non-compliance may be purposeful or non-purposeful failure to follow an approved research protocol, IRB requirements or decisions, or FDA or other federal regulations, state laws, local regulations, or institutional policies that were designed to protect human research subjects. Research non-compliance may be serious or non-serious and may involve major protocol violations or more minor deviations. Serious non-compliance can result in potential or actual harm to subjects, have a negative impact on study data integrity or validity, and compromise the institutional human research protection program. Continuing non-compliance is defined as an established pattern of multiple instances of investigator non-compliance. Protocol violations or deviations are any changes, or divergence or departure from the study design or research procedures that have not been approved by an IRB with oversight. Unanticipated problems are events that are unexpected, related, or possibly related to participation in the research, and places subjects or others at a greater risk of physical, psychological, economic, or social harm than was not previously known or recognized (Office for Human Research Protections, 2007). Unanticipated problems are required to be reported soon after the event, and may require significant protocol and/or consent form changes or corrective actions to ensure the safety, welfare, or rights of subjects or others. Failure to report these events in a timely fashion may result in a determination of research noncompliance. The most significant concern is with research non-compliance that is interpreted as both serious and continuing. IRBs are required to report this level of non-compliance to the FDA and/or Office for Human Research Protections depending on whether the study is FDA-regulated or not (Office for Human Research Protections, 2011).

The process for determining noncompliance varies across institutions or organizations. IRBs are required to have written policies and operational procedures that define serious and continuing noncompliance, with detailed description of the review process required, clear identification of the responsible person or group who makes noncompliance determinations, and reporting requirements to institutional officials, heads of departments or agencies, OHRP, and FDA (Office for Human Research Protections, 2016b). An analysis of 6511 incident reports received by the OHRP between January 1, 2008 and December 31, 2014 from 780 institutions showed that the most common type of event was serious noncompliance. The top two categories of serious and continuing noncompliance were changes in the research protocol without IRB review and approval, in which required study interventions were not performed, subjects were compensated more than described in the protocol, or inclusion or exclusion criteria were not adhered to, and informed consent issues, in which informed consent was not obtained prior to research, the informed consent document failed to describe risks of the research, or the informed consent document not signed by the subject prior to participation in research (Ramnath et al., 2016).

Revised Common Rule and Single IRB

The Common Rule is the policy described in Subpart A of 45 CFR 46 that gives fundamental guidelines for the ethics of all human research in the U.S. This Rule is based on the Belmont Report, created by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research, and published on September 30, 1978.2 The Common Rule provides additional protections for pregnant women, human fetuses, and neonates, prisoners, and children. The 2019 revised Common Rule required that NIH-funded multi-site clinical trials use a single IRB (sIRB) review process to enhance and streamline the review process and reduce variation in approval requirements set by multiple IRBs regarding human subject protections. Exceptions to this NIH policy are given for studies assessing career development, research training, or fellowship awards (National Institutes of Health (NIH), 2021).

The Common Rule is a federal policy regarding human subjects protection with main elements that include requirements for (1) research institutions to assure compliance, (2) researchers to obtain and document informed consent, and (3) IRB structure and function (Office for Human Research Protections, 2016a). The U.S. DHHS and 15 federal agencies and offices issued final revisions to the Common Rule in December 2017 to update and strengthen regulations to better protect human subjects in research, while reducing administrative burdens especially for low-risk research. The effective date of the revised Common Rule was January 21, 2019. Important changes in the final rule included a requirement that consent forms include a concise presentation of key information at the beginning of the document to help prospective subjects decide whether or not to participate in the research, as well as a requirement that multi-institutional research studies use a sIRB. The policy also required that studies obtain consent for use of identifiable data or biospecimens for future research, established new exempt research categories based on level of risk, removed continuing review for certain types of research studies, and required that certain federally-funded clinical trial consent forms be available publicly (Office for Human Research Protections, 2017b). Whether the sIRB policy and revised Common Rule will improve protection of human research subjects or reduce burden on investigators is an open question.

Research Involving Special Populations

Informed consent is a critical component of human subject protection in research. A valid informed consent requires that an individual is fully informed about the proposed research, has competence to make own decisions, and has voluntary participation (U.S. Food & Drug Administration, 2019a).

Vulnerable Populations

Generally, a vulnerable population is defined as a group of individuals that requires additional protection from potential risk when participating in research. Such individuals may be at a higher risk of negative outcomes when participating in a research study, they may have a reduced capacity or ability to give consent, or they may have special legal protections. The National Commission has issued three reports related to different vulnerable populations deserving of additional protections while participating in research These reports provide the basis for the additional protections incorporated into the Common Rule. In assessing research risk, IRBs must assess certain vulnerabilities using the categorical approach. Subparts B, C, and D to 45 CFR §46 assign specific protections to pregnant women, human fetuses and neonates, prisoners, and children respectively (Gordon, 2020). In addition, adults lacking to consent is a large vulnerable population. According to 45 CFR §46.111, the IRB must make the determination that additional safeguards be put in place to protect the rights and welfare of subjects who may be vulnerable are included in the study under review.

Subpart B: Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

It is recognized that research involving pregnant women is critically important to improve safety and outcomes. Pregnant women may experience illness and disease. The lack of adequate clinical evidence to make treatment decisions, both women and fetuses are subjected to risk of uncertain harms for uncertain benefits. A critical issue in conducting research with pregnant women is determining the acceptable level of research-associated risk to the fetus. IRB may approve research involving pregnant women or fetuses under 45CFR46 Subpart B (Mastroianni et al., 2017).

Subpart B is quite liberal for research offering the prospect of direct benefit to the pregnant woman, the fetus or both. In this situation, according to subpart B, the prospect of direct benefit is permitted if the risk to the fetus is "caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus" (45 CFR 46.204(b)) and the risk to the fetus is the "least possible" (45 CFR 46.204(c)) (Mastroianni et al., 2017). Research that has the prospect of direct benefit to the pregnant woman or the fetus is generally approvable even if greater than minimal risk when the other Subpart B requirements are also met. Consent of the pregnant woman alone is acceptable in this case unless the research has the prospect of direct benefit only for the fetus. If the direct benefit is only for the fetus, the consent of both the pregnant woman and the father is required unless the father is unable to provide consent. Reasons may include unavailability, incompetence, temporary incapacity, or the pregnancy resulted from rape or incest.

For trials that do not bring the prospect of direct benefit to either the woman or the fetus, IRBs have to insure that such a trial con pose no more than minimal risk

to the fetus and the "purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means." (45 CFR 46.204(b)). In trials where it is important to gain important biomedical knowledge enrollment of pregnant women maybe be needed. In such cases, the investigator must provide a justification in the protocol and the IRB must subsequently determine that the aim of gaining such knowledge cannot be achieved by enrolling only nonpregnant participants. Research involving pregnant women that is greater than minimal risk with no prospect of direct benefit to the pregnant woman or the fetus cannot be approved by the IRB.

Overall, subpart B allows broad support of research with pregnant women unless there is no direct benefit to the woman or to the fetus.

Subpart C: Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Prisoners participating as subjects in biomedical and behavioral are provided additional protection by Subpart C. Under such federal regulations, prisoners are considered a vulnerable population in need of special protection. A prisoner is defined as any individual who is "involuntarily confined or detained" (restricted from leaving the institution) in a penal institution (e.g., prison) having been under a criminal or civil statute, detained in other facilities which provide alternatives to criminal prosecution or incarceration or detained pending arraignment, trial or sentencing (45 CFR 46.303(c)) (Office for Human Research Protections, 2021f).

Non-exempt human subjects research involving prisoners must meet one of the 4 categories specified at §46.306. The first 2 categories include research that must present no more than minimal risk and not inconvenient to the subjects and that relate to the study of: possible causes, effects, and processes of incarceration, and of criminal behavior or prisons as institutional structures or of prisoners as incarcerated persons. The third category involves research on conditions affecting prisoners as a distinct population (for example, conditions that are much more prevalent in prisons than elsewhere or research on social and psychological that commonly affect prisoners such as such as drug addiction, alcoholism and sexual assaults). Studies in this category requires that the Secretary of Health and Human Services has consulted with experts including experts in prison medicine and ethics. The Secretary must publish an intent notice in the Federal Register to approve such research. Lastly, innovative research or research on accepted practices which may have reasonable probability of improving the health or well-being of the prisoners. Once again, the Secretary's office must provide appropriate oversight (45 CFR 46.306) (Office for Human Research Protections, 2021f).

Exempt research involving prisoners is not allowed in research approved under the pre-2018 Common Rule. Under the 2018 Common Rule research involving prisoners cannot be deemed exempt under 45 CFR 46.104(b), except for research

involving a broader subject population that only also includes prisoners (45 CFR 46.104(b)(2)) (Office for Human Research Protections, 2021c).

When investigators anticipate the participation of prisoners on the research, this intent must be indicated in the protocol and any safeguards for prisoner-subjects must be described. If a subject becomes incarcerated and the IRB and OHRP have not approved prisoner participation, the IRB must be immediately notified, and all research interventions must cease until IRB and OHRP approval have been obtained. However, if the investigator believes it is in the best interest of the subject to remain on study, the institutional IRB must promptly notify and permission obtained to continue activities needed to ensure the safety and welfare of the now prisoner-subject until the IRB and OHRP approval is obtained.

Regarding evaluating study risk, subpart C directs the IRB to ensure the advantage of participation do not undermine a subject's ability to appreciate and weigh risks of participating and that the risks are acceptable to a non-incarcerated population. To better protect prisoners from exploitation and coercion, subpart C review requires the IRB membership include a prisoner representative who has "appropriate background and experience to serve in this capacity" (45 CFR 46.304(b)) (Office for Human Research Protections, 2021f).

Subpart D: Additional Protections for Children Involved as Subjects in Research

This section briefly reviews the existing pediatric research federal regulations. Children are considered vulnerable when involved in research since they cannot protect their own interests. Children as a vulnerable population have special protection under U.S. federal regulation when involved in research. Investigators must pay special attention to the additional provisions at 21 CFR 50 (U.S. Food & Drug Administration, 2020a) and subpart D 45 CFR 46 (Office for Human Research Protections, 2021g) that provide additional protection when children are included in research. Children are defined as subjects "who have not attained the legal age for consent to treatment or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted" (Rose, 2017).

IRBs may approve research involving children only if it fits into one of three categories. A fourth category requires the approval of the Secretary of the Department of Health and Human Services (Office for Human Research Protections, 2021g). The three categories are as follows:

- Research not involving greater than minimal risk (21 CFR 50.51, 45 CFR 46.404)
- Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects (21 CFR 50.52, 45 CFR46.405)
- Research involving greater than minimal risk and offering no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the disorder or condition. (Note that the level of risk in this section is capped at "no more than a minor increase over minimal") (21 CFR 50.53, 45 CFR46.406)

46.404: Minimal Risk

Despite federal regulatory definitions, it is challenging for IRBs to define minimal risk as it applies to children and controversy remains. Minimal risk is defined as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" (U.S. Food & Drug Administration, 2020a). When the risks of the research are found to be no greater than minimal, any child may participate. Consent of a single parent and assent of the child (if applicable) are required for research approved under §46.404.

46.405: Greater Than Minimal Risk with a Prospect for Direct Benefit

The definition of direct benefit to subjects is generally defined as benefit obtained from receiving the medical intervention being studied. Research is determined to offer a prospect for direct benefit when there is a reasonable expectation based on previous research or pre-clinical data that participants will receive a meaningful, clinical benefit. The risk-benefit ration must be as favorable to the child as any available alternative approaches (45 CFR 46.405, 21 CFR 50.52). The IRB must assess that the evidence about a potential beneficial effect is sufficient. Regulations state that direct benefit is assessed at the level of each intervention or procedure in the research protocol. Any intervention or procedure that does not offer a prospect of direct benefit must not exceed a "minor increase over minimal risk" (45 CFR 46.406, 21 CFR 50.53) (Office for Human Research Protections, 2021a). As it is in minimal risk research, consent of a single parent and assent of the child (if applicable) are required for research approved under §46.405.

46.406: Greater Than Minimal Risk Without Prospect for Direct Benefit

IRBs can approve research activity that is purely for research purposes and is not for the participants' direct benefit if the risks are minimally increased over what is consider minimal risk. As discussed before, the meaning of the definition of minimal risk is controversial and the definition of minor increase is also controversial. The investigator has the responsibility to provide as much information as possible to the IRB about all possible harms from the procedure or intervention. This category of research can only be conducted in children with the disease or condition that is being researched. Children are consented to this research for because of benefit to

society or for aspirational benefit and to benefit future patients. Provision under §46.406 allow this provided that the prospective participants had the disease or condition targeted for drug development and the risks were a minor increase above minimal.

Consent of both parents and assent of the child (if applicable) are required for research approved under §46.406. In situations where one parent is not reasonably available, the consent of a single parent may suffice (Rose, 2017).

Requirements for Consent and Assent

Assent means that the child agrees to participate in research. Assent should not be deemed obtained simply because the child does not to object, absent affirmative agreement. Consent means the agreement of parent(s) to the research participation of their child. The regulations at 45 CFR §46.408 (Office for Human Research Protections, 2021g) includes the requirements for obtaining or waiving parental permission and assent of child participants. §408(a) defines when assent of children will be required and when it can be waived. The requirement of assent can be waived if either the child is not capable when the study holds out the prospect for direct benefit or the research meets the requirements as waiver of consent.

According to §46.408 "in determining whether children are capable of providing assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved" (Office for Human Research Protections, 2021g). The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research recommended that the assent of a child be required when they are 7 year of age or older (Jonsen, 1978). There are no federal regulations do not indicate an age at which assent is deemed appropriate. The assent process should be developmentally appropriate based on age and capability of the child to understand the information provided (Rose, 2017).

Research Involving Individuals with Impaired Decision-Making

In situations when an adult does not have the capacity to consent to participate in research then consent must be obtained from their legally authorized representative (LAR). Most adults with diminished capacity impaired neurological function usually associated with conditions such as congenital disorders, trauma progressive disorders or developmental disorders such as autism, intellectual disability, autism, or other. A plan must be developed by the investigator to assess whether the prospective adult subject has the capacity to consent. In a situation where they do not, the investigator must determine who is the designated LAR who can consent on the

adult's behalf. The November 30, 2006 Act 169 on Advanced Directives defines which adult has the capacity to consent to treatment and which are incompetent (Pennsylvania General Assembly, 2006).

Many individuals who are defined as incompetent can still retain the capacity to consent to research. For example, an incompetent adult may lack the ability to manage the complexity related to their health care or manage their daily affairs. However, they may have the ability to understand the elements of consent for a minimal risk research study, such as one involving a questionnaire or a simple blood draw. Such an individual might not have the capacity to comprehend a more complex randomized trial. They might have the capacity to understand enough to assent to their own participation once their LAR has consented for them to take part. Ultimately the investigator has the responsibility of ensuring that all LARs of subjects understands the elements of the research and can provide informed consent.

The 2018 Common Rule continues to require that possible vulnerable subjects have safeguards must be included to protect their rights and welfare against coercion or undue influence (45 CFR 46.111(b)) (Office for Human Research Protections, 2021c). As stated in Federal regulations, the issues involve minimization of risk and appropriate risk-benefit relationship under 21 CFR 56.111(a)(1) and (a)(2), equitable selection of subjects under 21 CFR 56.111(a)(3), protection of vulnerable subjects under 21 CFR 56.111(b), and informed consent under 21 CFR 50.52. However, the definition of vulnerability is not clearly stated in the regulations and instead provide examples that include "children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons."

In determining the capacity of the individual to consent to participate in research, a critical factor is the level of impairment of the potential research participant. Since the impairment may be full/severe or partial/minor, it may also be transitory or permanent. The investigator must presume that an individual has the capacity of decision-making unless it has been documented in the individual's medical record by an appropriately trained practitioner that the individual lacks capacity of decision-making or that a court of law has ruled the individual to be incompetent. An assessment of the capacity to consent allows a researcher to determine whether a subject has the appropriate functional capacity to consent (Biros, 2018).

Investigators and IRBs need to be clear about what process is in place to determine the capacity to consent. The assessment of a person's abilities to comprehend the information provided in the consent form and to make a reasonable choice based on that information is crucial evidence for the assessment of whether the person has the competency to provide informed consent. Procedure to assess these abilities need to be included in the protocols for studies that enroll individuals with decisional impairment and the process for making that determination should be outlined the process in the IRB application.

Prospective Assessment of Occurrence of Suicidal Ideation and Behavior in Clinical Trials

Prospective assessments of suicidal ideation and behavior should be carried out in all clinical trials involving investigational new drugs and biologics being developed for any psychiatric indication, antiepileptic drugs, and any drug with central nervous system (CNS) activity (U.S. Food & Drug Administration, 2018b). The risk of suicide has long been recognized to be associated with antidepressant medications, which led to an evaluation by the FDA to investigate the relationship between antidepressant medication usage and increased suicidal ideation and behavior (SIB). There are other drugs that have been identified to have possible suicidality risks, including, including isotretinoin and other tretinoin, beta blockers, reserpine, smoking cessation drugs, and weight loss drugs (U.S. Food & Drug Administration, 2018b).

There is a guidance for these prospective assessments from the FDA in the outpatient and inpatient settings, and in phase 1 trials involving healthy volunteers (U.S. Food & Drug Administration, 2018b). The objective is to identify individuals who are at risk for suicide and ensure their safety. Investigators must have a safety plan that describes how positive responses to suicidality are identified and managed in a timely manner. In some populations where assessing for suicidality would be difficult, such as those with cognitive impairment, critical illness, or children with no concept of death, suicidal assessment is not required (U.S. Food & Drug Administration, 2018b).

The Columbia-Suicide Severity Rating Scale (C-SSRS) (The Columbia Lighthouse Project, 2021) is one of the instruments recommended by the FDA to assess suicidal ideation and behavior that includes 5 levels of suicidal ideation (passive; active: nonspecific (no method, intent, or plan); active: method, but no intent or plan; active: method and intent, but no plan; active: method, intent, and plan), 5 levels of suicidal behavior (completed suicide; suicide attempt; interrupted attempt; aborted attempt; preparatory actions toward imminent suicidal behaviors), and the category self-injurious behavior, no suicidal intent.

Clinical trial sites covered under this FDA guidance indicated in a survey that investigators viewed prospective assessment of suicidality viewed positively (Stewart et al., 2013). An internet-based survey of clinical trial sponsors (industry employees and pharmaceutical companies) on approaches and challenges in the prospective assessment of suicidal ideation and behavior report a high rate of implementation in central nervous system studies, most use the C-SSRS, and frequent challenges on standardized assessments and summarizing and analyzing data (Chappell et al., 2014). In general, although there are implementation challenges, prospective assessment of suicidality is used for many indications and is perceived as contributing to patient safety.

Non-research IRB Functions

Investigational products or devices that are non-FDA approved can be used to treat individuals or groups outside of a research study under a treatment IND or IDE in special circumstances such as a life-threatening emergency or a treatment-refractory conditions for the benefit of the patient (U.S. Food & Drug Admnistration, 1996). Even though not research, the approval and oversight are responsibilities of the IRB with the goal of protecting patients who are vulnerable to exploitation. When used as a treatment for serious or life-threatening emergency, the investigational drug or device may be given to a patient prior to IRB approval if there are no other alternative treatment options and if there is a concurrence from another clinician who is not involved with the care of the patient, and an IRB Chair. The investigator is required to submit the treatment protocol to the IRB within 5 days after the test article is used.

Another mechanism that allows patients to receive investigational treatment outside of research is the Right to Try Act. This is a federal law signed in 2018 allows patients with terminal illnesses who have exhausted approved treatment options and unable to participate in a clinical trial to use unapproved experimental drugs and biologics that have completed phase 1 testing (One Hundred Fifteenth Congress of the United States of America, 2018; U.S. Food & Drug Administration, 2020c). This federal law does not include devices. Individual requests for Right to Try Act do not require IRB approval but requires a written informed consent from the patient obtained by the treating physician (U.S. Food & Drug Administration, 2020c). Unlike the IND process, the Right to Try Act requests are not reviewed by the FDA. This means that the FDA has not determined whether the investigational drug or biologic products are safe or effective (U.S. Food & Drug Administration, 2018a). Under the new law the FDA collects yearly reports from sponsors, however the reporting requirements are not clear at this time. In general there is a poor understanding of how the pathway works, successful requests are limited, and cost is a significant barrier for patients (Snyder et al., 2020).

Summary

This chapter describes the role of the IRB in protecting the rights and welfare of human subjects in research in the United States. Investigators must be knowledgeable with federal regulations, ethical principles, and local and international policies and procedures relevant to the protection of human subjects in research. Local IRBs are an excellent source of federal, state, and local regulations and policies and the changes in these that occur constantly. It is a must for investigators to conduct human subject research is a scientific, safe and ethical manner that is in compliance with research regulations.

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Chapter 16
Decision Making Within Institutions

Laura Palazzani and Carlo Casonato

Abstract The aim of the Committee's discussions is to contribute to giving the conceptual instruments to those in governments and to society, in a broad sense, so as to understand the complex, dynamic, changeable ethical issues and their importance and urgency, envisaging the possible scenarios and lines of action in social policies to be undertaken at public level. These lines of action should attempt, through the search for an ethical balance, to reconcile the needs of science and technology to progress with the protection of human beings, health, environment, and future generations. In this way, ethics committees play a key role in developing and implementing institutional ethics.

Keywords Bioethics committees · Decision making · Ethics · Institutional ethics · Science and technology

Bioethics Committees as Main Actors of Institutional Ethics: Roles, Functions, Approaches, Processes

Bioethics has become an institutional reality in every country of the world, and it is a fact that National Committees have been set up in several countries all over the world. The existence and increasingly intense activity of these Committees is tangible proof of the expansion and vitality of bioethics, and of the 'institutionalization' of ethics (There is abundant literature on the topic. See, for instance, the attention paid to the variety of bioethical approaches considered in the journal *Developing World Bioethics*. A general overview in Köhler et al., 2021; Moon, 2019).

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Despite the differences in the various experiences, it is possible to find a common definition of Bioethics Committees. They can be defined as a group of individuals who are committed to working together towards common goals, of public interest, in the field of bioethics. Relentless scientific-technological progress continues and will continue to raise new issues and questions in the context of ethics. Along with the 'classical' problems of bioethics (such as the beginning and the end of life), new issues are constantly appearing (neurosciences, brain-computer interface, synthetic biology, enhancement, biometry, nanotechnologies, telemedicine, artificial intelligence, robotics, etc.) (Ten Have et al., 2011).

The role and function of the Committees consists therefore in the difficult and delicate task, in the context of an interdisciplinary and pluralistic discussion, of finding an ethical mediation in order to advise governments (on possible regulation) and inform society. A role which addresses the relationship between science and technology, on the one hand, and society and government, on the other; an institutional role which must be reflected in the functioning and decision-making process of the Committees (Among others, Syväterä & Qadir, 2015).

The task of the ethical mediation (or institutionalization) is developed at various levels: a descriptive level, a dialogical-dialectical level, and, when possible, an advisory level.

(i) At a first level, the Committees usually describe emerging issues: the description is generally complex and requires both interdisciplinary discussion and specialist knowledge. The scientific and bioethical literature is now very extensive and difficult to control even by experts in the various disciplines. Therefore, within the Committees a great amount of work is done in study, research, in-depth analysis and constant updating, taking advantage of internal and external competencies. For this reason, from a functioning point of view, the decision-making process is usually supported by the common practice of holding hearings with experts from different disciplines.
(ii) At a dialogical-dialectical level, Committees represent a place for discussion, which is indispensable given the pluralism characterising today's societies and debate at a theoretical level. This pluralism is manifested both at scientific and ethical level. As a matter of fact, even in a scientific context quite often there is not just one single interpretation of phenomena. And the experience of the fight against Covid-19 has shown us how divided science can be, especially in the early and more uncertain stages of a certain situation. Coming to ethics, we know we live in the post-modern fragmentation of ethics, as different theories justify different values and principles to be applied, with different practical implications.

This is the primary task and the most important in the perspective of a pluralist and respectful construction of institutional ethics. From this point of view, it is necessary for the composition of the committees to be representative of all the main cultural positions in the country, and for the decision-making process to allow appropriate discussion times and means of participation for minority opinions. While these measures may complicate the decision-making process, they allow for

a full and comprehensive debate, upstream, and for a widespread recognition of the solutions reached, downstream.

(iii) The third aim of committees is, when possible, to elaborate common recommendations in order to give scientifically grounded, socially sustainable, and ethically justified advice for policymaking and regulation. Many committees have thus been recognised a specific function of suggesting to political decision-makers the most suitable balances on which to base legal regulations. However, not many committees have an ad hoc institutional channel to reach the official places of political and regulatory decision-making.

In carrying out their functions, the committees generally follow two different approaches (Palazzani, 2012; Neri, 2011).

(A) The first is the so called 'prescriptive' approach according to which the duty of the Committee is to express a majority opinion (and only one), through a voting procedure among different positions. In this perspective, the Committee's role is above all to exercise its *auctoritas* on the recipients of its Opinions (governments and citizens). The underlying *prescriptive* nature of the Opinions differentiates the reports drafted by the Committee from the documents produced by individual experts or centres, whose elaborations would instead be 'without *institutional recipient*'. The prescriptive role is defended by some scholars as necessary, in order not to limit the role of the Committee to the legimisation of the facts or values described.

(B) The second approach is called 'descriptive' and emphasizes the Committee's proactive role in raising awareness and sensitivity on specific issues among the general public and at the political level. In this perspective, Opinions explain at length all relevant aspects of the selected topic, pointing out in an impartial and fully representative way the scientific and ethical standpoints highlighted within the Committee, as well as outside of it and in society as a whole. According to this approach, there is no need to draw up additional final reports underscoring the contrast between majority and minority positions and the winning opinion. Although the 'descriptive paradigm' may produce a lower degree of certainty, there is an important theoretical option underlying it: ethics hinges upon rational rules and rationality in complex situations does not necessarily lead to one single solution. Instead, it may acknowledge 'equal dignity' to a number of different bioethical positions.

The Committee may choose one single approach or both, also depending on the actual situation and the topics discussed. There may also be an alternation of the descriptive approach with the prescriptive approach. And this methodology, which has great theoretical relevance, should be discussed within Committees, and may be defined in the internal rules of procedures.

Whatever the approach chosen, the discussion needs to be dialogical. Dialogue can only be realised in the exchange of rational opinions: justifying one's own position and letting others justify theirs; listening to and understanding the argument of others, so as to put one's own standpoint to the test, and verifying its consistency. In

this sense, the discussion makes it possible to interpret the principles and values of reference in the specific context, in the particular situation, critically questioning the standpoints at stake. Coming to the decision-making process, it is important that the rules of procedures contain specific measures to implement the dialogical perspective, and that the Presidency of the Committee closely monitors the whole procedure accordingly.

In terms of methodology, an ethical balance is achieved, at national and international levels, through a constant exchange of insights with regard to the theories and arguments held by others. This interdisciplinary and pluralistic approach succeeds insofar as every ethical concept has been adequately and consistently articulated and justified. The decision-making process must ensure that committee members are aware of the existing constraints and problems, and, as much as possible, are prepared to consider the arguments of others through the dialectical and dialogical dimension.

The most difficult and delicate part of a Committee's work concerns opinion sharing and the (joint) effort to search for common ground: to see to what extent one's own rationally justified position is shared by others, from different and even opposing standpoints. It is not a question of reaching a compromise, but rather a mediation, or better, a shared position. It may also entail partially giving up the 'maximum' expression of one's own theory to find common ground, avoiding irreconcilable conflicts, as far as possible (See, for instance, Moreno, Jonathan D. (1995). *Deciding Together: Bioethics and Moral Consensus*. Oxford University Press). This result is not always possible to achieve, but internal rules may provide useful tools to do so. For instance, minority group members are usually entitled to make personal declarations and comments, and to express integrative declarations, personal remarks, or concurring and dissenting positions, which are considered and published as part of the Opinion.

The aim of the Committee's discussions is to elaborate Opinions and Documents that can contribute to giving the conceptual instruments to those in government and to society in a broad sense so as to understand the often complex, dynamic, ever-changing issues, their importance and urgency, outlining the possible scenarios and lines of action in social policies to be undertaken at public level. These lines of action must seek a balance between the needs of science and technology to progress and the protection of human beings, as well as non-human beings (animals, plants and the entire environment).

Society needs to know the problems, acquire information in order to develop a critical awareness that may provide valuable orientation when faced with difficult choices in the application of new scientific discoveries and technologies: the importance of civic participation in debate on the ethical issues of biotechnologies is increasingly felt, and it is achieved, in some cases, through the direct participation of citizens' representatives in the committees. And in some cases, the representatives of a selected number of associations are *ex officio* members of the committee (In general, Kenyon et al., 2020).

Notwithstanding existing differences in establishment, nature and structural configuration, ethics and bioethics Committees play a key role, both at national and

international levels, providing scientific updates, and engaging in interdisciplinary discussion and ethical-legal analysis.

Another key role of Ethical Committees involves dealing with public engagement. In this perspective, Committees have also to display openness to society, by means of adequate dissemination of information, while, at the same time, undertaking consultation and monitoring expectations, as well as emerging concerns. Today, the role of 'active citizenship' is growing in importance, along with the need to build institutional platforms for dialogue and an interdisciplinary approach to pluralist discussion, which enable dynamic updating and active interaction between experts of new technologies and citizens (Gutmann & Thompson, 1997).

The purpose of this interaction is to adequately inform and educate citizens (the so called 'technological and scientific literacy' or 'citizen science': Among others, Vesterinen et al., 2016), alongside trying, on the one hand, to prevent an irrational fear of novelty in science and, on the other, a blind and uncritical trust, as both attitudes are emotional, non-reflective and inadequately justified. The goal focuses on raising social awareness and sensitivity, while enabling citizens to develop a critical consciousness, in order to ensure their participation and active involvement in ethical reflections on technological and scientific development, drawing up 'biolaws' and policy-making decisions.

The International and Intercultural Dialogue: Global Institutionalised Ethics?

While at national level the Committees were mainly created to analyse the problems in a specific way with respect to the social, moral, and legal context of reference, the need for internationalisation is increasingly felt. This need is expressed at different levels and in different modalities.

The need to pursue dialogue among cultures in the discussion on the diversities of the issues and contexts is becoming more and more evident, both in the internal and external discussion. There is an extreme variety of bioethical questions and answers in different cultures: the varying level of development and awareness of scientific knowledge in biomedicine raises different issues and nevertheless establishes a different priority in the urgency of solutions. The heterogeneous theoretical and practical context of the numerous cultures (beliefs, philosophical and religious concepts, values and principles, traditions, habits and customs), but also the peculiar way of the relating of cultures to technological and scientific innovation, besides the specificity of the political-legal-social context, undoubtedly constitute a powerful factor of diversification (most recently, Gielen, 2020).

Speaking about inter-cultural bioethics does not mean assimilation of minority cultures into the culture that is considered dominant, exposing to the risk of bioethical paternalism, and possible exploitation. Nor does it entail equivalence between the various cultures each keeping their own beliefs and customs as a 'right to be

different' and right to their own cultural identity without any limitations, being all relatively considered at the same level, tolerating any bioethics with no critical filter. This position may lead to beliefs or customs which contravene human rights. The objective is instead to foster the formation process of an inter-cultural bioethics that is able to create a place for discussion in the effort to integrate and accommodate diversities aiming to draft shared documents that highlight the commitment to seek common lines of thought at a wide level.

This is important both on a global level, given the ethical problems emerging in bioethics (genetic modifications, environment, pandemic etc.) and on the national or continental level, given our multicultural societies, where it appears increasingly evident that the beneficiaries of the treatment and use of the recent scientific technologies, but also the doctors and healthcare professionals using them, are individuals who, even though living together in the same social reality, often have different cultural roots, resulting in also different concepts of life, birth, pain, death, health and illness.

International bioethics also expresses the need for cooperation between high, low- and middle-income countries so as to guarantee equity in a dimension that gets away from localisms and considers the right to the protection of health as a universal human right. In this sense, it is possible to think of and realise a distribution of healthcare resources that can, in a common way, contemplate the applications of an inter-state and intercontinental justice. It is common knowledge that what characterises the world situation is the existence of a sufficient quantity of goods to meet the basic needs of everyone (with regard to survival and health) but they are distributed unequally (Data are collected by OECD Income (IDD) and Wealth (WDD) Distribution Databases: https://www.oecd.org/social/income-distribution-database.htm). There is therefore the awareness of a 'global injustice' and the need to enlarge the concept of health and the right to the protection of health in a dimension that goes beyond localisms and nationalism.

There is growing awareness that solutions to bioethical issues arising in one culture often have external implications, immediate or future, direct or indirect, with respect to the specific historical and social conditions out of which they were born. Sometimes, the range of impact is as wide as to embrace the whole planet and the future generations. Therefore, the need arises for a macro bioethics, enlarged in space (among cultures, States and Continents) and in time (among generations, the next and future generations): an international, intercultural and intergenerational bioethics.

Transnational and intercultural bioethical dialogue is developing the perception of the need, in a number of particularly urgent bioethical areas (such as environmental issues and the pandemic), to formulate a response that is effective and global and which will safeguard fundamental human rights of all citizens.

A case in point is the global coverage of Covid-19 vaccines and treatments. In the face of pre-ordered vaccines and storing by the wealthiest individual States, there has been a strong voice at international level (Unaids, WHO, Unesco, among others. See, for instance, https://en.unesco.org/news/unesco-calls-covid-19-vaccines-be-considered-global-public-good.) in favour of a more equitable

production and distribution of these vaccines. Specifically, the proposal to use the safeguard and flexibility clauses in the WTO Doha Declaration on the TRIPS Agreement in order to permit access to treatment and vaccine for all, and to ensure open access and the worldwide sharing of all Covid-19 related knowledge, data and technologies. It has also been proposed to establish a global and equitable manufacturing and distribution plan for treatment and vaccine against Covid-19, with transparent costs and supplies according to need, providing vaccines, tests and treatments free of charge to the most vulnerable people and poor countries.

In similar perspectives and many other angles, many international bioethics committees have come to play a key role. It is worth mentioning, among others, the International Bioethics Committee (IBC), the Intergovernmental Bioethics Committee (IGBC) and the World Commission for the Ethics of Scientific Knowledge and New Technologies (COMEST) at Unesco (See, among others, Langlois, 2013), and the Department of Ethics at the World Health Organization. In the specific perspective of this work, particularly noteworthy is that the statutes of these bodies provide for a very diverse composition, and for internal rules designed in order to give voice, directly or indirectly, to the highest number of cultures. Accordingly, the selection of members is made taking into great account cultural diversity and a balanced geographical representation (Friele, 2003). The statutes and rule of procedure typically design a decision-making process that guarantees appropriate consultations with all the parties concerned, particularly vulnerable groups: in addition to participants, it is common for observers to participate in the discussions, without voting rights. In order to reach a common (institutional) position on the ethical issues at stake, the different organizations usually endeavour to arrive at their decisions by consensus.

In addition to international committees, there is also a number of regional bodies, following similar rules. In Europe, we can remember the European Group on Ethics in Science and New Technologies (EGE) at the European Commission, the Bioethics Committee (DH-BIO) at the Council of Europe. And many National Bioethics Committees have started to pay more and more attention to global issues and to the ultra-national impact of their positions.

The Governance of Techno-science: New Challenges for Institutional Ethics?

Today we are facing a 'new technological wave'. The unprecedented characteristics of techno-science can be identified in the speed of development. The rapid expansion and dynamic evolution of techno-science in different sectors produces uncertain, unpredictable, and complex outcomes, with the consequent necessary need to rethink the traditional categories of risk assessment and management.

The *blurring* of the boundaries of application, often not clear and distinct as in the past, due to the convergent combination of different technologies (the traditional

distinction between the medical and non-medical sphere, health and well-being, research and treatment, current health and prediction of future risk, therapy and enhancement, etc.) or even the 'breaking' of the boundaries when the technologies developed for a purpose are used and applied in completely different contexts from those originally conceived (from the health context to the non-medical one, e.g. recreational or domestic, from civil to military and so on), is just one of the main novelties. This situation produces the so called 'disruptive transformative potential' of the impact of techno-science in society, and on political, economic, and cultural aspects. And with it, also comes the *pervasiveness*, especially in the digital sphere and in the deployment of artificial intelligent, due to the massive amount of information that infiltrates everyday life, along with *persuasiveness*, with a potentially increasing influence on individual and collective choices and behaviours.

In the face of these new characteristics of techno-science, experts on interdisciplinary and pluralistic bases, specialized in particular in the new fields under analysis, are required, especially in the arena of institutionalized ethics. The involvement of society and inclusion of the public perception of developments in science, articulated within the various cultures and social contexts through consultation, public debates, and participation are becoming more and more urgent.

The role of the various mentioned Committees, in this context, is becoming also an anticipation of the scenarios of techno-science innovation. 'Soft laws' and governance is taking the place of 'hard law', with several advantages: speeding up processing (shortening the length of the traditional law-making process), flexibility and the possibility of revision (compared to the rigidity of laws). This makes it possible to anticipate the imaginative projection which identifies potential and probable future scenarios (both in the near and distant future), the possible positive and negative implications of today's and tomorrow's technologies, guaranteeing an easier modification process. This type of governance is oriented towards 'soft' regulatory instruments, which allow changes, adaptations and revisions more easily, and do not necessarily require permanent systematic and formal regulation.

The inefficiencies, gaps and inconsistencies of laws constantly lagging behind the needs of science and technologies (the so-called *'law lag'*, i.e. the temporal distance between the progress of science and regulation) show the need to take new paths: among these are the discussions in the committees as premises for legislation, but also as an integration and support for the legislation in some areas of emerging technologies, providing guidelines and guidance for researchers on the one hand and the involvement of citizens on the other. In this perspective, avoiding the risks of a total self-regulation (such as conflict of interest, non-representativeness, non-democracy, etc.) the new wave of technology can be regulated in a dynamic and effective way. And committees can interact with scientists, experts in ethics, sociology, economy, anthropology, law in the development of knowledge and technologies to guide research, finding out new tools that foresee ethical conditions and requirements already in the design phase (ethics-by-design and ethics-in-design).

In this sense, ethics, bioethics and techno-ethics are becoming an 'institutional practice' in the field of health and beyond it. The Opinions and documents drawn up and approved by international, regional and national committees constitute an effort

of reaching 'institutionalized moral reasoning' with the task of involving scientists, experts, and citizens (as much as possible), in discussing and addressing governments and decision-makers. In this way, a new 'Integrated regulation' is not just a purely theoretical consideration: it is already a reality that can be strengthened in the future, with reference to the established and increasingly intense activity of the various national and international committees. A case in point, in Europe, is the proposal for a regulation of artificial intelligence, inspired by Opinions and documents of ethics, law, and ICT experts in the field (Proposal for a regulation of the European Parliament and of the Council laying down harmonised rules on artificial intelligence (Artificial Intelligence Act) and amending certain Union legislative acts, April 21, 2021: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52021PC0206).

The Toolbox of a Rights-Centred Institutional Ethics

The elaboration of institutional ethics also draws inspiration from the horizon of fundamental human rights as a conceptual framework, which form a crucial part of national constitutions and international documents. These documents have undergone, in recent decades, a process of explicit specification and interpretation, in light of emerging issues also stemming from scientific and technological development, through a wide range of declarations issued by a number of different international organizations generally dealing with the protection of fundamental rights or specifically aiming at developing the ethical discourse (*i.e.* ECHR, UNESCO, WHO, as well as the Union of African countries (COPAB); the Asian Bioethics Association; Regional Organizations of American States; in Europe, the European Group on Ethics in Science and New Technologies at the European Commission, the Committee on Bioethics DH-BIO of the Council of Europe). In addition, courts and tribunals at different levels (such as Constitutional Courts at national level, the Strasbourg level for the European Convention of Human Rights, the European Court of Justice for the European union) have also designed a dynamic (not always consistent, though) framework of fundamental rights, which, with the support of the legal doctrine, can be used as a toolbox for bridging law and ethics and meeting the new mentioned challenges.

The reference to human rights is guaranteed in legislation, at national level, by Constitutions both in national legislation and case-law, by international documents (declarations, conventions), European norms and judgments of the European Court of Human Rights and the Court of Justice of the European Union (Andorno, 2009, 2013; Barilan, 2012; Beyleveld & Brownsword, 2002; Ten Have & Gordijn, 2014). In this context, individuals, national legislation and European laws are called upon to refer to basic fundamental human rights, placed at a higher level.

The human rights framework in this context refers to the following documents.

At the level of United Nations: Universal Declaration of Human Rights (1048); Declaration on the Use of Scientific and Technological Progress in the Interest of

Peace and for the Benefit of Mankind (1975); Resolution 38/111 on Implication of Scientific and Technological Developments for Human Rights (1983); Resolution 38/112 on Human Rights and Scientific and Technological Development (1983); Resolution 1986/9 of the Commission on Human Rights on the Use of the Scientific and Technological Developments for the Promotion and the Realization of Human Rights and Fundamental Freedoms (1983); Resolution 1999/63 of the General Assembly on Human Rights and Bioethics (1999); Cartagena Protocol on Biosafety (2000); Declaration on Human Cloning (2005); Convention on the Rights of Persons with Disabilities (2006); New and Emerging Issues Relating to the Conservation and Sustainable Use of Biodiversity (2012).

At the level of UNESCO, the declarations written by the International Bioethics Committee (IBC) and approved by the General Assembly: Universal Declaration on the Human Genome and Human Rights (1997); International Declaration on Human Genetic Data (2003); Universal Declaration of Bioethics and Human Rights (2005).

At the level of the Council of Europe: Convention of the Protection on Human Rights and Fundamental Freedoms (1950, particularly articles 2, 3, 5, 8, 9, 12, 14); European Social Charter (1996); Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data (1981); Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (1999); especially Additional Protocol on the Prohibition of Cloning Human Beings (1998); Additional Protocol concerning Biomedical Research (2005); Additional Protocol concerning Genetic Testing for Health Purposes (2008).

Specifically, at the level of the Parliamentary Assembly of the Council of Europe: Recommendation 934 on Genetic Engineering (1982); on the Preparation of a Convention on Bioethics (1991); on Biotechnology and Intellectual Property (1999); on Biotechnology (2000); on the Protection of the Human Genome (2001), on Nanotechnology: Balancing Benefits and Risks to Public Health and the Environment (2013). And at the level of the Committee of Ministers of the Council of Europe: Recommendation on Regulations for Automated Medical Data Banks (1981); on Medical Research on Human Being (1990); on Prenatal Genetic Screening, Prenatal Genetic Diagnosis and Associated Genetic Counseling (1990); on Research on Biological Materials of Human Origin (2006).

At the level of the European Union: Charter of Fundamental Rights of the European Union (2000, particularly, articles 1, 3, 4, 10, 13, 24, 25, 26, 35); Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use; Directive 98/44/EC on the legal protection of biotechnological inventions; Directive 2010/45/EU on standards of quality and safety of human organs intended for transplantation; Directive 2004/23/EC on standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells; Directive 2011/24/EU on the application of patients' rights in cross-border healthcare. On 21 April 2021, the European Commission has published a Proposal for a regulation of the European parliament and of the council laying down harmonised rules on artificial intelligence (artificial intelligence act) and amending certain union legislative acts.

The discussion and production activity carried out by Committees of Bioethics, along with the elaboration, interpretation and clarification of fundamental human rights, within the various international and national institutional settings, has contributed to entrenching some shared principles, which can be seen today as (an integral and inherent) part of institutionalized ethics. The most important are listed below.

- The primacy of the human being and his/her dignity over the sole interest of science or society; the respect for physical and psychological integrity (safety, well-being); the ban on exploitation and commercialization of the human body, manipulation or arbitrary use of the body and its parts (cells, tissues); the ban on physical and psychological invasiveness (*i.e.* using devices, experimental treatments), arbitrary and non-therapeutic eugenic selection;
- Beneficence and non-maleficence: maximizing objective benefits and minimizing potential physical, psychological and social harm, applying the principle of appropriateness/proportionality (the risks should not be disproportionate to the potential benefits), from the perspective of a comparative risk/benefit assessment for the protection of the subject's wellbeing and physical, social and mental health;
- The protection of freedom, in both the sense of autonomy and responsibility (counselling and informed consent to medical treatment), especially with regard to those who are facing inability or particularly vulnerable conditions (children, mentally incompetent individuals, the elderly, pregnant/nursing women or of childbearing age, prisoners, military, poor);
- Justice or guaranteeing equal treatment for all, equity of access to healthcare, equality, non-discrimination and solidarity;
- Precaution, caution and prudence, in the face of uncertain or risky technologies, which are likely to cause serious and irreversible damage to human beings, humanity, the environment, and future generations.

These shared values and principles do not provide a clarified solution for each ethical problem. Some ambiguities and conflicts persist, particularly in the context of sensitive and controversial issues. We need to clarify, theoretically and practically, whether, for instance: dignity should be viewed as absolute (always and unconditionally) or relative (varying according to circumstances); if the proportionality/disproportionality of interventions should be defined on the basis of objective and/or subjective standards; if autonomy should be interpreted either in the sense of self-determination and self-reference or in relation to responsibility towards oneself and/or others; if justice is to be understood in liberal-individualistic or constitutively social-solidaristic terms.

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Chapter 17
Scientific Advances, Ethical Oversight and Legal Institutionality

Carlos María Romeo Casabona

Abstract Over the last decades, ethical oversight and legal institutionality have paid increasing and special attention to research related to the advancement of knowledge and technology, in particular human genetics and biotechnology, advanced medicines, such as neurosciences, information and communication technologies (ICT) and other emerging technologies, such as nanotechnologies (NT) and artificial intelligence (AI). This chapter reviews how ethical oversight and legal institutionality have influenced life-related sciences and technologies, and explores ethical and legal responses to conflicts of particular importance that have appeared in this connection. It will also be possible to verify how national legislation and international organizations have been oriented towards regulatory proposals aimed at framing the use of scientific and technological resources in contexts of safety and reliability, by opting for preventive approaches through various forms of control and supervision that do not hinder the advancement of scientific and technological knowledge when it is not really necessary.

Keywords Emergent technologies · Biolaw · Big data · Biosecurity · New rights' holders

Introduction

In this chapter I will review how ethical oversight and legal institutionality have influenced life-related sciences and technologies, as well as responses to conflicts of particular importance that have emerged, or at least, how they have been proposed and focused for their solution, even when no consensus has been reached

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(Soutullo, 2014). Throughout the chapter, we will be able to see how national legislation and international bodies have been oriented towards regulatory proposals aimed at framing the use of scientific and technological resources in contexts of safety and reliability, opting for preventive approaches through various forms of control and supervision that do not hinder the advancement of scientific and technological knowledge when it is not really necessary.

For several decades now, scientific research has brought up important ethical and legal challenges. Probably the most relevant challenge was the Human Genome Project, an initiative launched in 1990 by the Department of Energy (DOE) and the National Institutes of Health (NIH) of the USA, as well as a number of other groups of scientists from other developed countries that joined upon later. The objectives initially set focused on mapping genes with various characteristics. From the scientific point of view, due to its size, object, involved researchers, methodology, financial endowment, accompanying studies, etc., it was a relevant fact, a historical milestone of first magnitude. Its official conclusion was proclaimed, with the required solemnity, in June 2000, 2 years earlier than originally planned. Although the expected result of the project provided few new applications or practices, it opened the doors to an immense universe that was waiting to be explored with new applications that would give beginning to a new era of medicine.

At the end of the project, several questions arose by pointing out some consequences for ethics and law (Romeo, 2002). First, the need to adopt a position of greater sensitivity and responsibility towards the rest of animal life, and living beings in general. Second, the lack of biological support for racist ideologies that defend the biological superiority of some ethnic groups over others. In addition, from this project the discussion about the self-determination of the human being as an entity with moral responsibility arises, since the personality cannot be determined only by the game of genes (Warnock, 1998), but it is mainly influenced by the environment (epigenetics), especially throughout the early stages of life. Although the environment in which human beings grow and develop has a greater influence on their organic formation and configuration, it also has an influence on their personality (Urruela, 2004). Epigenetics has revealed many innovations for understanding the development of numerous diseases that, starting from a genetic predisposition, require the contribution of exogenous factors that intervene in the activity of genes without modifying their sequence. However, it cannot be said at this time that the spectacular emergence of neuroscience in recent years has cleared the issue, as the knowledge they are creating on the mechanisms of human behavior are still insufficient to be able to draw well-founded definitive conclusions from them (Crespo, 2011).

Law, Science and Technology: Towards a New Model?

Over the last two decades and entering the “post-genomic era” (Romeo, 2002), there have been substantial changes, not only in the goals, modes and procedures of genetic research and biotechnology, but also how ethical regulation and supervision intervene.

Law, Science and Technology: Necessary Legal Institutionality

The development of science in recent decades, together with the expansion of its aims in relation to its technological applications transferred to society, have not been indifferent to ethics or law. Both science and technology have had a decisive influence on understanding the relationship between ethics and law (Kemp, 2007). Probably, the particularity of the relations that have been established more recently between law, science and technology has also largely conditioned the characteristics of each of them, to the point that they have contributed to generating a new model for Law of Science and Technology. We shall see below to what extent this is the case and to what extent it is satisfactory.

It is true that a multi-dimensional and at the same time closer relationship between law, science and technology has been increasingly generated. This relationship has not only moved from law towards science and technology, in the sense of how these have been perceived and even absorbed by law, establishing the appropriate regulatory frameworks, but similarly the reverse path is being followed: from science and technology to the legal field. Indeed, scientific knowledge and emerging technologies have now become very valuable tools for rethinking one's own legal constructions. As an example, it is important the state of knowledge in determining the causal relationship between a human action and an outcome, which is necessary, but not enough, to establish, for example, objective criteria for the imputation of results (Romeo Casabana & Sánchez, 2010). Also, an instrument of legal progress is the discovery of DNA markers that are used as identifiers for the investigation of cadaver and missing people, paternity, or commission of crimes (Romeo Casabona & Romeo Malanda, 2010). In addition, in this context, information and communication technologies cannot be overlooked, as they are essential tools for the advancement of other more specific technologies, such as those related to living matter, that is, biotechnology.

In short, these two main axes are currently the two-way approach that is taking place between law, science and technology. However, very often, these relations have failed to escape from tensions and conflicts.

However, it should be pointed out that this link should not lead us to legal scientism, that is, to pretend that the optimal decision-making is based exclusively on the best technical-scientific criteria (Esteve, 2009). However, this connection is rather dominant relations between knowledges with different methodologies and purposes, in which law is at risk as it renounces its decision-making and formal expression procedures (norms production) in favour of science and technology's commands.

(Bio) Ethics and Law: A Necessary Symbiosis

As it has been argued in various forums, no one doubts that an important shift is taking place on the paradigm of the relationship between ethics (and law) and science (scientific research). This has been expressed, for example, by the Joint Report

of the Bioethics Committee of Spain and the Conselho Nacional de Ética para as Ciências da Vida of Portugal, Lisbon-Barcelona, October 24, 2011, entitled *Synthetic Biology.*[1]

The time lag between scientific discoveries and consequent ethical reflection is gradually fading away. What is currently designated as bioethics of emerging situations (cloning, procurement and use of human stem cells, nanotechnology, synthetic biology, gene editing, applied AI for predictive purposes of criminality in criminal proceedings, AI applied to health, in particular to Personalized Precision Medicine, PPM) (Romeo Casabona et al., 2018) has contributed decisively to this change. Today science continues its evolution and at the same time (bio)ethics continues its reflections on the possibilities of such and other advances, evaluating the risks and advancing proposals that, without being scientific, imprint important nuances to the rhythm of scientific development.

Just as I said about law, ethics has gradually approached science. Today ethical reflection appears, not as an extension, but as an important aspect of any scientific research. On the other hand, ethics is now increasingly faced with the uncomfortable situation that the scientific facts it has to evaluate, especially those linked to scientific research, are largely based on mere working hypotheses, without sufficiently measurable and predictable results. This makes it difficult to anticipate the potential benefits and risks and, consequently, the ethical reflection itself, and the proposals that law provides more specifically, as it does not count on premises enough from which it can draw conclusions and reliable solutions. If this kind of reflection seems appropriate in the framework of ethics, something similar could be sustained in relation to law. Having said that, it seems inevitable to think that law becomes the only instrument available for society to control and channel science and technology, as some support, probably with excessive optimism. Although another issue is to avoid the healthy dialogue between (bio)ethics and law of science and technology reaching a point where they overlap or confuse to each other.

The Transformation of Legal Institutionality

The expansion of scientific research in the field of biomedical sciences and the development of relevant technologies (Nanotechnology, Communication and Information Technologies, and Artificial Intelligence) has led to the intervention of law, for various purposes: i) to control and prevention of the risks -known, feared or merely hypothetical- derived from them; ii) to channel and establish strict requirements in view of the magnitude of these risks and their impact on human rights; iii) to channel benefits; iv) to prevent discrimination, including that based on genetic features or predictive proposals from artificial intelligence systems.

[1] http://assets.comitedebioetica.es/files/documentacion/es/CBECNECV_Informe_Biologia_Sintetica_24112011.pdf

Legal instruments have been promoted by international and regional governmental organizations, which have developed and expanded the scope of the human rights proclaimed more generally. Other new rights have also been identified (Rodotà, 2010). In the specific field of genetics, numerous human rights have been developed or identified, sometimes as part of the content of some fundamental rights proclaimed by most modern political constitutions (e.g., right to life, physical integrity, ideological freedom or freedom of conscience, and privacy, among others), as also recognized in the Universal Declaration (UDHR, United Nations, 1948), in international covenants or in regional conventions.

The Oviedo Convention (1997) and its additional protocols have identified new human rights or at least new perspectives on scientific developments (e.g. the rights to genetic integrity, identity and individuality, in relation to reproductive cloning and gene intervention, to know one's own biological origin, not to know or not to be informed, not to be discriminated upon genetic features, and the right to genetic privacy, among others), which has been a qualitative step to incorporate into the domestic law of several states some provisions with legal binding force.

Without binding force, but with an indisputable moral force of guidance for States, the UNESCO Declarations have been an important contribution on these matters.[2] The first of them proclaims, as a universal value, that the human genome is the basis of the unity of all members of the human family and of the recognition of their intrinsic dignity and diversity. In a symbolic sense, the human genome is "the heritage of humanity" (art. 1°). It is important to point out that such a high qualification does not mean that a legal sacralization of the human genome has been sought.

International Human Rights Law relating to biomedical sciences has been shaped around several peculiar characteristics, which probably constitute the germ of a new model of creation and configuration of Law of Science and Technology. Let us note below some of its features, whose consolidation, notwithstanding some personal proposals that are formulated, needs extensive reflection and remains open to the future.

Use of Softlaw

New International Human Rights Law relating to biomedical sciences has been configured as a soft law or not legally binding but exhortative law, as opposed to hard law, or mandatory law. Soft law reflects in multilateral agreements the expression of the parties' desire -the States- to regulate in the future with binding character certain subjects under certain criteria and principles that in the present do not enjoy such prescriptive character (López, 2012). Various non-binding legal instruments, such

[2] As they were enacted: Universal Declaration on the Human Genome and Human Rights (November 11, 1997); International Declaration on Human Genetic Data (October 16, 2003); and Universal Declaration on Bioethics and Human Rights (October 19, 2005).

as recommendations, statements, codes of conduct or good practice and positions of international governmental bodies or bodies belonging to them for advisory or supervisory purposes, are part of it as well; for instance, the International Ethical Guidelines for Health-Related Research, developed by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), whose latest version is from 2016.

This non-binding nature of such instruments has had a positive effect, facilitating, for example, the achievement of agreements to adopt the various legal instruments on matters that might be controversial in a society. This formula is therefore acceptable if it is taken as a transitional remedy until such soft law is transformed into binding legal rules. Even during this transition period, the principles of this exhortative law could be better defined, its contents could be revised and updated, and it could be familiarized with people the norm must rule. But if such a goal of transformation into binding law or hard law were abandoned, there would be a risk that this law's contents would definitively lose any coercive nuance and pretension, that the acquired moral force would be devaluated, and that their judgements become soft values or soft rights, that is, values, goods or rights without legal support to ensure their respect and effective legal protection.

Overlap or Confusion with Bioethics

The overlap between bioethics and law finds clear expression in American law, through the construction of criteria or legal resolutions related to biomedicine, in which there is a process of direct penetration of bioethics into the legal argumentation, although this process has not entailed the risk of confusion of the normative function of each of them. However, although bioethical discourse has been very fruitful in defining rights and establishing legal norms, the persistence of this confusion may be detrimental to the coercive nature of law – several precepts of the Universal Declaration on Bioethics and Human Rights incur in this confusion – as ethics and law have different fields of action, methodologies and purposes, although close to each other. Bioethics is neither a moral system nor is it intended to be a substitute for a moral system. At the same time, however, life sciences have fostered a new, modern and close dialogue between ethics and law, which had been almost completely banished from public discourse for decades, at least in the European framework.

The main problem at present is not trying to impose on society a set of values and rules proper of a religious creed (which may also happen), but that some specialists, usually outside the legal sciences, consider that only bioethics is a truly discursive discipline, and as such, it legitimizes the imposition of certain values in order to resolve conflicts arisen in biomedicine. Therefore, they seek to impose it on law, although this is normally related to discursive and dialectical spheres. These positions forget or ignore that law is essentially discursive in its construction, and that its solidification comes from such process and that it is based on the legitimacy that emanates from the Rule of Law, so its forcibility is based on such legitimacy. On the other hand, law has been able to create an axiological system whose greatest

achievement is the network of human rights, converted into fundamental rights in domestic law (Romeo Casabona, 2022).

The Direct Influence of International Human Rights Law Relative to Genetics and Biotechnology on Domestic Laws

This influence includes the highest normative level, that is, the political constitutions, in which it is already a common practice to collect a catalogue of fundamental rights and public freedoms. Constitutional law has enormous potential, both as a recipient of human rights that are considered more specifically to be involved in biomedical sciences, as well as an instrument for resolving conflicts arising from them. The emerging examples of the recognition of certain rights related to the human genome and biotechnologies are undoubtedly a novelty of contemporary constitutionalism (Romeo Casabona, 2020a, b).

Moreover, this expansive process, which in the beginning has been slow, is logical, since, if human rights related to these matters have been established in international law, it is reasonable that some fundamental rights have been accommodated in modern constitutional law, insofar as they offer new prospects for broader protection of citizens and their rights (Casonato, 2012). In this sense, there is no doubt about the influence that International Human Rights Law is exercising, and certainly will continue to do so in the future, on this Constitutional Right of Biomedicine (Gros Espiell, 2011). Nor is it idle to argue that "classical" fundamental rights are susceptible to reinterpretation, so that they can also offer their protective framework to vicissitudes that such rights may traverse in the context of these activities.

Rights and regulatory principles explicitly and directly related to human genetics, biomedicine in general and biotechnology that have been incorporated into the constitutions of several States are diverse, by way of example: personal identity as such or linked to genetic experimentation and the development of linked technologies, genetic intimacy, genetic engineering, the environment in relation to biotechnology activities, etc. (Switzerland,[3] Portugal,[4] Greece,[5] Venezuela,[6] Ecuador[7]). As

[3] Art. 119: "Reproductive medicine and genetic engineering in the human sphere. 1. Every human being must be protected against abuses of reproductive medicine and genetic engineering. 2. The Confederation shall legislate on human germ and genetic heritage. In this regard, it shall ensure the protection of human dignity, personality and family and shall respect in particular the following principles …". See also arts. 118b, 119a and 120.

[4] Art. 26.3: "The law shall guarantee the personal dignity and genetic identity of the human being, in particular in the creation, development and use of technologies and genetic experimentation".

[5] Art. 5: "All people will enjoy full protection of their health and genetic identity".

[6] Art. 122: "Indigenous peoples have the right to comprehensive health care that considers their practices and cultures. The State shall recognize its traditional medicine and complementary therapies, subject to bioethical principles".

[7] Art. 14.2: "The preservation of the environment, the conservation of ecosystems, biodiversity and the integrity of the country's genetic heritage, the prevention of environmental damage and the recovery of degraded natural spaces are declared in the public interest". See also art. 15.

a supranational body, the EU Charter of Fundamental Rights should be recalled, which prohibits eugenic practices, in particular those aimed at the selection of individuals, and reproductive cloning of human beings.[8] The constitutional reform of the German R. F. deserves particular attention, although its relationship is apparently indirect, through which it has introduced in its Basic Law the category of future generations as holders of rights or at least tax protection by the State.[9]

From a material point of view, it seems clear that there is a broad consensus that the basic framework of activities related to genetics, human biotechnology and advanced medicines, and with technologies and their limits, is found in both classical human rights (fundamental rights and public freedoms) and in those renewed and new. In addition to the individual and, by its nature, subjective perspective of human rights, there is usually also an objective perspective (from which legal goods are derived) and another collective, which refers to the ownership of peoples, communities and groups (even with different cultural traditions), which are neither exclusive nor reductive of their inalienability for the individuals who comprise them.

This perspective opens the door to new legal assets, or better-defined legal assets, which could or already be subject to criminal protection, taking into account the classical criteria of the legal relevance of these goods and the seriousness of the attacks on them.

New Rights' Holders?

Concern about the negative impact of the application of genetic knowledge and biotechnology has sometimes led to the need to expand the number of rights holders considered to be most vulnerable: the in vitro human embryo (including germ and totipotent cells? The clone? From what moment?); the human species, ethnic and cultural collectivities; future generations; and the environment.

Thus, the changing reality tells us that certain rights of the embryo (in vitro and in vivo) and the fetus are claimed, such as the right to genetic privacy or the protection of their genetic data, which will accompany them almost immutable from conception to birth (if it happens). It is true that this legal protection should be guaranteed in a very similar way to those born from these antenatal phases assuming that they will be born, because waiting for this event would be useless and ineffective.

When we refer to the ownership of rights, we are referring to people, because only they achieve that ownership. Will it mean, then, that opening up the field to new rights' holders entails modifying the concept, at least as a legal one, of a person, extending it, in order to give adequate space to them? Law, as an instrument created by human beings to determine the conditions in which interpersonal, social and public relations are established, could be modified and adapted to new

[8] On the binding nature of the Charter for EU Member States v. art. 6 of the EU Treaty.

[9] Art. 20 bis: "Conscious also of its responsibility towards future generations, the State will protect the natural bases of life …".

situations or realities. From a technical and legal point of view, however, this is not a simple task. First, and regardless of whether they were qualified as persons, all these supposed new holders would need a legal representative to look after their rights and interests, but what would these be? In the case of future generations, it would be difficult to identify the ownership of individuals that are still non-existent and of whom it is not known who they will be, because actually what matters are not hypothetical individuals, but the collective as such (also non-existent). However, it is clear that it is almost technically impossible to put into practice a similar concept, or to assume the conflict that would mean for so many legal elaborations assumed today in a peaceful way. On the other hand, it does not seem necessary to build mechanisms of recognition and legal protection of these entities, except if their purpose is to obtain legal resources from maximums, which is not the case under law.

For these reasons, it can probably be sustained with more property, and without the need to force certain consolidated legal concepts and institutions, that better than being holders or subjects of rights could be granted the nature of legal goods, whose intensity of protection would be based on the nature and social consideration of the entity (the pre-implantated embryo) or reality (the environment), the intensity of the offense and the nature of the arisen conflict. It is true, however, that we are faced with certain and very significant differences between the various State legal systems, as is the case with the status granted to in vitro embryos, which is an evidence of different social positions.

In any case, neither in international law nor in domestic law do we find definitive answers that somehow reflect this option of extending the ownership of subjects. Not even a similar status has been granted to future generations, but it has been established in terms of legal responsibilities instead of duties, which present (existing) generations have towards future generations.[10] Domestic law has recognized in isolation that the unborn is subject to certain rights (in particular the right to life), as the German Federal Constitutional Court has stated twice.[11]

Control Mechanisms

This phenomenon is increasingly widespread in other sectors of regulated human activity, but it has been in this area where there is greater interventionism, especially through requirements and controls before the activity begins.

[10] The authors of the Declaration on the Responsibilities of the Present Generations Towards Future Generations, adopted on November 12, 1997 by the 29th General Conference of UNESCO, were aware of the limitations noted in the text and that other avenues would be possible: "Article 6 – Human genome and biodiversity. "The human genome, in full respect of the dignity of the human person and human rights, must be protected and biodiversity safeguarded. Scientific and technological progress should not in any way impair or compromise the preservation of the human and other species."

[11] See, BVGE. May 28, 1993.

Ex Ante Controls

The establishment of ex ante controls (Romeo Casabona & Nicolás, 2010) at the beginning of various activities (especially research and clinical trials with humans, with material of human origin, and certain innovative therapies, still in experimental phase) pursues a fundamentally preventive objective, usually based on ignorance of risks' scope that this activity can entail for the human being and other living entities, and for the environment and the ecosystems that make up it. Let us remember two different instances that complement and interact to each other.

(1) This function is usually entrusted to collegiate bodies appointed by the administrative authorities, which are usually not or should not be subordinate to them. To this end, specialized, multidisciplinary and independent evaluation committees have been set up or upgraded to issue mandatory and binding reports. Thus, ethics committees of biomedical research, in particular medical clinical trials and other medical devices; and more recently, protocols of genetic studies, often linked, although not always, to the previous ones. In Spain, for example, the National Commission for Assisted Human Reproduction and the Commission for Guarantees on the Use of Human Tissues and Cells exist at national level; both bodies also perform mandatory evaluation functions for certain research projects linked, to reproductive mechanisms and the beginning of human life or, in relation to the use of embryonic or other functionally similar cells; however, the so-called iPS cells are no longer subject to prior evaluation, according to a recent legal amendment.[12]

    Accepted the legitimacy of usual procedures for appointing members of these national or local evaluation committees, which are currently usually regulated by relevant sectoral regulatory provisions (it is not necessary, then, to base its legitimacy on democratic election procedures), the question that sometimes arises is to guarantee its independence, its transparency and procedures to be able to challenge their opinions when they are unfavourable. Its legitimacy really lies in these aspects. However, this legitimacy can be undermined when these bodies are vested with the power (rather than authority, which would be the starting point) that confers the status of specialist or expert, which would exclude any other interlocutor lacking such qualification (Esteve, 2009).

(2) Public authorities exercise ex ante control when granting specific licences, accreditations or authorizations in relation to biomedical activities. They may also exercise other, rather later, forms of control in the exercise of inspection and monitoring functions.

[12] Law 14/2007, of July 3. In accordance with the First Act of Law 17/2022 of September 5 amending Law 14/2011 of June 11 on Science, Technology and Innovation, a new paragraph 3 is introduced in the aforementioned Art. 35, which acknowledges the evaluation of iPSC research to the relevant research ethics committee.

Ex Post Controls

A number of checks may be carried out after the activity is done. I will mention the courts, which have been dealing with matters relating to biomedicine and human genetics and biotechnology in particular. Some of their decisions are of extraordinary importance, both because of the nature of the cases they have resolved and because of the doctrine they have developed to support their resolutions, notwithstanding the fact that they have not always been received uncritically (European Court of Human Rights,[13] Inter-American Court of Human Rights,[14] Court of Justice of the European Union,[15] constitutional courts[16] and the ordinary jurisdiction of States[17]).

[13] See S. and Marper v United Kingdom, judgment of December 4, 2008 (illegal archiving of DNA profiles for criminal investigation purposes); H.H. and others v Austria, judgment of November 3, 2011 (Under the Convention, the Austrian legislation prohibits the donation of eggs, and semen is only authorised when it is introduced directly into the woman's uterus); Costa and Pavan v Italy, judgment of August 28, 2012 (undue prohibition of pre-implantation diagnosis).

[14] Artavia Murillo and Others (in vitro fertilization) case, judgment of November 28, 2012 (annuls the judgment of the Constitutional Chamber of the Supreme Court of Costa Rica, cited below, prohibiting in vitro fertilization).

[15] O. Brüstle v Greenpeace eV, judgment C 34/10 of October 18, 2011 (patent for human stem cells); judgment of October 9; 2001 (on the challenge to the directive on the legal protection of biotechnological innovations, 1998).

[16] Brazil (Federal Supreme Court with constitutional review functions), judgment No 3150 of 2008 (human embryo research); Costa Rica, judgment No 2000–02306 of March 15, 2000 (unconstitutionality of in vitro fertilization); Spain, judgment No 207/1995, December 16 (obtaining a biological sample from the body of the accused to test the DNA identifiers for criminal investigation); Spain, judgments 212/1996, December 20, and 116/1999, June 17 (on the constitutionality of the laws on the use of embryos, foetuses, human cells and tissues and on assisted human reproduction); Portugal, judgment No 101/2009 of March 3 (constitutional conformity of the law on assisted reproduction techniques).

[17] USA, Supreme Court, Association for molecular pathology et al. Myriad Genetics, Inc., et als., judgment of June 13, 2013 (a naturally obtained segment of DNA, in the case of BRCA1 and BRCA2, belongs to nature and is not patentable simply because it was isolated; a segment of cDNA if patentable because it was obtained unnaturally; very interesting the judgments of previous lower courts); Spain, Supreme Court (Civil), cases of "wrongful birth", judgments June 6, 1997, February 4, 1999 and June 7, 2002; France, Court of Cassation, Nicolas Perruche case, judgment of November 17, 2000 (right to compensation, because a defective prenatal analysis did not detect very serious fetal anomalies and the mother could not terminate the pregnancy: "wrongful life"); Iceland, Supreme Court,, judgment of November 27, 2003 (protection of privacy in relation to the processing of databases in the health sector); Italy, Trieste Court of Appeal, judgment of September 18, 2009 (Genetics as a relevant factor in the criminal imputability trial).

The Discursive Paradigm of Some Conflicting Issues

Over the last two decades, issues, discoveries and innovations have emerged giving rise to or consolidating new ways of conceiving and practicing clinical medicine. These are called predictive medicine, regenerative medicine and personalized medicine. Controversy has sometimes arisen around them, occasionally resulting in real ethical and legal conflicts. Next, as relevant examples, I will mention controversial legal aspects of some matters that go beyond such practices.

Personal Data: The Potential of Big Data and the Need for Its Criminal Protection

The legal regime of the protection of personal data has undergone a profound change, due to the technological modifications of its processing, including large quantities of data (Big Data), as well as the widespread use in our societies, both by public bodies, private sector and by the citizens themselves as individuals. The idea has been that personal data directly affect various fundamental rights and public freedoms of citizens, as reflected in both international and national legal instruments, including political constitutions. It has also been proven the great economic value that these data have as key elements in financial and business traffic, and hence the enormous pressure that has been generated, especially from the private sector, to access personal data. The approval of the General Regulation on the Protection of Personal Data (RGPD)[18] has generated high expectations both for the necessary legal modernization of data processing and for the opportunity to reconcile access and processing with legal guarantees aimed at protecting fundamental rights, beyond the right to privacy and data protection.

A particular issue arises around a very peculiar feature of Big Data: the high risk of identification or re-identification when these data are still anonymous or have been anonymized (Focarelli, 2015). In this case, the issue should not be resolved by broadening the notion of personal data, as has eventually been defended (Focarelli, 2015: 32), but by referring to the legal framework on the protection of personal data. Indeed, if the re-identification occurs, so that it is already data of an identified or identifiable natural person, the current legal framework on data protection will apply with all its resources (Romeo Casabona et al., 2018: 35). A different issue is that if reidentification is indeed easy in relation to big data, preventive measures of a different nature (not only legal) should be taken to prevent actions aimed at identification or re-identification.

Another important issue addressed by the European Regulation concerns the enormous capacity of data handling by AI systems that allow people to be profiled, classified into groups and then make fully automated decisions. It is the great risk

[18] General Regulation on the Protection of Personal Data, of April 27, 2016.

that human beings face given such powerful technological tools. Therefore, the General Regulation on the Protection of Personal Data has established limitations, such as, that the data subject has the right not to be subjected to a decision based exclusively on an automated processing of his data, including his profiles, which may affect him in a significant way (Article 22). These fears and warnings are echoed by the internal state regulations, which establish very clear principles on anonymous or anonymized data, but more flexible on pseudo-anonimized data, in particular when it comes to scientific research.[19]

Genetic testing of individuals can reveal very important personal and family information (biological family) such as biological data on certain phenotypic traits of the affected person, including ethnic traits, also about their present (diagnosis) and future (predictability) physical and mental health; as well as about the risk of transmitting hereditary diseases to their offspring or to confirm having received them from their parents. On the other hand, this information may also indicate relations with third parties (such as paternity, participation in the commission of a crime) or facilitate their identification in certain circumstances (dead bodies in cases of accidents or disasters), in both cases through the information provided mainly by non-coding DNA (DNA identifying profile markers). In short, most genetic information is projected on the health of individuals, but as seen, not all of it should be identified with health.

As is well known, genetic tests are a daily reality of health, with the valuable information they provide and, thanks to the progress of research, are continuously expanding their information-gathering spectrum while gaining in accuracy and predictive capacity. This information is of great interest not only to the subject from whom it comes, that is to say, to those who have undergone genetic analysis, but also to third parties, such as their biological relatives, which can lead to conflicts over access to such information by the affected parties and the preservation of the privacy (genetic intimacy) of the affected subject. But it can also be extremely important for other persons or entities, as long as the guarantee of a potentially healthy body is required as a budget to participate in certain activities, even for the State in its political action to prevent diseases and promote a healthier population; but, above all, at the present time, to facilitate genetic research (archiving, collection and exchanges of genetic data and biological samples in biobanks).

A new challenge will emerge by making the complete sequencing of the human genome widely available, as its cost makes it affordable to broad spectra of the population. Likely, new situations and new demands will arise, for example, how to treat, manage and store so much sensitive information, what protocols to adopt to treat a high sensitive information on genetic predispositions of any kind (first on diseases), and unexpected findings, among others.

As a result of this range of new possibilities, it seems necessary to rethink what new dimensions are presented in relation to the protection of privacy rights, as well as any form of discrimination or stigmatization based on the genetic characteristics

[19] LO 3/2018, on Protection of personal data and guarantees of digital rights.

of each individual. Legal instruments, including criminal ones, assume the protection that genetic data deserve as personal health-related data under special protection, given the vulnerability of the individual to third-party access. But it has also been seen that part of this privacy might be sacrificed in order to promote the advancement of science.

The Ambivalence of Genetic Engineering: From Therapy to Eugenics and Enhacement

At the present time genetic engineering appears very promising for the intervention in human genes against various serious and incurable diseases of hereditary origin. In the face of different intervention techniques in genes, which showed their insufficiencies, limitations and contraindications, the so-called gene editing using CRISPR-Cas9 is shown, in light of what the researchers indicate, as efficient, simple, affordable and probably -this will also have to be demonstrated- without serious negative side effects. However, we must not forget that genetic engineering, therefore, also genetic editing, goes into the description of manipulation of human genes that configures the typical action of the crime of manipulation of human genes. We must therefore go a little further in finding out what forms of manipulation and for what purposes they may be left inside the crime or, on the contrary, outside it.

Gene therapy aims at curing or preventing serious diseases or defects due to genetic causes. These are genetic defects of various kinds, and their theoretical application does not exclude oncological diseases, some infectious (virus-related) and cardiovascular ones. Their results have so far been inconclusive, and after some time of pessimism, researchers are continuing their work, perhaps now more aware that making progress in this sector is not an easy task, nor will their expected achievements be available in the short term, especially those applicable in the germline (germ cells: gametes and zygote), but they maintain the idea that it will be a great scientific achievement when the technique of genetic editing is mastered. Initially, such conduct would be excluded from the crime of genetic manipulation.[20]

As is known, neither any genetic treatment of a disease linked to the patient's genes uses genetic engineering, nor any intervention in a person's genes must necessarily seek to treat a disease in order to cure it or to prevent it from happening, but other aims can be pursued, such as those of a perfective nature, which explains why it has given rise to intense philosophical, ethical and legal debates, because genetic engineering will at the same time opens the doors to the selection or perfection of

[20] The Spanish Criminal Code typifies genetic manipulation as a conduct carried out "with a purpose other than the elimination or reduction of serious defects or diseases, by manipulating human genes in a manner that alters the genotype" (art. 159 CC).

certain human being's traits considered "desirable," that is, the so-called positive eugenics.

Concern about this future therapy or about perfective interventions on the germline, is also that genetic modifications would be transmitted to next generations of the treated lineage. Hence, gene therapy is valued with some caution, and attention is drawn to the prudence that should preside over any such action, especially interventions in the germline (Romeo Casabona, 2021).[21] To this end, apart from other considerations on actions at international level (e.g. European Group on Ethics in Science and New Technologies [EGE]), it seems necessary to approve a list of serious diseases genetic engineering might be applied on. Fortunately, they are being resolved in a balanced way in attention to research, society and the benefit of patients. Indeed, it must be borne in mind that their urgency is less, because we are not yet considering the treatment or prevention of serious prognostic diseases that some people are already suffering or are likely to suffer, as well as the question of the protection of gametes and the zygote as such, but the reproductive capacity of individuals to have children free from the disease they suffer or can transmit to offspring.

Regarding the potential scope of these interventions for the human species, the first consideration concerns whether where these techniques can be applied with sufficient safety and control, they do not entail the risk of changing the genetic characteristics of the human being, that is, its genome, namely, its species' genetic traits. This discourse starts from the hypothesis that such a risk would exist when the germline is affected, since only through it the altered genetic traits from one generation to another could be biologically transmitted. What these effects would be and what scope they would have for the permanence of the biological properties that characterize and single out the human species from other existing species, and how their identity might be affected, not only the biological one, but also that which derives from its higher faculties, are questions that remain open. For this reason, there is also concern about the effects that may result from practices of chimerism or hybridization of human and animal genetic material, not for research purposes but in reproductive contexts. Although such acts may constitute an offence insofar as they involve the fertilization of human eggs for any purpose other than human procreation.[22] In the Spain's Biomedical Research Act of 2007, the legislator has chosen to consider them as serious or very serious administrative infringements; this is the case, for example, with the production of interspecific hybrids using human genetic material; and with other similar forms, (including keeping live embryos or fetuses outside the uterus for any purpose other than procreation).

[21] In this sense, the European Group on Ethics in Science and New Technologies (EGE), *Opinion on the Ethics of Genome Editing*, Brussels, 2021.

[22] Article 160.2 of the Spanish Criminal Code provides: "Those who fertilize human eggs for any purpose other than human procreation shall be punished by imprisonment from one to five years and special disqualification from public employment or office, profession or trade from six to 10 years".

In this set of doubts it is also necessary to place the perceived possibility for the future that these interventions in the genome can be focused directly on selecting, enhancing or introducing certain traits into the offspring, by mere aesthetic or other similar desires (Romeo Casabona, 2012); or on, directly, seeking the selection of people, for eugenic purposes. In the latter two cases, the identity of the human species may once again be at stake, and in all the cases mentioned, we can slide down the slope of eugenics, with its positive aspects as well its as doubtful ones, and others rather objectionable (Bachelard-Jobard, 2001).

The misgivings such effects entail, which are not yet well known, have led some specialists or institutions to propose an absolute ban on this form of therapy, and others have requested a moratorium until more information is available on the therapeutic possibilities themselves, their indications and their accompanying effects on the genetic heritage and on the children. Thus, the Universal Declaration on the Human Genome and Human Rights rejects intervention in the germline as a practice against human dignity (Article 24), and the Oviedo Convention prohibits such practice if it implies a modification of the hereditary characteristics of the offspring (article 13).

The scope of such article, even the desirability of modifying or deleting them so that the Convention is more open to new developments that can be brought about by current research on genetic editing or any other technology of similar effects, has given rise to an intense and varied debate in recent years, and several proposals have been made: (1) maintain the current wording of this precept; (2) agree a more open interpretation of this precept, without ignoring the risk of distorting its current legal meaning, whether satisfactory or not; and, (3) modify this article (which could be done, for example, through an Additional Protocol to the Convention), so that certain human germline interventions can be allowed with the necessary controls, for example for preventive or therapeutic purposes against serious or very serious diseases, even if it involves modification of the genome of the unborn human being.

While this article took into account the recognition of the positive perspectives of genetic modification with the development of knowledge of the human genome, it also had in mind the greater possibility of intervening and controlling genetic characteristics of human beings, which raises concerns about possible misuse.

At its 18th plenary meeting (June 1–4, 2021), the Bioethics Committee of the Council of Europe adopted conclusions on genome editing technologies. A year later, at its plenary meeting in June 2022, it approved and added several clarifications to this document. The resulting text was forwarded to the Committee of Ministers of the Council of Europe in September of the same year and made public shortly afterwards. Given the enormous interest generated by the correct understanding of Article 13 and its possible modification, I think it is appropriate to convey this position literally to the reader. It can be pointed out that, prudently and respecting the principle of legality, the Council of Europe has opted for an interpretative readjustment of Article 13 of the Oviedo Convention, placing this precept more appropriately in areas of scientific research and for preventive, diagnostic or therapeutic purposes.

The sum of the scientific instruments mentioned together with the genetic analyses in a reproductive context (preconceptive, pre-implantation and prenatal analysis) (Emaldi, 2012) can be used in favor of these currents, which have now re-emerged as "new eugenics" or "neoeugenics," in view of the fact that it presents new aspects and approaches different from any previous conception. It is posed by couples, and therefore, subject to their individual decision initially as a matter of offspring's health and reproductive responsibilities of themselves. Yet, this "soft" eugenics is also subject to limitations and goes through the definition of "disease" (Rodotà, 2010). Nevertheless, some States have reverted to coercive eugenic practices, which are absolutely unacceptable as intrusive, as they go beyond mere impartial advice (AAVV, 1998).

In conclusion, when these techniques are better known and mastered, and their harmful side effects can be ruled out, we will have to think about lifting or limiting these prohibitions, at the same time establishing criteria according to which this form of treatment is permissible, at least to prevent or treat serious diseases, even if the genome of the offspring is modified and other improper uses can be controlled.

Security in Biological and Cybernetic Settings

Biosecurity is an issue that has received increasing attention. This interest has arisen in particular in view of the risks associated with biological accidents involving recombinant DNA (r DNA) technologies applied to various living organisms (GMOs), as they might reach catastrophic dimensions, with injuries and damage to life and integrity of humans, animals, plants and the environment. On the other hand, it is doubtful whether adequate and effective preventive resources and procedures are available, especially after a biological accident. Likewise, despite the brakes that have been established in international law for years against conventional (bacteriological) biological weapons, the availability of GMOs is of particular concern to the authorities and bodies responsible for safety in general.

Biosecurity in its various dimensions should now be a priority for States and international organizations. It can be argued that biological weapons have an enormous potential for mass destructive effectiveness, as bacteriological weapons used in armed conflicts have demonstrated in the past. Although the tendency of international organizations has been to press for and reach agreements for States to renounce the use of such weapons, the new front that is opening up for these instruments is that of the international terrorist phenomenon. Therefore, in relation to these gangs or organizations, little can be done by international legal instruments as a preventive means, nor by the criminal responses of the states, except for the repressive ones once the criminal acts have been committed. Here, the principles and agreements of extraterritorial application of criminal law, such as the real principle of protection of states' interests and that of global justice, can be relevant, as well as intensifying other means of cooperation between them, such as judicial assistance,

extradition agreements, etc. In short, deploy a number of resources that have been built over the last few years against international organized crime and terrorism.

As regards non-criminal preventive measures, and taking into account the issue of dual use of biotechnologies, companies in the sector should be required to adopt extreme safety measures, not only in order to avoid biotechnological accidents, but also with the aim of avoiding the theft of information on the production of GMOs or directly of manipulated biological material that could end up in the hands of criminal groups or international terrorists. Nor should other types of actions, along the lines of those included in the so-called US Bioterrorism Act, aimed at controlling food chains be excluded; as well as the preparation of protocols to be followed by the authorities and the civilian population in the event of biological disasters, whether accidental or intentional.

In the field of biotechnology, biosafety and preventive law, emphasis should also be placed on the usefulness of the precautionary principle in view of the changing nature of living matter, of the unlimited interventions that are expected to be made on the same, although without a precise knowledge on the adverse effects that could derive from these manipulations (Esteve, 2009).

In the field of cybersecurity, in particular criminal law has probably played a more important role than the current one, which is practically residual and reveals itself for the moment in crimes against privacy, specifically in the offence of access to files containing reserved personal data, but especially in the so-called offence of intrusion. Therefore, the protected legal good is cybersecurity or the security of computer systems (Carrasco, 2010).

Criminal Law before Artificial Intelligence

AI is invading many areas of social life. Criminal law is also being involved in various ways and probably more in the future. So we have to anticipate to establish in what aspects, how and to what extent AI colonizes present life.

The possibility of attribution of criminal responsibility in the context of the intervention of diverse AI systems is already beginning its discussion. And it is also at the door of the debate whether this responsibility can also be directly attributed to autonomous intelligent systems. Without being able to go much further in this exciting debate, I can point out two premises that will help to situate the issue more correctly: 1) the indispensable principle of human control of AI systems (meaningful human control)[23]; 2) the opportunity to establish compliance procedures or the attribution of preventive obligations or duties to human beings related to such systems, in a similar way to that established for legal persons (Romeo Casabona, 2020a, b).

[23] European Group on Ethics in Science and New Technologies (EGE), *Opinion on Artificial Intelligence, Robotics and 'Autonomous' Systems*, Brussels, 2017.

Contemporary criminal law is basically based on its preventive function, that is, on the use of legal remedies (legal and criminal consequences: penalties and security measures, mainly) aimed at preventing the commission of crimes, accordingly, to avoid their future commission. Several methods are available to determine the risk of re-offending (criminal dangerousness) before sentencing. The actuarial method through the use of algorithms is automated and maximized through its digital processing using AI systems.

It is foreseeable that if there is a highly improved and sophisticated development of AI in this sector, it will be able to objectively predict the illicit behavior of a criminal without entering into the study of his personality. Some US court rulings have already resorted to this technology, using an AI program (COMPAS).[24] The result was that the program ruled a risk of recidivism and that the conviction imposed a more severe penalty. The main issue, surprisingly, was not the technique itself, which leads to the evaluation process resting on not sufficiently proven computer systems, but on the efficiency or otherwise of due process for the defendant (compatibility with the right to due process in US law) and the possible collision with other fundamental rights, such as the right to protection of personal data. Legal arguments of the defence and the judgment itself revolved mainly around the following: first, the reliability of the programme, on which the court refuted that the chamber was in a position to assess this aspect, even if it were not conclusive that it had done so; second, the denial to the defence of access to the AI system to verify its operation and reliability, which was also rejected for putting the industrial secrecy of the private company that manufactured and marketed it before the defendant's procedural rights.

The controversy sparked by the judgment referred to above has been particularly polarised around procedural cases which, being very important, do not focus on the substantive issue, that is, if it is acceptable that an AI system can become a determining or decisive instrument to impose certain legal-criminal consequences based on the supposed predictive capacity of the former. We already know that in the European area it is forbidden to take decisions exclusively automated or based on the profiling of people or their stratification or classification into groups to make similar decisions for those who are part of the same group.

It is certain that both current and automated actuarial procedures through future AI systems will perform ancillary or additional, possibly even relevant, tasks, but they should be in the context of individualizing conceptual premises, such as criminal dangerousness. In addition, the human being must continue to be able to impose himself on intelligent automated systems, taking his decisions autonomously, certain that having in view all the pertinent reports, within the framework of the free appreciation of the evidence, which must not be renounced. Effective protection of fundamental rights and the judicial system and procedural law must ensure this.

[24] Specifically, the Supreme Court of the State of Wisconsin, State vs. Loomis (July 13, 2016).

Final Remarks

The course of these last decades has allowed us to banish definitively a prejudice that, to a large extent, had its origin precisely in the jurists themselves: the obvious fact that the of human genetics and biotechnology and that of ICTs and AI, especially in its relations with advanced medicines, is not science-fiction law, neither today nor 30 years ago. During this time there has been a constant and growing production of specific regulations in these sectors, so that the internal rights of many countries have a broad, well-founded and hopefully powerful and efficient normative acquis. In addition, it has generated some litigation before the courts in various sectors, which is where real life law is reflected.

It is therefore expected that normative production will continue where necessary, both in the sphere of states and in the sphere of influence of international and European governmental bodies. Legal tools will continue to be a reliable and socially valued resource for establishing regulatory channels that favour balanced attention to the interests and pressures of the various groups involved. They will also be relevant for introducing or strengthening mechanisms for protecting individuals and the communities and groups in which they are integrated, especially through human rights.

It is also true that it would be naive to assume that everything would be resolved or channelled along this path. Other non-legal channels are also needed, such as the acceptance of the ethical relevance that many of these activities entail and that it should preside over or inspire attitudes and behaviors of the various actors, starting with the assumption of responsibility (principle of responsibility).

During this long but rapid period, jurists have made efforts to develop human rights or to identify new rights holders. In doing so, account should also be taken of the contributions to the plural ethical debate generated by the issue, in particular the principles or values that may be relevant to science and technology. It is only by doing so that the risk has been averted that the law lacked horizons and objectives, and that it acted disoriented and even blind.

Law on the human genome and advanced medicines, although we have seen that it has much of its origin in a soft law, especially in the field of international human rights law, it has been moving steadily in domestic legal systems towards a law characterized by rules of determination, by its binding nature, since they are increasingly backed up by sanctions and other legal consequences of various kinds and importance, and since such a law has been incorporated socially to a large extent through case law.

I must conclude with a reflection similar to how I began this work. Criminal law must protect relevant legal goods against the most serious offenses that might be suffered by them, but it must also continue to be dependent on the system of guarantees, inherent in liberal criminal law, and governed by known principles that limit its intervention.

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Chapter 18
Membership and Structure of Institutional Bioethics Committees

Toby Schonfeld and D. Micah Hester

Abstract The complexities of health care create situations where even the most well-meaning professionals and the most invested patients can fail to navigate difficult issues, concerns, and decisions. Hospital ethics committees have developed to address these ethically challenging cases in clinical care. In this chapter, we review the three functions of hospital ethics committees, devoting more space to clinical ethics consultation in order to describe the range of approaches to this function. We then provide guidance on the committee's administrative location, charge, and membership as a way of demonstrating the benefits a committee might bring to its institution.

Keywords Hospital ethics committee · Clinical ethics committee · Ethics consultation

Introduction

Hospitals and other healthcare institutions are complex environments, aimed at providing beneficial care to patients through the services of healthcare professionals in multidisciplinary teams. The complexities of health care, however, create situations where even the most well-meaning professionals and the most invested patients can fail to navigate difficult issues, concerns, and decisions. A physician may want to perform surgery while a patient prefers "natural" and "holistic" alternatives. A nurse may judge an order from a physician to be unwarranted given the patient's

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presumed long-term outcomes, but believe they are powerless to do anything other than fill the order. The family of a patient may request medical interventions when the healthcare team believes those are ill-advised or even "futile." Many of these kinds of situations are not solved through a rigorous attention to physiology and pharmacology (though those may both be important). Instead, these situations push on issues of values, interests, and beliefs that need to be weighed and balanced. They speak to obligations, outcomes, and character, not just skill or knowledge. Over the last 50+ years, hospitals have developed mechanisms for addressing these ethically challenging cases in clinical care. In most cases these mechanisms take the form of a committee charged with addressing ethics concerns in the institution—known variously as hospital, healthcare, clinical, or institutional ethics committees.[1] The purposes of these committees is to improve the quality and delivery of health care through the identification, analysis, and resolution of ethical questions or concerns. These committees might be able to diffuse tensions, clarify the meaning of terms like "medical futility" and "comfort care," and suggest a way to reconcile conflicting obligations. Further, they could create educational programs to prepare the staff for similar situations in the future, and even develop policies that would help resolve future conflicts that appear intractable. Such a group is a healthcare ethics committee (HEC), and these three activities in fact constitute its typical charge.

The history of the development of HECs is recounted in Baker's chapter herein, but as we come into the second decade of the 2000s, most US, Canadian, and European hospitals have an HEC. They are slightly less common in European hospitals than in the US, with the percentages even lower but still existent in Asian Pacific and Middle Eastern countries (Hajibabee et al., 2016). Given the ubiquity of HECs in the US, we will use it as our primary reference point throughout this chapter. In fact, HECs are so common that a conservative estimate would be that 40,000 people (and maybe half-again that many) in the United States currently serve in some manner on an HEC.[2] Further, while the American Society for Bioethics and Humanities (ASBH)—the 2000-member professional bioethics organization in the US—only began certifying clinical ethics consultants in 2018, at least one study estimates that more than 20,000 individuals across US hospitals consider themselves to function in the clinical ethics role (Fox et al., 2021a). With so many institutions and persons involved, and their growing influence across the world, it is therefore important to understand how HECs are structured and operate to understand better the relationship between form and function, membership and service.

[1] Note, this chapter focuses on clinical ethics, not research. Thus, the chapter's references to ethics committees are to hospital/healthcare ethics committees—aka, clinical ethics committees—not research ethics committees (as they are called in Europe and elsewhere) or institutional review boards (as they are called in the US).

[2] These numbers, while rough estimates, are supported not only by Fox's data from a survey in 2000 (Fox et al., 2007 and more current data in 2021), they are supported by informal survey data (2020) showing there are approximately 5000 accredited hospitals in the US and an informal online survey showing that there were over 1200 HEC members in just 65 of those hospitals.

Three Functions of HECs

As developed by the President's Commission in 1983, there has come to be three traditional activities of an HEC—consultation, education, and policy review/development. A further, but uncommon, function of the committee that may or may not tie to the traditional activities performed is organizational ethics, sometimes added to a committee's charge. The most visible and often controversial role is to provide case review or, as it is often referenced, to consult on ethical issues raised by complicated clinical situations. Equally important, though sometimes forgotten, are the other two activities: formulating institutional policies consistent with the organization's function and mission to guide the professional staff in making ethical decisions, and educating hospital personnel about these policies and about healthcare ethics in general.

Function 1: Case Consultation

As noted elsewhere in this volume, ethics is a specialty discipline with its own domain of inquiry. It leads to the development of moral norms and a deliberation of values in light of those norms. Thus, when an acute *ethical* problem arises in clinical care, turning to individuals with special education and/or experience to address it is akin to consulting a cardiologist when the patient has heart-related medical concerns. This explains the need for the ethical case consultation, and several different models are effective ways of achieving these ends; brief descriptions of the three most common models follow below.

- **Individual Consultant**: The individual consulting model requires individuals with trained expertise (and now certification) to provide consultation. The individual's training typically consists of education in healthcare ethics (formally or informally) often supplemented with demonstrated competence in an academic discipline that informs the field (such as philosophy or religion), as well as familiarity with the clinical setting. Increasingly, they must also pass a certification exam, providing them with a credential as a healthcare ethics consultant-certified (HEC-C).
- **Multi-Disciplinary (a.k.a., "whole" HEC) Committee**: A model that is common in smaller hospitals is that of a multi-disciplinary committee that conducts consultations. A multi-disciplinary committee ensures a variety of ethical and professional perspectives and gathers partial expertise from a larger number of individuals.
- **Consultation Subcommittee (a.k.a. "Team-based" approach)**: A third, quite popular, approach across a wide range of hospitals involves the appointment of select members of an HEC onto a consultation subcommittee. Members of the group are chosen for their special abilities and training in ethics and process in order to be available to provide help. This model attempts to incorporate some of

the best features of both the individual consultant and the whole committee models, and as an interdisciplinary group, it would be expected to contain different ethical perspectives as well as differing sets of skills and experience.

Choosing from among these models involves matching the needs, resources, and scope of the HEC to the institution or organization more broadly. An HEC should consider carefully which model best suits the institution and provide specific support for the chosen model in order to help it succeed (ASBH 2011).

Function 2: Policy Development, Review, and Implementation

Many policies in a hospital deal with ethical concerns. Some have obvious ethical content, such as policies that govern advance directives. Others that are not overtly ethical in content may still have ethical dimensions—for example, policies concerning admission, discharge, and transfer of patients. When done well, writing or revising policies provides HEC members with an opportunity to engage in meaningful interdisciplinary work with the clinical departments likely affected by the (proposed) policy. Policy work is some of the most important work undertaken by HECs: the very character of the hospital is expressed, in part, through its policies, and thus, the ethical climate of any institution is determined in large part by the policies it adopts.

This is particularly true when considering policies that govern the organization. Good policies help individuals make good decisions and thus prevent some ethical problems from arising. They may also help to shape the institution's policies on workplace conduct, hiring practices, and the allocation of resources broadly construed. Per the dominant US accrediting body for healthcare institutions, The Joint Commission, every institution must address "organizational ethics," (Joint Commission 1993) but it remains an open question how much responsibility the HEC should take on regarding these issues with some hospitals opting for a separate organizational ethics office/officer/committee.

Function 3: Education

Last but not least, the educational role of an HEC is two-fold: looking internally at the HEC membership and externally at the institution's staff. The great majority of HEC members will have little academic training or other formal background in healthcare ethics; some training, then, is necessary for this new role.[3] But in

[3] Fox et al. (2021a, b) note that ethics knowledge is the single most desired attribute of a ethics consultant, followed closely by interpersonal skills. Both of these can be trained, and should be the focus of intracommittee education.

addition to this, an HEC should also provide education to the entire hospital community. This becomes particularly important when policy is adopted or revised that has ethical dimensions, when a specific ethical concern comes to the committee repeatedly or for some other reason seems to gain traction in the institution, or simply to address perennial issues in healthcare ethics—like surrogate decision-making or the allocation of scarce resources.

HEC Constitution and Authority

While some states and countries do have laws regarding some aspects of HEC work, most HECs do not operate under required legal or regulatory standards. Similarly, the Joint Commission fails to articulate expectations of an HEC (or even the processes by which ethics is addressed in the hospital). Thus, there are no definitive and authoritative guidelines about how the committee should be developed: its administrative location, its charge, and its membership. However, we can provide some guidance based on considerations of the benefits a committee might bring to its institution.

Location and Accountability

All institutional committees are established by a particular administrative unit. They are given a purpose or charge and are responsible for reporting on their activities to the parent unit. There is no one single "home" for HECs. HECs have been created by the medical staff, by the hospital administration, and even some by the hospital's board of directors (Prince et al., 2017). Although it may not be a crucial decision, the location of the HEC in the institution's administrative structure can have some practical consequences, since guidelines for constituting and operating the committee may vary according to the group to which it reports.

In some hospitals, for example, medical staff committees must be chaired by physicians, thus restricting the options for filling this important position. On the other hand, as a medical staff committee intent on quality improvement, it may be easier to shield proceedings of the HEC from any potential legal scrutiny. Where the organized medical staff has yet to embrace fully the concept of an ethics committee, it might be advisable to establish the HEC as a unit of the hospital administration. If it is an administrative committee, however, its purpose must not be perceived as making the hospital run smoothly. The third possibility, board committee status, can carry both positive and negative messages. On the one hand, the HEC is answerable only to the highest authority, which gives it significant status. On the other, this may carry the implication that its purpose is to oversee and perhaps report on medical and administrative decisions, creating distance from the very people it is intended to help. Given all these potential benefits and detriments, determining the best place

for an HEC to be "housed" within the organization will involve many subtle factors that vary from place to place and may change over time in any given institution.

Leadership

Committees are rarely effective if they do not have good leadership. Thus the chair of an HEC is always a critical position to fill. The chair(s) often will become the de facto face of the committee and should be someone who enjoys respect and credibility among the many professions in the institution. The most important quality, however, is commitment to the idea of an HEC. The chair must believe in the mission of the committee and consider the position an important part of their job. Meetings will be perfunctory and unproductive unless the chair takes care to construct a meaningful agenda.

Where should one look for a suitable chair? There are good reasons to support a physician as chair of an HEC. A physician chair tends to have more immediate credibility with physician-colleagues, perhaps making it easier for them to call on the committee for help. As we have noted, in some institutions, the committee is under the auspices of the medical staff, and only a physician is allowed to function as chair. However, in other hospitals, no such rules exist, so there may be a diversity of leaders. A professional ethicist may chair the committee in these instances, which lends credibility to the work of the group given the professional training and general expertise of the leader. This will work only in cases where the committee and the chair are well-respected members of the organizational community, and where the chair has clear partners with other key stakeholders. Nurses, social workers, and other healthcare professionals may serve well as chairs, too. Consider a co-chair model, as well; co-chairs can help gain credibility from different constituencies in the hospital, and they can share the workload in order to keep the committee moving forward, not getting stale. Regardless, there are no hard-and-fast rules; committee founders need to assess the available resources and the pragmatics of the institution to determine who should chair the HEC.

Membership and Structure

Importantly, an ethics committee allows for an array of knowledge and perspectives to be brought to bear on consultation, education, and policy issues; otherwise, the hospital might as well be served by one or two individuals. Thus, the committee should be multidisciplinary, composed of members with a variety of professional perspectives and disciplines on clinical care (physicians, nurses, allied health professionals) and on broader social issues (for example, social workers, chaplains, and ethicists) (Prince et al., 2017). Second, a committee allows for a variety of expertise. General familiarity with ethical issues in health care is desirable (Fox et al., 2021a, b).

Particular physicians and nurses with training or deep interest in ethical issues are obvious targets for membership. At the same time, policies or cases tend to cluster in or overly affect certain units. Thus, it might be important to have, say, a critical care specialist on the committee, as cases from acute care units are often fraught with ethical concern.

Of course, individuals specifically trained in clinical ethics are desirable, though not always available. Given, though, many HECs do perform ethics consultation, ASBH has developed a credentialing process, the Healthcare Ethics Consultant-Certified Program, as a way of professionalizing the practice of providing clinical ethics consults. This program focuses on individual knowledge and skill, requiring individuals to get hundreds of hours of ethics-related experiences in the healthcare setting and then pass an exam. Earning the credential (an HEC-C) reflects endorsement of a minimum knowledge of key concepts and skills in healthcare ethics (ASBH, 2021). Because it only reflects basic competency, many people with certification are well-suited to work with and in HECs, rather than as solo consultants.

Special knowledge is desirable on the committee; however, some areas of expertise deserve special consideration. For example, some committees include a member of the hospital's risk management or legal team, and some include members of hospital administration. The issue that arises for these particular roles focuses on potential conflicts of interest.[4] While ethics committees are *institutional* committees, they are charged to be "objective" in their deliberations, looking out for what is the best solution to a difficult case or complicated policy from a dispassionate perspective. As a result, the outcome of deliberation may not be an action that is in the best interests of the institution more generally. Thus, to the extent that the risk manager or hospital administrator also has a responsibility to protect the institution, this conflict of interest may raise tensions given their roles. On the other hand, having a representative from hospital administration or risk management could prove quite beneficial to the committee; this is particularly true when the committee considers organization-level decisions (like policies on resource allocation) or when there are real questions about how a state statute may apply in a particular case. In addition, having a member of hospital administration on the committee may lend it legitimacy, and may enable resources to be allocated to the committee for education or other purposes that might otherwise be devoted elsewhere. It may be desirable to create ex officio (w/out voting privileges) positions for such roles, but regardless, these are issues about which an HEC should be thoughtful when deciding on its composition.

Another unique category of membership is that of the "community" member. While not a requirement, many HECs, perhaps following the 1983 President's Commission's recommendations or structuring themselves after the IRB model,

[4] Prince et al.'s survey of US HECs in 2017 noted that 225 of HECs purposefully excluded and administrators and legal officials. A survey of Canadian HECs from 2010 showed roughly half had lawyers on the committee and three-quarters had administrators (Gaudine 2010). A limited survey of 5 Chinese hospitals from 2013 indicated that all five HECs had lawyers (though, interestingly, none had specialty physicians) (Liu et al. 2013).

employ community members—that is, persons not directly associated with the institution. The purpose of the role is to provide a "check" on the singularity of institutional members of the committee. This is a daunting role to perform. It may be difficult to identify persons to fill the role. In fact, the person filling the role often has some relationship with the institution (e.g. ex-patient, former employee, member of a hospital advisory council, etc.), raising questions whether that individual can adequately fulfill the intended role of the community member. Nevertheless, some committees may find it useful to have a community member, even two, on the committee, especially when the committee is particularly involved with issues that impact the community directly.

In addition to their knowledge and positions in the institution, a number of personal qualities of its members are critical to the success of an HEC. While about a quarter of HECs require references and interviews to become a member, some have an expectation that members will also demonstrate character traits like integrity and honesty (Prince et al., 2017). Further, members must demonstrate a sincere belief in the importance of the committee's work and be willing to devote significant time and energy to it. They should also try to take advantage of opportunities for self-education. Moreover, for an HEC to function smoothly and effectively, members must respect one another and the various perspectives they represent; egalitarianism should pervade the committee's work. Differences of status within the organization should be left at the committee room door: it is intent to do good and right with cogency of reasoning that should matter, not position in the institution. Members should be respectful but not deferential to one another, and anyone who expects deference should be dropped from the committee.

Bylaws

Like any other working committee, an HEC needs a set of bylaws or a detailed committee charge to give it structure and allow for necessary changes in an orderly manner. In addition to leadership and categories of membership, the by-laws should address size of the committee, terms of membership, frequency of meetings, and the scope of the three roles of consultation, policy review, and education.

HECs vary in size. One survey showed that larger hospitals (550 or more beds) can have over 30 members on the HEC, while smaller hospitals may have memberships as small as 10 persons. Further, length of service on the committee varies as well. About half of the HECs in the US have unlimited terms, while others have restricted terms as short as 1 year (Prince et al., 2017). Short terms and a rapidly rotating membership will result in instability and inexperience, whereas indefinite or permanent membership may burden a committee with uninterested and unproductive members. The reasonable solution to the extremes is probably a compromise, such as staggered, fixed terms of several years with the possibility of

reappointment. Uninvolved members can easily be dropped and committed ones retained as long as they contribute to the group.[5]

Frequency of meetings is another item the bylaws should address. Regular mandated meetings is an expectation. While it is easy for overburdened professionals to slip into the "only when necessary" mode, which in effect means only when there is a consult to conduct, without regular meetings the "preventive" work of the committee—education and policy review—will suffer. Self-education and self-assessment will also falter, affecting the quality of the consults, and the committee will lose a sense of its continuing importance to the life of the hospital. Quarterly meetings are the minimum to retain a sense of continuity, with more frequent meetings highly desirable.

Ultimately, committee members should be encouraged to own each function of an HEC, and as such, the bylaws should define as clearly as possible the role that the HEC is to play in all three of its primary activities. The educational function will probably be left entirely to the committee, to design and implement programs that it can offer on its own or through departmental meetings (having a budget for this purpose is highly desirable). Further, the bylaws might specify a base level of ethics education that committee members themselves should have.

With respect to policy review, the HEC should be charged to recommend changes up through the administration or to the medical board. In this it is similar to every other committee in the institution, as committees are generally created to make recommendations rather than final decisions about policy matters. If there are particular policies the committee is to "own" or review regularly, they should be specified in the bylaws, or a list should be kept as part of the HEC's standard processes and operations documents. And in other situations, the HEC may initiate the creation of a policy based on a series of clinical consultations; members should consult institutional procedures for performing such an action.

The most important function to clarify in the committee's bylaws is case consultation, both in terms of what role it plays and outcomes to expect. An HEC may take on the consulting task itself or may provide oversight of a consulting service that is established separately from the committee itself. Further, although committees are typically charged only to make recommendations to others, some are in fact constituted (often through a specific policy) to make binding decisions about particular cases. Nevertheless, there is sometimes considerable apprehension about the ethics committee "taking control" of a case when called to consult. Committee bylaws should specify that the committee is advisory only and does not make decisions about patient care. Some committees build this into their name (e.g. "Medical Ethics Advisory Committee") to make clear the limit to their authority. There may be a small subset of cases that the committee is given explicit authority to decide; if so, these should be spelled out carefully in the committee bylaws.

[5] A 2014 review of practices of the HEC at Mass General shows that attendance of members is a persistent problem with no greater than 35% average attendance of the last 15 (reported) years of the committee (See Courtwright 2014).

Conclusion

The Healthcare Ethics Committee is a firm and ubiquitous fixture in hospitals, yet, like any complex institution, it is still defining itself. The concept has been scrutinized in the scholarly and professional literature for some 40 years, including several books and countless articles focused on the consultative function of an HEC. There are ethics committee networks in many states and regions of the country. There is no lack of resources to aid an institution in organizing, educating, or revivifying a moribund committee. In the end, however, the general idea of an HEC must be adapted to the particular structure, mission, and size of the institution, and just as important, to its professional and community resources.

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Chapter 19
Foundations of Bioethical Decision-Making in Bioethics and Biolaw

Jacob Dahl Rendtorff

Abstract This chapter discusses the theoretical foundations of bioethical decision-making and provides the basis for bioethical judgment in bioethics and biolaw. The age of technology challenges the ethical views of humanity of earlier times. At the same time, developments in biomedicine, biotechnology and human genetics require reflection on the appropriateness and consequences of biomedical and biotechnological interventions. Therefore, it is important with a bioethical turn in ethics where we include the whole living world in ethical reflections. Here, the chapter discusses bioethics, bioethical judgment, and responsibility in relation to the person, body and its boundaries. Ethical theory of the good life, utility, biomedical principles, freedom and justice in health care are presented in order to formulate a theory of bioethical judgment and applied bioethics. On this basis, the chapter develops reflections on the foundations of bioethical decision-making based on the philosophy of the basic ethical principles in bioethics and biolaw. This approach to bioethical decision-making can also be considered as the basis for bioethical decisions in ethics committees and for ethics and values-driven management in hospitals and health care organizations.

Keywords Judgment · Ethical decision-making · Bioethics and biolaw · Ethical principles · Bioethical turn

Introduction

The modern world is characterized by forgetting the being of being, which in bioethics emerges as oblivion of life, nature and corporeality. The age of technology challenges the ethical views of humanity of earlier times. At the same time, developments in biomedicine, biotechnology and human genetics require reflection on the

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appropriateness and consequences of biomedical and biotechnological interventions. Therefore, it is important with a bioethical turn in ethics where we include the whole living world in ethical reflections (Lebech, Rendtorff & Kemp, 1997). Not least in the time of the Anthropocene where humanity as such has a changing impact of living conditions and sustainability of the globe. One way is to develop bioethics in a modern perspective as an extension of classical person and body ethics in Aristotle and Kant. Here, human bodily existence is described as part of an organic living world, and this can be the basis for formulation of bioethical principles to help to formulate boundaries and guidelines for intervention in life, nature, and corporeality. In Greek, bios means life, so bioethics can be defined as an ethics of life. Ethics means norm, custom, so bioethics deals with setting boundaries and defining the framework for human intervention in the living world. In an ethical sense, life has significance as self-organized processes that can perish. The question is what ethical integrity ethical reflections imply for human beings, living beings and living organisms in general. The basis of bioethics is a definition of our implicit moral preconception of the inviolability of life, a phenomenology of the lifeworld that leads to formulation of bioethical principles as basis for bioethical decision-making such as respect for personal autonomy, corporeality, the good life, justice, virtues and ethos that form the basis for a later analysis of specific ethical issues. This can be determined as the foundations of legal and ethical decision-making and judgment in bioethics and biolaw (Rendtorff, 1997). In this sense, bioethical decision-making is also the foundation for decision-making in bioethics and biolaw (Kemp, Rendtorff & Johansen, 2000). On this basis, we will in the following develop reflections on the foundations of bioethical decision in bioethics and biolaw, based on the philosophy of the basic ethical principles in bioethics and biolaw (Rendtorff, 1998, 1999a, b, 2000, 2009). This approach to bioethical decision-making can also be considered as the basis for bioethical decisions in ethics committees and for ethics and values-driven management in hospitals and health care organisations, based on basic ethical principles of bioethics and biolaw (Valdés & Rendtorff, 2022).

Bioethics as the Ethics of Life

The technical civilization can ironically be called the eighth day of creation, where human beings have become masters of their own history and as engineers of life on their own can change their nature. A tragic dialectic of Enlightenment (Bech, 1988a, b), in which the one-dimensional reason and mastery of nature that were to create freedom turn into their dialectical opposite: totalitarianism and unification. There is a danger that a modern hereditary hygiene, where science, by intervening in the human body, the very basis of the person's freedom and subjectivity, dominates and annihilates the human person. At the same time, plundering of nature, extinction of species, waste of resources and pollution threaten to undermine the basis of human existence.

Current debates about biomedicine and biotechnology, however, show a societal concern that something may be irreversibly lost by the human interventions in the living world. The reason is not only that society also perishes if nature and living things are destroyed through industrial exploitation. Rather, one is concerned with the dignity of life that as such attaches intrinsic value to nature. Humanity is characterized by mortality, temporality and finitude and this existence makes human beings constantly fear nothingness and loss. Through its implicit existential understanding of the possibility of the loss of the other human being and of the transience and fragility of the living, humanity must have a concern and responsibility for the living world. This can be documented with a study of our moral feelings, which reveals an existential care for the living world, which results in a commitment to protect and develop society's proper relationship with nature and corporeality.

A very simple moral phenomenology: a description of our moral feelings and attitudes towards nature and the living world thus shows that humanity does not behave indifferently, but the question of the integrity and inviolability of life is the basis of concern for the continued richness and existence of nature. One only needs to engage in discussions about abortion, nuclear power, nuclear war, whales, organ donation, to see that the framework for the discussion is not only functional arguments about ecological sustainability, but also a concern of how society can ensure the right relationship between culture and nature. One presupposition is that the basis of morality is humanity's emotions, the human being's bodily-sensory relationship with nature and the universe, where an immediate cohesion with and openness to nature precede mastery of the living world.

Moral feelings are not subjective and private, as some positivists claim. On the other hand, they are common for all people and can claim universal validity. Otherwise, it would not be possible to discuss ethics. With the German philosopher Max Scheler, one can say that values are intersubjectively grounded. It is the task of moral phenomenology to describe these values, which are grounded in freedom and understanding of the law of morality as a sense of emotion. Pursuing moral phenomenology is not an invention, and many previous philosophers have argued that morality must find its basis in human experience and emotional life. Rousseau and Hume speak of compassion for other human beings, and Kant speaks of the respect for the law of morality as fundamental to human existence. It is the task of public debate about bioethical issues and bioethical decision-making to find the correct application of these universal principles of ethics.

The Intrinsic Value of Life and Bioethical Judgment

The American legal philosopher Ronald Dworkin takes a provocative starting point following this line of thought in the work *Life's Dominion* and he claims that the background for the emotional debates about ecology and biotechnology that characterize the Western world in these years, is precisely humanity's moral commitment to express respect for life and take care of the living nature. A premise is that life as

such has intrinsic value, i.e. exists for its own sake without being only a purpose for anything else. We rejoice in nature's organized processes for their own sake. Human life is given intrinsic value in our moral experience and daily life as sentient beings. We honor art and culture as invaluable values and things in themselves, and the survival of humanity as well as the existence of future generations is enforced as an end that is self-evident and impossible to dispute.

The holiness, the right to existence and the inviolability of the individual human being is of intrinsic value. The individual creates his or her own life as a work of art and life has infinite value for the subject. And one can compare nature and the living world with a work of art that we as ingenious creations honor for its own sake (Dworkin, 1994, p. 70). As with our relations to the great and eternal art, we do not attribute to nature exclusively subjective or instrumental value, but we rejoice in the existence of nature for its own sake. Our concern for plants, trees and for the extinction of species comes from this respect for life as a value, just as we are critical towards radical genetic manipulations based on our appreciation of the self-organizing process of evolution.

The problem is, however, how this idea of the inviolability and sanctity of nature and human life is to be interpreted. It can hardly be everything in nature that has intrinsic value. Natural disasters, COVID-19, or HIV viruses and cancer are aspects of nature that can be combated without resorting to violence against the sanctity of life and nature. And a fetus that threatens the life of the mother seems to be entitled to be killed without being said to disgrace the inviolability of human life.

And one can no longer refer to an original nature as a measure of the actions of civilization. The modern world has socialized nature in such a way that the concept of nature is created in and by society. The body is a product of Western industrial society and humanity is so foreign to nature that the concept of nature is very much a social construction, where reference to something as being "natural" or "authentic" often functions as ideology, conservatism and legitimization of power relations.

Although the phenomenology of our moral emotions shows a basic respect for life, human corporeality and nature's self-organizing processes, this respect must be seen in relation to individual and particular situations, so taking care of nature is a process of interpretation where life is respected in different ways in different contexts, and respect for the dignity of life can thus best be enforced in certain contexts by eliminating that which threatens life and aims at destroying the living world.

The Principle of Responsibility in Bioethics and Biolaw

The foundation of bioethics, respect for the sanctity and inviolability of life, is the background for another principle, developed by the philosopher Hans Jonas in the book *The Imperative of Responsibility*. Jonas also argues from the idea of the inviolability of life. Nature has its own teleology that is independent of human mastery. Humanity is a part of nature as a living physical organism. As freedom and subjectivity, humanity transcends nature and relates to its own nature. Through the

self-maintenance drive, humanity says yes to life and no to death and therefore attaches value to life in itself, a joy of life that is the basis for the moral feeling of being responsible for life (Jonas, 1979, pp. 142–157).

In the technical age, where humanity has expanded power to intervene and change the living world, this leads to an expansion of basic ethical imperatives. The reverence for the moral law is going to involve respect for the self-organizing natural processes that evoke the human sense of responsibility. This responsibility arises from the power of humanity and from the fact that there is a non-reciprocal relationship between human beings and nature, where nature is dependent on the will of human beings. Human responsibility applies not only responsibility for other human beings, but responsibility for the entire living world (Rendtorff, 2008). Respect for life implies a responsibility towards the vulnerability of nature and a fundamental concern for preserving the living world.

Humanity must consider the consequences of its actions so that the integrity of the biosphere is recognized, and no predation is carried out against the species. Jonas reformulates Kant's categorical imperative in a modern perspective in the sense that it is an absolute and universal duty to ensure that real human life also exists on earth in the future. This principle is the axiom of ethical action at the sociopolitical level. Although the suicide of the individual in extreme situations can be allowed, humanity does not have the right to commit suicide collectively, as this would prevent future generations from living and acting. Decision-makers in bioethics must not only be guided by realpolitik and short-sighted interests but they must always consider the transience and uniqueness of the living world with self-organizing natural processes towards higher levels of natural perfection. The principle of responsibility involves an ethics of the future, where society in connection with interventions in the living collective world is committed to protect and take care of future life in nature and society. In this sense, the principle of responsibility is the foundation of the basic ethical principles of autonomy, dignity, integrity and vulnerability (Kemp & Rendtorff, 2009).

The Person and Its Boundaries

What does it mean to respect human life? A person can be referred to as an expression of the living person. Classical ethics defines the human person as a sensible animal and in ancient Greece, for example, with Aristotle the aristocrat, unlike the slave and with John Locke, only the free citizen with property has the person's rights and duties. Only in modern times are all people recognized as free persons and here has arises the notion of the universal inviolability of human life, where everyone, regardless of kin, class, race, and age, is considered free persons.

However, biomedicine and biotechnology challenge the traditional concept of a person, as it is possible to manipulate the person's being to a much greater degree than before. The issues of the person's boundaries and permissible interventions in persons, embryos, fetuses, body parts, transplants of organs that do not violate the

inviolability of life and the person's rights have become important ethical issues. But how should the person be defined? And what about the toddler or the demented old man? When does the person start or stop? What is the relationship between person and corporeality, and what does it mean to respect the person in borderline situations and in the different stages of human life?

Human freedom means that the concept of person cannot be given a fixed definition. Humanity's existence escapes its essence, and a human being cannot be reduced to a mere object or thing. Jean Paul Sartre argues in *Being and Nothingness* (1943) that humanity is characterized by being free and questioning his or her own being (Sartre, 1943). A human being is the being who gives everything else meaning being and with its self-reflective capacity is able to give everything the value of its own existence. Consciousness transcends itself and relates to the being of things in the world. The person emerges as a person in continous Sartre 70 self-interpretation. Therefore, humanity escapes a fixed scientific definition, as it is precisely characterized by the ability to transcend, and humanity implies the will and freedom to value life and live with an existential project together between human beings. However, valuing life, both positively and negatively, should not be understood as a rationalistic intellectual ability, so only especially conscious people are considered as persons. Already in the first sense of existence, one relates to life and shows oneself as a human being. And just the slightest expression of life manifests a conscious choice of an existential goal as an expression of the personhood of human beings.

Affectivity and Physicality in Medical Treatment

In the *Genealogy of Psychoanalysis* (1987), the French philosopher Michel Henry describes life, which is the basis of the person as affectivity and corporeality (Henry, 1987). There are no people without bodies and the individual person becomes an individual and emerges as a unit through his body. One must keep in mind that a human being is bound to a bodily reality that determines his sensing and action. Consciousness and self-reflection between presence and absence are grounded in the body's existence. The lived body is neither the biological body nor the dead body, but as Nietzsche and Freud emphasize, life is an experienced and lived desire and bodily life is force in which a human being claims to be happy. The person interprets him- or herself in interaction with other people and becomes an individual in a natural, historical and cultural context.

The body and the person also have an objective dimension that the individual does not control: the body's biological-genetic external characteristics. Humanity is determined by gender, age, bodily characteristics, genetic code and other bodily characteristics. These aspects of existence are subjected to an objective scientific description that cannot predict how the person in his or her existence will relate to his or her biological-bodily situation. For the person, sexuality and corporeality

only make sense based on the existential-affective project that interprets his or her corporeality.

Sartre calls this freedom in a "situation" where being human means to be able to relate existentially to one's life situation. The body as a thing, as a genetic-biological fact gets in the experienced existential life meaning from the person's relationship to oneself. The biological corporeality is interpreted on the basis of a vision of life and existence and an existential project that fuses the subjective and objective dimension of the body in the concrete lived, existential life. In *One-Self as Another* (1990), Paul Ricoeur describes the person's narrative and life story as the putting into language of this existential relationship (Ricoeur, 1990). Humanity interprets its own bodily existence as a fragile synthesis of suffering and happiness, of putting emotion and action into a temporal body that is the basis for a personal, social, and cultural identity of the individual human being.

Respect for the sanctity of the person is essential for the recognition of human freedom as a creative life project in the interpretation of existence and self-understanding. This is reflected in society's recognition of dignity, autonomy, and self-determination, in the perspective of concern for modern fundamental rights within a democratic framework, i.e. as long as this does not violate the freedom of other people. The commandment "thou shalt not kill" common to most religions embodies in European cultural history this respect for the infinite value of the individual. One recognizes the inviolability of life by giving the individual the right to decide for him or herself over his or her own life. In traditional biomedical ethics, this respect is formalized in principles such as the person's right to self-determination, informed consent, the requirement that the treatment must be to the person's advantage, and that the person must not be harmed (Beauchamp & Childress, 1979).

Limits to Personhood in Biomedicine

The problem, however, is how the dignity of the person can be recognized when it comes to human life on the border of the traditional concept of person, fetuses and coma patients. Should all form of human life be respected at all costs, whether personal, vegetative, biological and cellular? Does it make sense to describe embryos without developed nervous systems as individuals. And what about people who are demented or irreversibly have lost consciousness? Here it is useless to refer to autonomy as an expression of the person. Yet many people would argue that people who are vulnerable and unable to express their own needs are entitled to protection. This expresses the need to recognize human life at the person's boundaries, a type of respect and protection that is different from the one we bestow on the ordinary person.

Although a human being can only be considered as a person when he or she can relate affectively to life (after birth), this does not mean that embryos, fetuses and newborn babies are not entitled to ethical protection. These are human lives, potential people who can become real people and therefore express the dignity, integrity

and holiness of human life. Thus, there are limits to biotechnological manipulation of human life and potential individuals, even if these cannot be recognized as existing, actually living individuals. Since the fetus in the early stages or the embryo is not a person but a kind of biological life that can lead to the formation of a person, abortion can be considered legitimate based on respect for the mother's life in the early stages of pregnancy. Unlike the fetus, the mother is a truly existing person. Not to allow abortion would thus be to neglect the mother's existential dignity and right to individual freedom and autonomy. When abortion is not allowed in the later stages of pregnancy, this can conversely be justified on the basis of the fetus' development in life. And allowing abortion does not necessarily mean that aborted fetuses may be used directly for experiments, tissue transplantation, or for commercial purposes. Here the dignity of the fetus and of the embryo as a biological human life must be taken into consideration.

Similarly, respect for the sanctity and dignity of life is expressed in relation to the person who needs to be treated in health care. A coma patient who no longer has brain function cannot be described as a person. After all, there is no affective perception of the universe or the world, and the body simply lives on as a biological vegetative life. The person can die before or after the body, and the body can still live on biologically, even if the subjectivity of the person as experienced self-relationship no longer exists. However, the living biological-vegetative body as the person's remnant is still an expression of the person and must therefore still be given dignity. One must respect the biological body as an expression of the person, but precisely this respect can manifest itself in interrupting the biological life or leaving the body for organ donation, if this is expressed in accordance with the person's will.

The Rights of the Body in Bioethics and Biolaw

Dead bodies, organs or tissues emanating from persons are at once things, but at the same time parts of the human person and are therefore entitled to a special ethical protection. The task is to take care of these bodily things, which on the one hand are expressions of the person but on the other hand have differed from the bodily living person. The body's products and body parts have in ancient cultural understanding been perceived as sacred things, at once expressions of the person, but at the same time as separate from the person, they are no longer entitled to the same protection as the person. Bioethics and biolaw focus here on the ethics of the human body related to the ethical responsibility and autonomy of the human person (Rendtorff, 2001a, b, 2002a, b, 2003).

In the book *The case of the stolen hand* (1993), the French legal historian Jean Pierre Baud analyzed culture's perception of body parts and body products as such sacred things that have sacred status in the social community (Baud, 1993). Body parts have a sacred character and are entrusted to certain persons, such as the priest or the doctor. The treatment of dead bodies and corpses is an example of this. Modern society's categorization of blood and semen in donor banks as generous

gifts are examples of this relationship, where separate body parts are given a trusted status that the commandment to respect the sanctity and inviolability of life.

Thus, bodily integrity can also apply to organs that are separate from the body. A recent case in the German legal system, in which a man sued a clinic that for inexplicable reasons had negligently destroyed his semen, which he had stored for the purpose of later wanting to have children, due to a cancer operation, is an example of this. In the court order, the semen was treated as an expression of the person and the destruction of the semen was ranked as similar to bodily harm. But also, in connection with cloning, gene therapy, and other genetic engineering interventions, respect for the person must be a guiding principle, so that organs and body parts are not used for experiments and transplants, when this is contrary to respect for the person's freedom and autonomy.

Respect for the person's inviolability is thus necessary, as long as he or she is able to value life in affective perception and action. However, the advent of biotechnology leads to situations where the traditional concept of person cannot be used. Here, human life manifests itself as biological human life, potential persons or body parts. The protection required here is not the same as that granted to the human person, and it is necessary to extend human rights to the biorights of the body in order to protect the special character of human life at the person's borders. In this context, it is important to refer to the legal status of the body and define the rights of the body in the perspective of the body's status as an expression of the vulnerability, integrity and dignity of human beings. The body's bio-legal rights as protection rights of human beings ensure that interference with the life and use of bodies does not lead to an unjustifiable breach of the principle of the person's autonomy and freedom, while ensuring human dignity in situations where the person is not present or where body parts are separated from the body.

The Ethics of the Good Life

Recognizing the dignity of life does not mean giving all living things the same value. And at the same time, the respect for the inviolability of personal life must be seen from an ideal of the successful life. A human being is experiencing happiness in active sensing and action, and it is the task of bioethics not just to protect every kind of life, but to promote the ideal of the good life. The use of biomedical technology must not only turn human beings into the object of manipulation, but intervention in the body and human life can ultimately only be justified on the basis of an ideal of the person's happiness and good life. But what can be said about the good life in a pluralistic society that leaves it up to the individual to choose life, life projects and meaning of life?

The ideal of the good life is a determination of the connection between bodily freedom and authentic existence. Happiness is realized in the lifelong friendship and fellowship. This is neither based on interest nor usefulness but is motivated by a common ideal of the good life formed from a genuine lack and need for the other

as an independent free human being. The ideal of friendship is a relation of giving and receiving between free and autonomous people. Happiness is rooted in the ideal of free reciprocity with the other human being, which is grounded in a mutual affection, where caring for the other's irreplaceability and fragility is a condition for personal and shared happiness (Ricoeur, 1990, p. 227). The person unfolds in his or her existence projects in the hope of achieving happiness with other people in a just society.

In his life project, the individual is not morally neutral, but commits him or herself through his or her actions to a vision of the good life in the fragility and finitude of existence. In action, one sets a norm for good and evil, and this norm is universal, in order not to contradict oneself, one must presuppose that this norm can also apply to all other people. Together, the people overcome their immediate finitude and realize themselves in the public political space in the action and immortality of human creation of a community of mutuality. The ideal is "the good life for and with the other in just institutions (Ricoeur, 1990)". But since freedom is to be created as a project of existence, respect for rights and inviolability of the individual is fundamental to the good life in society, where freedom, equality and reciprocity of friendship are a model for the distribution of goods and opportunities in the political community.

Benefit, Utility, and Quality of Life

This ethical ideal of the good life in friendship and society as the overall ethical aim and benchmark can in combination with the notion of the person's integrity, dignity and inviolability be seen as a basis for sound social application of biomedical technology, radical interventions in the person and for decisions about life and death. The ideal is the consideration of the person's auto-creativity and self-determination as essential for bioethical decision-making.

Thus, one can hardly imagine the legitimacy of measurement of the quality of life by basing it only on the idea of the good life based on utility calculations and economic calculation, as it is naively and irresponsibly attempted by certain philosophers and as it is prevalent within parts of the health sector. Following the principle of "the greatest possible benefit and welfare to the greatest possible number", it is believed that the use of resources can be made more efficient. The treatment is adapted according to its usefulness, its return of quality of life and possible societal benefit. Priority is given to those patients who have the greatest chance of surviving and of not burdening society financially. The measure is QALY (Quality of adjusted life years), where the person's possible lifespan of a particular treatment determines the prioritization of patients for transplants or other treatments. Credentials for this calculation are pragmatic considerations and society's demands for practically operationalizable decision-making principles.

However, this necessity does not justify globalizing the concept of utility and defining the measurable quality of life and using it to assess practical

biomedical and health interventions. And even though there are limited resources, and one has to prioritize patient care in long queues, this does not have to mean that some patients get worser and less developed treatment. Inequality in the health sector is mostly an expression of poor planning and can under no circumstances be justified by dubious quality of life measurements.

Quantification of the meaning of life as quality-of-life rests on the premise that one can compare happiness and suffering in evaluation of the individual human life. It is claimed in a paternalistic way to be able to determine the usefulness of the person's life and to define this as a basis for societal decisions. Utility ethics operates in a hedonistic way with the meaning of life as the absence of pain and is based on the promotion of as much desire as possible (Cf. J. Bentham and J. Stuart Mill) and the utilitarian believes that one can measure the overall happiness and suffering associated with various biomedical interventions. This development is dangerous, as the overall health economic priority, depending on abstract cost-benefit considerations, cancels the empathy and understanding of the person's existence project and vision of the good life. This leads to abstract reasoning about the necessary health economic priorities of certain operations over others, that is in service of the overall utility, the prioritization of young before the elderly and old, those who have the greatest chance of survival rather than the sickest, etc. should be considered. Instead of this kind of prioritization it is necessary to deal with the concrete treatment reality of specific patients.

Furthermore, the notion of individual freedom and the good life is undermined by the introduction of quantifying parameters for measuring the usefulness of life for society, an objectifying human description that disregards the infinite value that life has for the individual human being. Likewise, there is a danger that the health system operates in a paternalistic way with preconceived ideologically moralizing notions of disease and health that govern the citizen's bodily poetic vision of the good life in relation to the other human being based on simplistic preference and utility calculations that disregard complexity in the individual treatment situation, and therefore in no way ensures an effective biomedical prioritization, but merely increases the distrust and distance between biomedicine, health system, state and citizen. Thus, in decision-making in ethics committees as well as in bioethics and biolaw in the context of the development ethics and law, it is important to rely on basic ethical principles of concern for protection of the human individual in biomedical development.

Can the Good Life Be Measured?

In a democratic society, it is important not to soak up the ideal of the good life in quantifying utility calculations. Although one can quantify welfare ideals health economically, the good life remains dependent on the individual's life project and freedom. The ideal of the good life depends on the specific situation, where many different factors come into play, and one does not determine in advance the actions

that can best serve the person's bodily good life for and with the other person. Here, the individual's body rights and bio-rights must precede the placement of the individual in the health system as a function of economic prioritization and measurement of society's overall quality of life.

The notion of the good life should instead be a guide for treatment and decision priorities. But this notion can never be completely formalized in fixed principles but acts as a universal ideal that directs concrete action. It is an ironic self-reflection (Rorty, 1991), which is always based on the individual case, and challenges fixed norms and prejudices. In addition to the person's bodily dignity as a benchmark, this notion follows society's ideal of happiness and community in friendship and politics, leading to decisions about life and death in the health sector. The good life is concretized in the situation of action, taking into account the person's ethical convictions, the character of human nature, the person's bodily rights, secondary rights, and the coercion of the situation and the impact of the circumstances on the individual human being.

In the end, only the individual can be held morally accountable for his or her project of existence, so that biotechnological interventions must be based on respect for the individual's informed and free assessment of his or her own situation. The assessment of the situation is based on the autonomy of the free person may sometimes require that one intervenes in the life of the person against the person's will, but at the same time the person's interests and general notions of the good life need to be taken into account.

Quality of life calculations, based on respect for the good life and for the person's autonomy, can only apply in borderline situations where the person no longer exists, or cannot act autonomously at all. This applies to situations where the human being is not a person in the traditional sense when it comes to a purely vegetative and biological condition or when a treatment is completely useless, and the person is no longer able to appreciate this treatment. But here the priorities are based on the notion of the person's bodily good life, and what is at stake is a prioritization between personal and non-personal life, ie. between persons who can give life infinite value and take into account the reduced vegetative or biological life without point of view, without the possibility of expressing personal freedom, perception of the good life and existential authenticity.

Justice and Freedom in Health Care

The basis of justice in a democracy are political and social fundamental rights, and bioethics must allow for the possibility that the determination of biomedical justice to go hand in hand with such a conception of democracy. In his book *Facticity and Validity* (1992), the philosopher Jürgen Habermas describes the justice ideal of democracy as a form of government in which the individual possesses political rights as a decision-maker in the political sovereignty of the people (Habermas, 1992). It is the task of the state to protect the rights and personal integrity of the

individual. Free and equal citizens jointly determine the progress of the republic and provide citizens with political and distributive justice. The freedom of the citizen is expressed in their negative freedoms that help to move forward towards the just political and social community. This republican procedure's conception of justice and political community is a modern discourse-theoretical interpretation of the conceptions of justice in Rousseau and Kant.

However, this notion of justice is getting into trouble when it comes to new bioethical technologies. The concept of popular sovereignty operates with the decisions of free and equal individuals as the basis for the concept of justice. Instead of the principle of equality, in biomedicine the right to diversity must be emphasized as a fundamental democratic principle. In the treatment of individuals, the individual has the right to be treated according to his or her needs, which differ from individual to individual. Living in the community of the welfare state implies the protection of the individual's bodily integrity in confrontation with biotechnology's possibilities for unification and normalization.

How can this be linked to the living as an object of biotechnology. Bodily integrity and the body's legal rights are boundary concepts in relation to the previous justification of justice. Likewise, potential persons, biological and vegetative human life and future generations stand on the border of this discourse-theoretical justification of people's sovereignty, as these cannot express themselves in the political and legal community. Therefore, it is necessary to develop a biomedical concept of justice, which is at once a continuation of the principles of democracy, but at the same time involves basic ethical ideas, built on the ideal of caring for the vulnerability of life and for the well-being of the other person.

A Biomedical Sphere of Justice

Concepts such as fundamental rights and distributive justice are not automatically transferred to the biomedical sector. As part of the healthcare sector, special principles of justice apply to the application of biotechnology and decisions at the beginning and end of human life. The problem is how to do justice to life and respect all living things. In this context, attention can be drawn to Michael Walzer's concept of spheres of justice in the book *Spheres of Justice* (Walzer, 1983).

There are many different benefits in society, of which health is just one. Therefore, one can well afford to have asymmetry and inequality in treatment as needed in the health care system, as this inequality is offset by a complex justice in confrontation with other sectors of society. Justice in particular spheres expresses the appropriate realization of the concept of justice in a particular situation and way of life. Health care and biotechnological interventions take place in such a sphere of justice. The application of utilitarian principles would simply disregard the particular problems of health care by focusing only on the societal benefits of the collective, since on that basis one cannot provide protection for future and nursing life and the rights of

the body where one can does not take into account the person's hedonistic preferences.

Likewise, it would be a categorical mistake to build the biomedical health sector according to contract theoretical principles with equal distribution of resources, as in health care there is no reciprocity, because the weak need many resources and treatment, while the strong do not need treatment at all. Principles of justice in the biomedical sector are instead based on people's common understanding of the other person's vulnerability and the obligation to provide assistance in a situation where the other person is suffering. It is the openness and understanding of humanity's and life's vulnerability and care for the weakest that motivates health care and justice in the health care sector. Such communicative action is not based on equal rights but is motivated by the radical asymmetry between the self and the other (Levinas, 1961). It is the encounter with the other person's vulnerability and nudity of existence that motivates treatment and care in the health care sector, so that the bioethical notion of justice does not depend only on equality but is based on the concept of the inviolability of life and the notion of the good life.

The right to health and well-being is thus at the limit of the concept of equality-oriented justice. Biomedicine is in the Hippocratic tradition, where it is the doctor's task to always be completely available to the individual patient and in the best possible way meet the person's need for care (Shelp, 1985). Care and treatment take place in a tension between justice and ethics, where ethics manifests itself through the golden rule of love and charity towards one's neighbor when the individual suffers envy. The distributive and rights-oriented conception of justice comes second in the field of biomedicine in relation to interpersonal emotions such as compassion, sympathy and love. Here the person is seen as not only as an object of disease, but as an irreplaceable part of human society.

Biomedical Justice Principles

The protection of the person's rights in connection with biomedical research and intervention in life can, based on these ideas, be concretized in several fundamental principles as a guideline for the treatment of persons, bodies and body parts and human life at the person's boundaries. Justice manifests itself here as protective rights with the notion of the dignity of life as the guiding principle. Indeed, this is important for the philosophy of the basic ethical principles of autonomy, dignity, integrity and vulnerability (Rendtorff & Kemp, 2019, 2000; Rendtorff, 2014, 2015a, b, 2016, 2020). Principles are thus not only rights-based, but also follow the intention to do the right thing in the individual situation. These aspects reflect the ethical self-understanding of society.

The care for the person is expressed in the fact that the treatment must take place according to the patient's needs and always be to the patient's advantage. Medical trials must in the first instance be motivated by the therapeutic consideration of the individual patient and be in the patient's interest. This involves acknowledging the

person's bodily autonomy through informed consent and self-determination in connection with the use of body parts, organ donation or hospitalization of the person during a particular treatment. Principles in medical ethics such as equal approach to treatment, not to hurt, and to promote the good for every human being are here the basis for biomedical treatment.

Likewise, the defenseless living human beings, who cannot itself express its autonomy, for example fetuses, embryos, body parts, newborns, old, are included by these rights to protection and must benefit persons without violating democratic principles of distributive justice and respect for the dignity and inviolability of life. Individuals cannot be transferred to "organ banks" against their will and the use of organs must be based on voluntary generous donation.

Respect for the living can be concretized in the notion of a preventive bioethics. Society must avoid placing itself in difficult bioethical dilemmas, caused by unnecessary use of biomedical technology or wrong societal priorities such as acute instead of chronic disease and excessive hospitalization, determined by macroeconomic power relations and systemic functional problems. Respect for life and the person's autonomy is realized through the search for solutions to societal problems that do not constantly challenge and put the integrity of the living human beings at stake. The use of biotechnology must be motivated by real societal needs and problems and not be the result of random scientific, social fantasies and popular notions of what is fashionable.

Distributive justice means that biomedical technology is not used to undermine society's ideals of freedom and equality. The burden and advantage of biomedical technology must not be shifted, so that certain members of society are disadvantaged by the use of biotechnology. Examples of such an unfair distribution are selective abortion of female fetuses in certain third world countries, use of prisoners with the death penalty as organ donors, social and economic racial discrimination of people with bad genes, social discrimination by using poor women as foster mothers, or manipulation with future generations through negative and positive hereditary hygiene, so that they are, for example, turned into work slaves, by radically changing their personal identity through biotechnological interventions.

Virtues and *Ethos*

However, the concepts of dignity of human life, the good life and justice have no meaning if they are not realized in the self-understanding of society and culture. In his critique of Kant, Hegel has shown that it is not a matter of having abstract ideals of duty, but these ideals must be part of the actual norms of society. One must live in a biomedical ethos with associated virtues to realize the principles of bioethics. With Hegel in his philosophy of law, one can speak of the "Sittlichkeit" of bourgeois society as the concrete realization of the ideals of ethics.

The human rights that few today really question can be seen as a realization of such democratic principles as an international societal ethos. Likewise, one could

argue for the realization of bioethics as an actual custom and not just as an abstract moral ideal. In the face of the irresponsibility and individualism of our contemporary risk society (Bech, 1988a, b), it is important to turn the bioethical principles and virtues into part of actual action at the societal level. It is not enough to have moral principles, but these must be observed in daily life by those who in practice deal with biotechnological issues.

Hippocratic Virtues

The basic attitudes of medicine are traditionally characterized by a mixture of Greek virtues about the doctor's wisdom, patience, generosity, openness to the patient and Christian notions of humanism and mercy, which still play a major role in the hospital's daily life as a basis for decisions. (Shelp, 1985). It is important to see the relationship to biotechnology, the person's boundaries and the living nature in this perspective.

Here, ethics is an expression of an excellent attitude, a moral ability and deed, which manifests itself in the decisions and actions that are the result of the consideration in the concrete moral situation. The virtue of biomedicine is health and the right relationship with the body. Daily practice and virtue as an ability to gear the right actions are intimately connected. Virtue and practice are part of the biomedical institutions, where a certain attitude characterizes the actions of the researcher and the doctor and other medical personel. Here, respect for the good life is embodied in those who practice biomedical practice. It simply becomes a part of daily practice to say the good and the right. Health and bodily well-being are installed as the highest good and as a basis for concrete practice.

In this context, it is the ability of the researcher and the doctor to make the right decisions in the situation that guarantees the realization of bioethics. Nurses and doctors with years of experience have a sense of the meaning of life and violation in specific treatment situations. By virtue of their professional virtues, they can judge when it would be justified not to treat a premature newborn child at risk of brain damage, they have an understanding of the proper notification of the relatives in connection with organ donation and decision on fetal diagnostics. Ethics must not forget this concrete practical knowledge as an inherited part of the practice and tradition of biomedicine.

However, this practical sense is often neglected in modern society. Abstract utilitarian considerations and complicated rules and circulars are introduced that override the situational judgment that the ethically committed person possesses by virtue of the embedding in practice and tradition. Instead of acknowledging the importance of judgment for the right ethical decisions in the healthcare sector, decisions are made to depend on technological innovation and progress.

Ethos of Responsibility

This practical judgment is closely linked to the need for an ethos of responsibility as a basis for societal decisions in the field of biotechnology. Bioethics is a public ethics that not only applies to parts of society that are in the strongest contact with biotechnology but must be extended to include all decision-makers and responsible citizens. One can compare this ethos of responsibility towards the living being at the person's boundaries and nature with the statesman who ensures to do good to his subjects in the state (Jonas, 1979) The good politician acts not only for his own sake or in the interest of realpolitik, but is aware of the consequences of its actions, and therefore does not engage in risks that threaten the well-being of the state and its citizens. Or with parents who, out of spontaneous love for their children, say to cherish their integrity and growing development (Jonas, 1979).

A biotechnological ethos wants to promote democratic and pluralistic virtues. It applies to the citizen's right to bodily integrity, diversity, and self-determination. Instead of relating to an ideal state, where people are manipulated according to the interests and necessity of the state, it is the state's task to protect the citizen's randomness, finitude and diversity, so that human nature is not degraded in favor of presumptuous notions of the superman and the perfect man.

This ethos of responsibility must be realized at the societal level, so that one not only thinks about one's own survival, but is conscious of future generations, all forms of human and animal life and of the whole of living nature (Dower, 1989). This responsibility cannot be justified as based only on contract theory or utilitarianism but is based on respect for the present and future life on the globe. One recognizes here the integrity of species and ecosystems and is aware of unintended consequences of societal action.

Such an ethos of responsibility is not only a local ethics but must be extended to apply globally as well. Bioethics is not only realized in the national state system, but as such it is transnational, so that it also applies to other states and societies. At the same time, however, it is not certain that it is the same harmonized solution to the biotechnological problems that suits the individual societies, as ethics is precisely characterized by being embedded in a way of life and in a sphere of justice. Thus, the bioethical ethos arises in the field of tension between universal validity and common norms of society in the concrete context of bioethical decision-making.

Judgment and Practice

However, it is not enough to put forward several deontological principles and some teleological preconditions for concrete ethical action. The question is whether such principles and guidelines have any significance for the analysis of the specific practical issues. One must thus take a closer look on the relationship between the ethical principles and the relationship between the given action situation as a basis for

thematic ethical analyzes of bioethical topics. Judgment is guided by a concrete effort to read the problems that arise in the conflict between different views of biotechnology, the human body, and the inviolability of life at its beginning and end.

The hermeneutic circle of judgment ensures the interplay between philosophical and ethical principles and current situations. The interplay between principles and substantial ethical notions is thus the basis for a concrete ethical reflection on the correct treatment of nature and the human body in science and everyday life. The application must be sensitive to the moral case from the point of view of practical wisdom. It is not a simple subsumption of moral principles, but its application implies a creative-innovative behavior in relation to the individual moral problem. We must go beyond the ivory tower "and relate our decision-making closely to the concrete moral situation of action.

The Application Problem

The question is what a philosophical ethic can contribute to the treatment of concrete ethical problems. How should this application be interpreted? The relationship between ethical ideas and principles can be determined with Gadamer in *Truth and Method* (1964) as the hermeneutic application problem (Gadamer, 1964). With Gadamer one can see an analogy between text interpretation and applied ethics. In both cases, it is important to give a universal content, the ethical principles or the meaning of the text, significance for the interpreter or the ethical person in a concrete practical situation. The ethical understanding is only fulfilled when the published principles are realized in a concrete ethical action. According to Gadamer, the interpreter stands in a hermeneutic circle, where the concrete situation makes sense from the perspective of the whole.

Gadamer understands the problem of application as a game between proximity and distance. A fusion of horizons is precisely to bring the hermeneutic principles into play between distance and belonging in the concrete ethical situation. Thus, it is important to apply the moral principles so that they make sense in relation to new historical situations in combination with scientific data, socio-theoretical assumptions, and to the uniqueness of the specific case.

One can put forward several ideal types for understanding this concept of applied ethics. These simultaneously reflect problems and possibilities in the concrete application of general ethical principles but can at the same time be seen as subaspects of a hermeneutic theory of applied ethics. These various forms of analysis could, for the sake of convenience, be referred to as the sophisticated, the Socratic, the Platonic, and the Aristotelian approach to applied ethics with reference to various philosophical notions in classical Greece. These types of ideals characterize the current debate about developing theoretical analysis models of concrete ethical problems, but all suffer from various flaws that are remedied with a hermeneutic-critical form of analysis.

The rhetorical approach is characterized by the fact that it does not assign the philosophical analysis does not come with any preconceived bid for the right. Rather, the possible arguments and the built-in consequences of the different attitudes that come into play in relation to the individual ethical case are analyzed, for example in connection with the proposal to introduce new bioethical references and problems. However, it is not considered the task of ethics to come up with special instructions for action. Another type is the critical power analysis (e.g. Foucault). Here the ideological, political and economic coercive mechanisms implicated in the individual moral case are presented. The critical power analysis reveals mystifications of how life is mastered and turned into a thing, but often the analysis is so radical that it is almost impossible to come up with a constructive ethical proposal for action based on the analysis.

A third type of analysis is the Platonic deductive form of analysis. As Plato operates with eternal ethical principles of truths. Here one begins with ethical well-established assumptions, which are said to be directly introduced in specific situation. With a deductive method, one directly applies the principles as premises for the understanding of the ethical right in the specific case. The philosopher is the expert, the ethical engineer, who sovereignly decides the ethical right decision in the specific situations. The problem with this model is that it does not leave the possibility of adopting the ethically specific dimension of the individual situation. A fourth model can be described as the Aristotelian-inductive model, which is based on the individual situation and the specific practice, and from there analyzes oneself to the ethically correct relation in the specific situation. However, this model can quickly become captured in the situation of published custom and will therefore not differ much from an already given practice, which means that it is difficult to relate critically and constructively to this practice.

A Hermeneutic-Critical Model of Applied Ethics

A hermeneutic-critical model of applied ethics attempts to incorporate aspects of all these approaches. At the same time, there may be a critical-constructive relationship between the specific situation and the ethical justification of preconditions. This is not a direct deduction from the moral principles, but, as we have seen, principles are derived in the beginning from the moral practice. Thereafter, principles are used as rational justification for analytical approaches and applications to new situations. The hermeneutic-critical model is a constant back and forth movement between belonging and distance (Ricoeur, 1985).

One can compare this critically constructive hermeneutics with Rawls' concept of a reflective equilibrium in *A Theory of Justice*. This is an interplay between moral intuitions and an original position, a rational construction to justify these fundamental principles of justice (Rawls, 1971). This impartial distant view is the basis for the justification of a particular moral behavior, determined by the affiliation to the situation. The impartial position tests the value of a particular situational practice. This

model is not based on a deductive relationship between principles and situations, but instead pleads for the greatest possible coherence between theoretical bioethical principles and moral intuitions in the situation (Rendtorff, 2008). Intuitions and principles are mutually tested against each other in the assessment of possible courses of action in the situation. In this way, the critical awareness in relation to practice in the situation is ensured.

Critical reason manifests itself as the clarification of presuppositions and moral arguments without completely distancing itself from the conditions that apply to the individual case. By analyzing concepts and arguments in the situation, the built-in preconditions for moral analysis are determined. However, this is not just an application of universal principles, but ideals and situations must be thought of together in a concrete unit. The ethics used, however, are predominantly situation-oriented, and it is on the basis of the situation that one must apply universal principles of the good life, justice and the inviolability of life. The critical-constructive hermeneutic analysis, as will be seen in practice takes the form of an interplay between factual conditions and bioethical ideals. This is the basis for bioethical decision-making in health care organizations, hospitals and ethics committees.

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Chapter 20
'Just Doing Bioethics': Policy, Principle, and Process

Roger Brownsword

Abstract This chapter considers how a bioethics body might perform if, hypothetically, it was to be insulated against any background pressure of policy, politics, and power, if it were to be instructed 'just to do bioethics'. It is suggested that, whether this hypothetical body sought to articulate and be guided by fundamental principles or took a more processual approach, the outcomes would be disappointing. In particular, there would be concerns that the processual approach, suffers from a degree of opacity and arbitrariness; that there is no clear hierarchy in the various principles, values and interests that are involved in the process; and, that, whenever the body tries to put some critical distance between its guiding principles and community views, there are no compelling foundations for the resulting bioethical judgments. Responding to this discontent, it is suggested that the right background is given by an understanding that differentiates between the critical infrastructure for human social existence (answering concerns about the foundations for bioethics), the fundamental values of particular communities (answering concerns about hierarchy), and the accommodation of conflicting interests within those communities (which, it has to be conceded, will be 'messy' in some cases). Accordingly, the central point of the chapter is that what bioethics bodies need is not insulation from, but an appreciation of, the right policy background, one that serves to ground fundamental bioethical principles, to contextualise its processes, and to clarify the responsibilities of its practitioners.

Keywords Balancing · Bioethics · Community values · Global commons · Policy · Principle · Process

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Introduction

Bioethics bodies, whether they are Councils, Commissions, or Committees, whether operating in the public or the private sector, whether established by governments or trusts or by industry, whether national, regional or international, do not come out of nowhere: there is always a background of policy, politics, and power (which we can refer to as the 'policy background'). There is always a story (and there are always questions) about what prompted the establishment of the body, about whose idea it was, about the purposes and interests that its sponsors intended it to serve, about its funding arrangements, about its accountability, and so on. These features of the policy background invite further questions about the relationship between the body and those who fund it and to whom it accounts: the body may purport 'to do bioethics' but to what extent is it (its membership, its agenda, and its recommendations) independent of its sponsors, to what extent do the latter exert control or influence over the former (Turner, 2004)? To what extent might it be possible to insulate a bioethics body from the policy background? Is it naïve even to ask such a question or to entertain such a thought (Bimber, 1996; Jasanoff, 2005; Pellegrino, 2006; Andorno, 2007; Salter & Salter, 2013; Gabel & Moreno, 2019)?

In this chapter, somewhat counterfactually, I will ask readers to imagine that we can put clear water between a bioethics body and its policy background, that we can imagine bioethics being done, so to speak, in a 'bubble'. Imagine, then, a philanthropist who, at the turn of the century, followed Francis Fukuyama in being deeply concerned about the capabilities that seemed to be foreshadowed by the sequencing and potential manipulation of the human genome; and who, unlike Fukuyama (2002), was also deeply concerned that we might develop an addictive reliance on the Internet which might expose new vulnerabilities as we moved our transactions and interactions online. Acting on these concerns, our philanthropist invited a group of world-leading bioethicists to join a think tank whose remit was simply 'to do bioethics'. That was it, just do bioethics—do it in any way that the group might think appropriate; no strings attached; no interference; no funding reviews; no hidden agenda; and, for 20 years, no need to report back.

Twenty years later, when the group reports back, the philanthropist is disappointed. In this chapter, it will be suggested that there is a certain inevitability about this, that no matter which way the group decides to 'do bioethics', our philanthropist will be disappointed or discontent. In other words, it will be suggested that, even under ideal funding conditions, we might not find a satisfactory way of doing bioethics. This is not to suggest that the group will have 'bungled' its bioethics. Not at all, the ways in which I assume that the group might have proceeded will all have precedents. This is not a story, like Lon Fuller's allegory of Rex I (the hapless ruler), who teaches us how to do governance by rules by first getting everything wrong (Fuller, 1969). However, it is a story that suggests that to do bioethics for the Twenty-First Century, we do have to think outside the box (Brownsword & Wale, 2020) and that, when our philanthropist elects to make a fresh start, the group will be directed to do just that.

The chapter takes us through this story in four parts. First, the two principal ways in which the group might choose to do its bioethics—bioethics by principle and bioethics by process—are sketched. Secondly, the reasons why the philanthropist might be disappointed or discontent with the group's work, no matter what its approach, are identified; and, we will note how this discontent chimes in with what Sarah Franklin (2019) takes to be a crisis in bioethics reflected in the decline of reference to guiding principles and a new faith in the integrity of processes. Thirdly, responding to such discontent, a fresh start is proposed and elaborated. The proposal is that our thinking should be orientated towards the preconditions that are essential for not only human existence itself but also for all purposive human activity in our biosphere (including the activity of doing and debating bioethics). These preconditions represent the most critical infrastructure for human communities and the protection and preservation of this infrastructure, it will be argued, is the first priority for humans. This is not to suggest that bioethics should abandon its concern with guiding principles or deliberative processes, but principles and process have to be placed in the bigger picture that is founded on an appreciation of the undeniable (literally, undeniable) importance of the critical infrastructure. Finally, completing the circle, we get to the practical matter of whether the work of the bioethics group, having been given a fresh start and a second chance, and having been insulated from the world of policy, power, and politics can now be plugged back into it. Even if, under ideal conditions, we can get our bioethics right, can we translate this back to non-ideal global conditions?

There are a number of take-home messages. However, the key point of this chapter is not so much that it is difficult to escape the policy background to bioethics, that 'just doing bioethics' is something of a pipedream. Rather, the point is that bioethics needs the right policy background, one that serves to ground its most fundamental principles, to contextualise its processes, and to clarify the particular (and various) responsibilities of its practitioners.

Doing Bioethics

There is more than one way of doing bioethics. Indeed, according to Harald Schmidt and Jason Schwartz (2016), there is a kind of North/South divide in the way that groups 'do their bioethics'. While some groups adopt a 'rigid-grid' approach, declaring their ethical principles and then applying them consistently in a top-down way, others practise a 'flexible-focus' approach, an approach that 'does not impose ethical principles or norms in a top-down fashion, but identifies them anew for each topic or report' (Schmidt & Schwartz, 2016: 443). So, for example, if we were to apply this distinction to bioethics bodies in the United Kingdom, we might say that, while the approach of the now defunct Human Genetics Commission instantiates the former approach (see Human Genetics Commission, 2002), the bottom-up consultative and deliberative approach of the Nuffield Council on Bioethics exemplifies the latter (Brownsword & Wale, 2018). Similarly, looking across the Atlantic, we

might say that, in the USA, this distinction captures the different approaches of the President's Council on Bioethics headed by Leon Kass (where the emphasis was on human dignity: Kass, 2002; Gabel & Moreno, 2019) and the Presidential Commission for the Study of Bioethical Issues that was chaired by Amy Gutmann (where the emphasis was on deliberative democratic process).

Adapting this insight, we can say that, broadly speaking, a group will seek to do its bioethics by orientating itself to one or more guiding principles (or values) which it will consistently apply, or it will be guided topic by topic by the views that emerge from a consultative and deliberative process. Like any North/South distinction, this does not leave much room for nuance. Accordingly, we have to be ready to recognise that not all groups will do their bioethics in a way that is guided consistently by top-down principles or by bottom-up processes; and that, even if groups are not inconsistent and ad hoc in their practice, they might operate in a way that combines these approaches.

'Just Doing Bioethics'

Given that bioethics can be done in more than one way; how might our think tank proceed? In this part of our story, we will start by sketching how our think tank might do its bioethics, noting the variants of principle and process that are available to it; we will explain why, no matter how the group approaches bioethics, whether its approach is some version of (rigid-grid) 'bioethics by principle' or some version of (flexible focus) 'bioethics by process', it is destined to disappoint our philanthropist; and we will then relate this to Sarah Franklin's critique of modern bioethics.

Principle

Let us suppose that our hypothetical expert group starts by surveying and mapping the bioethical literature. This is quite a task. The members of the group agree that there are many different and plausible approaches—various kinds of utilitarian, egalitarian, communitarian, and republican approaches, theories based on rights, theories based on duties, virtue ethics, and so on (Brownsword, 2003). Although some proponents of these approaches claim that their approach is 'right', the members of the group are not persuaded that any one approach is clearly right; and, indeed, they also agree that none of the standard approaches is clearly wrong. Rejecting the suggestion that some of these approaches might be welded together, the group reasons that their function as a bioethics think tank is to apply the logic of each approach to the questions/topics as they arise for discussion and decision.

While each analysis undertaken by the group is rigorous and careful, some members of the group anticipate that their work might get mixed reviews. Where all approaches converge on a particular conclusion, there is an actionable outcome.

However, where different approaches lead to different conclusions, the group fears that reviewers will find the outcome disappointing. Accordingly, in an effort to take their work to another (more normative) level, the members of the group agree that they will gloss their analysis with a statement of which approach they, as a group, judge to be the better view. Following this line of thinking, the group declares that it takes its lead from 'liberal' rights theory.

Having adopted this approach, however, the group now worries that this might compromise its position and that it will be seen as being partisan and lacking impartiality. Accordingly, it revises its declaration to say that it treats liberal principles as guiding, not only because it judges that this is the better view in bioethics but also because this is largely in line with the position taken in its community where there is a public commitment to respect human rights.

When the group reports back to our philanthropist, its implementation of bioethics by principle is not well received. First, as the group feared, its early attempts simply to work through the logic of a plurality of approaches is not what the philanthropist expected. Illustrating his disappointment, the philanthropist points to Fukuyama's concern that genetic engineering might compromise human dignity. Speaking to that particular concern, it seems that the best that the group can do is to say that there are different conceptions of human dignity, such as the conceptions of 'human dignity as empowerment' and 'human dignity as constraint' (Beyleveld & Brownsword, 2001), that some conceptions are more conservative than others, that some are more inclined toward prohibition than permission, and so on. To be frank, our philanthropist is underwhelmed. Secondly, while the group's change of direction (from 'descriptive-analytical' to normative) is welcomed, our philanthropist is not impressed by its adoption and characterisation of a particular ('liberal') approach as being the 'better view'— 'What exactly does that mean? Better relative to which criterion?', our philanthropist asks. If the so-called 'better view' is simply a proxy for liberal values, then we are left with the question of why the group thinks it appropriate to take liberal values as criterial. Thirdly, to then switch from a supposedly better view simply to follow the commitments of the community seems like more than a concession; as our philanthropist sees it, it is to abandon the critical distance that a think-tank should have. All in all, the outcome is a disappointment; and the funding is terminated.

Process

By contrast, let us suppose that the group agrees that the best approach is to gather the community's views on a particular topic and to identify a consensus or, if not that, then to identify a range of plausible accommodations of interests. Following this approach, the group works topic by topic, its guiding principles and values being specified afresh for each new case. Sometimes, there is a clear consensus but, often, the group finds that it is pushed towards a middle ground, even a relatively anodyne, position that reflects the push and pull of the principal opposing views on

a topic (compare Nuffield Council on Bioethics, 2005 and 2017). For example, when it addresses the topic of NIPT (non-invasive prenatal testing), the group stakes out a compromise position that accommodates, on the one side, those who argue that the reproductive autonomy of women should be prioritised and, on the other, a number of views that express concern about the signals being given about respect for the disability communities (Brownsword & Wale, 2018).

After a while, the group becomes concerned about a number of features of this approach. One such concern is that that there are often a number of middle ground positions that are plausible; but, then, there is no good reason for preferring one such position rather than another. In an attempt to respond to this, and to underline its 'ownership' of its favoured positions, the group agrees that, from the range of possible and plausible accommodations, it should specify its own preferred view. However, this is constrained by the process that it follows. The fact of the matter is that there is a worrying lack of consistency and coherence in the principles and values that it treats as relevant and in the positions that it takes up. To be sure, this reflects a degree of inconsistency and incoherence in the community's own thinking but this is no comfort so long as the group sees its role as brokering an accommodation of interests that originate in the community's responses to its consultations.

In a further attempt to strengthen its approach, the group combines a processual approach with a principled privileging of what it takes to be the community's fundamental values. This has the attraction of eliminating some views as inconsistent with the community's own aspirations; there is now a degree of coherence in the process. However, other weaknesses that the group identified remain and, overall, the process seems to be one of 'messy' brokerage (Ashcroft, 2010).

When the group reports back, our philanthropist, too, is dissatisfied with bioethics by process and its outcomes. The processual approach, he says, seems to do no more than hold up a mirror to the community and its values. Doing bioethics has to be more than that, and more than brokering compromises where the community's views do not all pull in the same direction. If we are to take bioethics seriously, its judgments have to signify more than that a certain position is 'acceptable'. Moreover, if the group limits itself to engaging with the views expressed by a particular community, bioethics seems to have no cosmopolitan aspirations. Once again, the outcome of the exercise is disappointing and funding is terminated.

Franklin's Critique

In a recent essay on the history of bioethics and a provocative assessment of its current state, Sarah Franklin (2019) claims that amongst bioethicists there is a 'sense of ethical bewilderment' with a 'feeling of being overwhelmed [being] exacerbated by a lack of regulatory infrastructure or adequate policy precedents' such that '[b]ioethics, once a beacon of principled pathways to policy, is increasingly lost, like Simba, in a sea of thundering wildebeest.' Indeed, '[i]n the wake of the "turn to dialogue" in science, bioethics often looks more like public engagement—and vice

versa.' Or, putting this in the words of this chapter, Franklin detects the decline of bioethics by principle and the rise of a muddling bioethics by process—moreover, the resulting process is one that offers little resistance to the promoters of new technologies who are quickly able to persuade the public of the benefits to be gained.

Speaking to the decline of bioethics by principle, Franklin remarks that a 'single, Belmont-style umbrella no longer seems likely, or even feasible.' Instead, she concludes,

> the new holy grail is the ability to create trustworthy systems for governing controversial research such as chimeric embryos and face-recognition algorithms. The pursuit of a more ethical science has come to be associated with building trust by creating transparent processes, inclusive participation and openness to uncertainty, as opposed to distinguishing between 'is' and 'ought'.
>
> In short, expert knowledge and reliable data are essential but never enough to enable enduring, humane governance to emerge. So there is now more emphasis on continuous communication and outreach, and on long-term strategies to ensure collective participation and feedback at all stages of scientific inquiry. The result is less reliance on specialized ethical expertise and more attention to diversity of representation…
>
> The implication of this new model is that the most ethical science is the most sociable one, and thus that scientific excellence depends on greater inclusivity. We are better together—we must all be ethicists now.

Whether or not we agree with Franklin's assessment of the loss of expert direction in modern bioethics, the point is that a turn to bioethics by process is no more the way to respond to a lack of confidence in bioethics by principle than a reversion to the latter would be the way to respond to disenchantment with the former. We are missing something; and what we are missing is, actually, glaringly obvious. If we ask ourselves what it takes to do bioethics in the first place—not the funding and the fancy facilities, but the minimal conditions for doing bioethics—we are on the right track. In response to our question, it goes without saying (but it is very important to say it) that there need to be humans (which implies that there need to be conditions for humans to exist) who understand that simply because we can do certain things it does not follow that we ought to do them (which implies that the conditions enable humans to form a view about what can be done and what ought to be done). So, the focus for the fresh start that we are looking for is not principle or process but the preconditions for the human enterprise of bioethical reflection and governance by bioethics. Bioethics has become a box that we now need to think outside.

A Fresh Start

If our philanthropist is to be persuaded to give bioethics and the bioethicists a second chance, it will be evident from the work of the group that there are three urgent concerns to address: first, there is the discontent with the opacity and arbitrariness of 'balancing' conflicting interests to arrive at an acceptable accommodation, or as we might say to ground a 'social licence' for an act or practice; secondly, there is the

need to establish some hierarchy in the various principles, values and interests that are involved in the process; and, thirdly, there is the need to identify where we have foundations for bioethical judgments and where the line is to be drawn between cosmopolitan bioethics and community bioethics. Of these three challenges, it is the third that is the key to a fresh start; so, we can begin with it and then work back in reverse order through the other two challenges.

Foundations

How are we to justify our bioethical judgments? In each particular community, we can appeal to the values that are fundamental to the commitments and aspirations of our people. However, when one person, from one community, exchanges bioethical views with another person, from another community, how is that exchange (assuming the views are consistent relative to each community but that they are conflicting inter se) to be arbitrated? Where can we go beyond a plurality of communities? In some cases, we might appeal to an international cross-community consensus, but often there will be no relevant consensus of this kind (Brownsword, 2005); and, even if there is, in what sense is a consensus 'foundational'? The answer is that it is not. What we are looking for is some kind of value or principle, lying beyond each community, that gives all community members reason to treat it as binding and overriding. The $1000-dollar question is: what could that value or principle possibly be?

The answer is really very simply—bioethics operates out at third and fourth base but it cannot do any of that without having got to first and second base. What we are looking for (and what we have at first and second base) are the values and principles that reflect the importance of the conditions that make it possible for humans to exist and to form communities—or, as we might say, the context for the 'viability' of human agency (Fairchild, 2021: 143). If we treat these conditions as the 'global commons', this can be expressed as the principle that the global commons should be protected and respected. What makes this fundamental and foundational is not so much that a certain number of humans assent to this proposition but that no human can coherently deny it. No human who is a member of a community, or who is prospectively or potentially such a member, can accept that it is permissible to act in ways that compromise the critical infrastructure on which all communities and all human members of such communities depend. Accordingly, the starting point for bioethics is with the principle that no action can be justified if it will compromise the global commons.

To elaborate, it is important to understand that the conditions that make up the commons are neutral as between humans and as between human projects, whether they are projects for individuals or communities; and, in the same way, the infrastructural conditions are impartial as between particular views of self-interest and particular criteria for moral judgments. Infrastructural conditions that are not neutral and impartial in this way might well be important but they will not be part of the

critical infrastructure that supports human social existence. So, the global commons is not the only infrastructure but its conditions are relatively thin, setting the minimum conditions for human social existence.

How, then, should we specify these conditions? What are they? Stated shortly, the global commons, has two dimensions: one relating to human existence; and the other relating to the human capacity for (self-interested and other-regarding) agency.

First, the *human* species is defined by its biology; and the prospects for human life depend on whether the conditions are compatible with the biological characteristics and needs of the *human* species. Most planets will not support *human* life. The conditions on planet Earth are special for *humans*. However, the conditions are not specially tailored to the needs of any particular human; these are the generic conditions for the existence of any member of the human species. It follows that regulators should take steps to protect, preserve and promote the natural ecosystem for human life (Rockström et al., 2009; Raworth, 2017). At minimum, this entails that the physical well-being of humans must be secured; humans need oxygen, they need food and water, they need shelter, they need protection against contagious diseases, if they are sick they need whatever medical treatment is available, and they need to be protected against assaults by other humans or non-human beings. It follows that the intentional violation of such conditions should be viewed as a crime against, not just the individual humans who are directly affected, but humanity itself (Brownsword, 2014a).

Secondly, it is characteristic of human *agents* that they have the capacity to choose and to pursue various projects and plans whether as individuals, in partnerships, in groups, or in whole communities. Sometimes, the various projects and plans that they pursue will be harmonious; but, often, human agents will find themselves in conflict or competition with one another. However, before we get to particular projects or plans, before we get to conflict or competition, there needs to be a context in which the exercise of agency is possible. This context is not one that privileges a particular articulation of agency; it is prior to, and entirely neutral between, the particular plans and projects that agents individually favour; the conditions that make up this context are generic to agency itself.

It follows that the conditions for meaningful self-development and agency need to be constructed: there needs to be a sufficient sense of self and of self-esteem, as well as sufficient trust and confidence in one's fellow agents, together with sufficient predictability to plan, so as to operate in a way that is interactive and purposeful rather than merely defensive. Let me suggest that the distinctive capacities of prospective agents include being able: to freely choose one's own ends, goals, purposes and so on ('to do one's own thing'); to understand instrumental reason; to prescribe rules (for oneself and for others) and to be guided by rules (set by oneself or by others); and, to form a sense of one's own identity ('to be one's own person'). Accordingly, the essential conditions are those that support the exercise of these capacities (Brincker, 2017; Hu, 2017). With existence secured, and under the right conditions, human life becomes an opportunity for agents to be who they want to be, to have the projects that they want to have, to form the relationships that they want, to pursue the interests that they choose to have and so on.

It also follows that the commons must secure the conditions for bioethics and, more generally, for an aspirant moral community, whether the particular community is guided by teleological or deontological standards, by rights or by duties, by communitarian or liberal or libertarian values, by virtue ethics, and so on. The generic context for moral community is impartial between competing moral visions, values, and ideals; but it must be conducive to 'moral' development and 'moral' agency in a formal sense. So, for example, in her discussion of techno-moral virtues, (sous) surveillance, and moral nudges, Shannon Vallor is rightly concerned that any employment of digital technologies to foster prosocial behaviour should respect the importance of conduct remaining 'our *own conscious activity and achievement* rather than passive, unthinking submission' (Vallor, 2016: 203, emphasis in original)—or, as I have argued on many occasions elsewhere, we should be concerned if technological management leaves agents with no practical option other than to do what those who manage the technology judge to be the right thing (Brownsword, 2008a, 2011).

Reasoning impartially, each human agent will see itself as a stakeholder in the commons; and, it will be understood that these essential conditions must be respected. While respect for the commons' conditions is binding on all human agents, this does not rule out the possibility of prudential or moral pluralism. Rather, the commons represent the pre-conditions for both individual self-development and community debate, giving each agent the opportunity to develop his or her own view of what is prudent as well as what should be morally prohibited, permitted, or required. However, the practice of articulating and contesting both individual and collective perspectives (like all other human social acts, activities and practices—including the practice of bioethics) is predicated on the existence of the commons.

Hierarchy and Community

In the proposed scheme of thinking, the global commons is a platform for humans to form their own particular communities: if the global commons is first base, humans start building their communities at second base. It is here that they declare their distinctive values, and define themselves as the particular people that they aspire to be.

From the middle of the Twentieth Century, many nation states have expressed their fundamental (constitutional) values in terms of respect for human rights and human dignity (Brownsword, 2014b). These values clearly intersect with the commons' conditions and there is much to debate about the nature of this relationship and the extent of any overlap—for example, if we understand the root idea of human dignity in terms of humans having the capacity freely to do the right thing for the right reason (Brownsword, 2013, 2018), then human dignity reaches directly to the commons' conditions for moral agency (Brownsword, 2017). However, those nation states that articulate their particular identities by the way in which they interpret their commitment to respect for human dignity are far from homogeneous.

Put somewhat bluntly, whereas, in some communities, the emphasis of human dignity is on individuals having the right to make their own choices, in others it is on the constraints (in particular, relating to the sanctity, non-commercialisation, non-commodification, and non-instrumentalisation of human life) by which individual choice is limited (Beyleveld & Brownsword, 2001; Caulfield & Brownsword, 2006; Brownsword, 2008b). These differences in emphasis mean that we frequently encounter protagonists on both sides of a debate invoking human dignity in support of their positions[1]; puzzlingly, according to some, there is dignity in dying (choosing to die) while, according to others, there is dignity in living (life being maintained). This also means that communities articulate in very different ways on a range of beginning of life and end of life questions as well as questions of human enhancement, the use of human embryos for research, property rights in detached human body parts, and so on (Brownsword, 2009, 2018).

It is, of course, essential that whatever the fundamental values to which a particular community commits itself they should be consistent with (or cohere with) the commons' conditions. It is the commons that sets the stage for community life; and then, without compromising that stage, particular communities form and self-identify with their own distinctive values.

While a plurality of communities, each with its own distinctive fundamental values, can militate against cross-community consensus, there can be cases where the bioethical judgments of one community converge with those of another. By way of illustration, recall the convergent bioethical condemnation of the conditions in migrant border camps (such as those at the US border with Mexico). Bioethicists from both Europe and the United States are agreed that the conditions are unacceptable, indeed degrading. However, while Europeans (referring to the opening Articles of the EU Charter) will see this as a violation of human dignity, Americans articulate their critique in terms of a failure to respect persons, as unnecessarily harmful, and as unfair (see the letter of concern signed by 800 bioethicists, Cook, 2019). For both Europeans and Americans, the conditions are unacceptable relative to the fundamental values that define and distinguish their particular communities. For each community, relative to its particular values, this is a fundamental wrong.

That said, once the idea of the global commons is brought into the picture, those who condemn the conditions might want to uprate their critique and claim that, actually, the conditions are so threatening to life or so compromising of agency that they do touch and concern the commons; that they do represent a first-tier wrong. We know that human dignity goes deep and, with the global commons on the radar, we can appreciate just how deep it might go (Brownsword, 2021).

[1] For a particularly complex instance of this phenomenon, see Möllers, 2013 (case study of *KU v Finland*, Application no. 2872/02, 2008 at the European Court of Human Rights).

Opacity and Balancing

Within each particular community, the day-to-day topics for bioethical consideration will often concern matters that neither touch and concern the global commons nor engage the community's fundamental values. For example, the adoption of new technologies (robots, AI, and so on) in healthcare is a case in point. While some patients will regret the loss of the human touch, others will welcome 24/7 intelligent care. More generally, while some will push for a permissive regulatory environment that is facilitative of beneficial innovation, others will push back against research that gives rise to concerns about the safety and reliability of particular technologies as well as their compatibility with respect for fundamental values. Yet, how are the interests in pushing forward with research into potentially beneficial health technologies to be reconciled with the heterogeneous interests of the concerned who seek to push back against them?

A stock answer to this question is that regulators, neither over-regulating nor under-regulating, should seek an accommodation or a balance of interests that is broadly 'acceptable'. If the issue is about risks to human health and safety, then regulators (having assessed the risk) should adopt a management strategy that confines risk to an acceptable level; and, if there is a tension between, say, the interest of researchers in accessing health data and the interest of patients in both their privacy and the fair processing of their personal data, then regulators should accommodate these interests in a way that is reasonable—or, at any rate, not manifestly unreasonable.

While a 'balancing' approach of this kind might be the best that we can do, it is open to a number of objections. First, it is not clear on what basis it regards the particular interests that are pressed on regulators as legitimate or illegitimate, or indeed whether it differentiates between interests in this way. In order to distinguish between legitimate and illegitimate interests, a theory of legitimacy is required; and, this balancing approach simply does not have any such theory. If, on the other hand, no distinction is drawn between legitimate and illegitimate interests, then illegitimate interests might be allowed to shape an accommodation of interests that will be claimed to be 'legitimate'. Secondly, all interests (whether legitimate only or legitimate and illegitimate) are flattened in the balancing process. No distinction is drawn between 'higher order' and 'lower order' interests. Indeed, there is no ranking of interests (whether higher order or lower order). To do this, a theory of value would be needed and, again, this strategy simply does not have any such theory. Thirdly, a proposed balance of interests will be presented as legitimate if it is 'reasonable' or 'not unreasonable' relative to the interests put forward for consideration. Not only is this a weak view of legitimacy, it allows for more than one accommodation to be legitimate; and, recalling the concerns of the bioethics think tank, the process approach has no resource to explain or justify why one reasonable accommodation is to be preferred to another. Finally, it is unclear whether the burden of justification is on those who argue for permission or those who argue for prohibition or restriction; and, nor is it clear whether, at any stage, the burden is transferred from one side to the other.

While the proposed scheme of thinking does not answer all of these objections to balancing or to bioethics by process, it does provide a basis for differentiating between legitimate and illegitimate interests or preferences (the test of legitimacy being compatibility with the global commons and with the fundamental values of the community); and it also introduces some ranking of interests. Nevertheless, there are still many questions to be answered.

Questions Now Arising

Let us suppose that our philanthropist is sufficiently attracted by the proposed scheme of thinking to task the group with its further development and elaboration. More specifically, the group is now instructed to report back on a number of questions, including the following.

First, admittedly a question of a somewhat theoretical nature, we might wonder how we should characterise commons' protecting reason. Is it prudential or moral or both or neither? Arguably, it is both prudential and moral because the protection of the commons is in the interest of everyone and it is categorical, exclusionary, and overriding. Or, should we simply say that, for human agents, the protection of the commons is rationally required, or 'first base', or even self-evident? Would this mean that prudential and moral reason only kicks in *within* communities (at second base and beyond)?

A second question concerns the relationship between values that some communities identify as fundamental, quite possibly entrenching them in constitutional declarations, and the values that underwrite the global commons. Do some of these community-defining values reach through to the stewardship of the commons? For example, some might argue that values such as autonomy, privacy, and human dignity are fundamental not only to the constitution of a community of rights but also to the context for agency that is one of the dimensions of the commons' conditions.

A third question, related to the second, is how we can hold the line against the abusive or opportunistic self-serving expansion or extension of the commons' conditions. To be sure, any proposed condition must be impartial/neutral between humans and their particular interests and values. Nevertheless, we must expect this to be a pressure point because the imperative to respect the commons' conditions 'trumps' all other considerations, even the values that define a particular community as the community that it is. For communities who wish to export their values, there is an imperialistic temptation to present their fundamental values as aspects of the global commons. There is also the related question of how we view proposals to 'enhance' or 'improve' the global commons. If the proposed enhancements or improvements meet the test of neutrality/impartiality and if they work in the way intended, is there any reason not to adopt them? Indeed, should we not be trying to enhance the global commons?

Fourthly, although the lexical ordering of the proposed scheme brings with it clear guidance on the hierarchy of interests and how 'vertical' conflicts of interest are to be resolved, it does not guide on 'horizontal' conflicts within a particular tier

of interests. It is conceded that resolving conflicting interests and negotiating a social licence at tier three will be messy; we have a considerable jurisprudence relating to conflicting interests (constitutional values) at tier two; but, how are conflicts between the existence and agency dimensions of the global commons to be resolved? Is the default that we have to prioritise the existence conditions because, without existence, there is no agency?

A fifth question, a much more practical question, and one that is vividly highlighted by the recent experience with Covid-19, is about the coordination of our stewardship responsibilities. In principle, we are all stewards for the global commons and, as such, we can 'do our bit'—for example, we can comply with the necessary restrictions on our movement or association that are put in place to prevent the spread of the virus. However, in practice, the restoration and maintenance of the global commons needs international leadership (Brownsword, 2019, 2020). In the case of a pandemic, it is the WHO that is the obvious candidate. However, if the WHO is to be hobbled and undermined by great powers that conduct international relations in an entirely self-serving nationalistic way, there has to be some other approach (Joseph & Branswell, 2020).

Let us suppose that the ethics group arrives at satisfactory answers to these and other questions of this kind and that it is now ready to take its ethics to the world. How might we expect this to go? Is this a story that ends well? This is our final topic.

Plugging in Again

Back in the real world, the cynical view is that bioethics will sometimes be an exercise in persuading a constituency to buy into, or to accept, a practice; sometimes it will be about reputation and risk management; often it will be about legitimation rather than legitimacy; but, only rarely, will it be purely and simply about doing the right thing. Moreover, on those rare occasions when an ethics body is purely aspirational in its ethics, it is likely to find that it is whistling in the wind. Reflecting on a world that is no longer hospitable for bioethics, Franklin (2019) observes that:

> Much basic science is privately funded and therefore secretive. And the mergers between machine learning and biological synthesis raise additional concerns. Instances of enduring and successful international regulation are rare. The stereotype of bureaucratic, box-ticking ethical compliance is no longer fit for purpose in a world of CRISPR twins, synthetic neurons and self-driving cars.

According to Franklin, in its post-millennial state, bioethics has

> become more global, less canonical and more reflexive. The field no longer relies on philosophically derived mandates codified into textbook formulas. Instead, it functions as a dashboard of pragmatic instruments, and is less expert-driven, more interdisciplinary, less multipurpose and more bespoke. In the wake of the 'turn to dialogue' in science, bioethics often looks more like public engagement — and vice versa. Policymakers, polling companies and government quangos tasked with organizing ethical consultations on questions such as mitochondrial donation ('three-parent embryos', as the media would have it) now

> perform the evaluations formerly assigned to bioethicists. Journal editors, funding bodies, grant-review boards and policymakers are increasingly the new ethical adjudicators.It follows, that if our ethics group expects its pronouncements to be embraced and taken onboard domestically, let alone internationally, it is likely to join its philanthropic funder in being disappointed.

Given the three tiers of the proposed background scheme, it is at the level of the global commons that the group's ethics is likely to encounter the deepest resistance. This will be particularly where 'precautionary' measures are advocated. After all, at the other levels, the group treats bioethics as pluralistic and contestable. However, in relation to the global commons, the ethical demands are mandatory; and, in practice, the problem is that governments (for the sake of short-term national interest) and industry (for the sake of short-term profitability) will resist any attempt to coordinate stewardship of the commons where this impinges on their self-serving interests.

Even if we accept that the ethicists' vision is compelling, we have to take into account the realities of international relations. One of these realities is that there are at least three kinds of international citizens: first, there are functioning states amongst whom many are good citizens of the international order (respecting the rules of international law); secondly, there are functioning states that are also superpowers (who largely dictate and veto international initiatives as well as playing by their own rules); and, thirdly, there are rogue states (who play by no rules) (Simpson, 2009). If the regulatory stewards were drawn from the good citizens, that might be fine insofar as an agency so populated would be focused on the right question and motivated by concerns for the common interest of humans. However, they might find that they are blocked in their efforts to introduce necessary measures of precaution and restriction (Andorno, 2007).

A second reality is that, where the missions of international agencies include a number of objectives, trade (rather than human rights or environmental concerns) will often be prioritised (Leader, 2004) —in other words, commerce will be prioritised over the commons. It follows that, if the regulatory stewards are within an international agency, the mission must be limited to the protection of the commons. Even then, there would be no guarantee that the stewards would be immunised against the usual risks of regulatory capture and corruption, or inter-agency conflict (Andorno, 2007). In short, unless the culture of international relations is supportive of the stewards, even the ideal regulatory design is likely to fail.

The moral seems to be that, if the common interest is to be pursued, this is a battle for hearts and minds. As Neil Walker (2015: 199) has remarked in relation to global law, our future prospects depend on 'our ability to persuade ourselves and each other of what we hold in common and of the value of holding that in common.' An international bioethical agency with a mission to preserve the global commons might make some progress in extending the pool of good citizens but to have any chance of success all nation states need to be on board. Sadly, even if there is no coherent denial of the proposition that the protection of the commons should be the number one priority for humans, and even though it is self-evident that the need to maintain the commons is the one thing that we humans do hold in common, our

practice falls short. Our philanthropist might continue to worry about the longer-term implications of genetic engineering but, already, the Anthropocene places a major questionmark about the existence conditions for humans (Brownsword & Somsen, 2021); the only term now might be the short-term. At the same time, the emergence of surveillance capitalism, in conjunction with AI-enabled devices, places a serious questionmark about the integrity of the context for human agency (Zuboff, 2019; Hildebrandt, 2015; Frischmann & Selinger, 2018).

Conclusions

As we intimated in the introduction, this chapter suggests a number of take-home messages. These include that there is more to bioethics than simply a rigorous exchange of opinions. Opinions can be tested for their consistency with the community's declared fundamental values but, as the proposed scheme highlights, they should always be tested for their coherence with the protection of the conditions of the global commons. To this extent, bioethics has foundations. However, this is not to say that bioethics leaves no room for interpretation; even the conditions of the global commons are open to interpretation. Nor does it mean that bioethics leaves no room for plurality. Far from it, each community, forming in its own distinctive way, with its own identity, adds to the plurality (subject only to the overriding constraint of the global commons). It is also in this distinction between the commons and the community that we find the line between what is cosmopolitan and what is local (Brownsword, 2021).

Above all, though, the take home message is that we should not do bioethics without a policy background—or, to avoid any misunderstanding, we should not do bioethics without the right policy background. Once we can do something, the role of bioethics is to ask whether we should do it: at one level, this might be asking no more than whether in our particular society it would be 'acceptable' to do it (or to identify the terms and conditions for its acceptability); at another level, the question is whether doing it would be compatible with a particular community's fundamental values; but, most importantly, bioethics should pose the question whether doing it would in any way compromise the global commons. 'Just doing bioethics' might seem like a privilege or a luxury but, where the global commons is under threat, it simply is not an option.

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Chapter 21
Ethics Education and Institutional Ethics Committees

Ercan Avci and Henk ten Have

Abstract Ethics consultation, which emerged at the end of the 1970s and beginning of the 1980s in the United States and gradually spread to some other countries, shoulder a crucial responsibility in clinical ethics by contributing to the quality of healthcare services through ethics consultation, case analysis, policy development, and ethics education. Institutional Ethics Committee is a type of that effort to identify, analyze, and resolve ethical issues but also used interchangeably with ethics consultation. Each function of institutional ethics committees refers to a substantial role in the therapeutic relationship. However, ethics education carries a higher potential to increase ethical knowledge, improve ethical skills, develop ethical behavior, and promote cultural competence by providing committee members, healthcare professionals, and patients and their families with continuous educational activities. Performing ethics consultation through bioethicists and other professionals having education in bioethics would help to achieve these goals and enhance the impact of bioethicists in clinical decisions.

Keywords Ethics education · Ethics committees · Bioethics · Ethics consultation · Clinical ethics

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Introduction

The Institutional Ethics Committee (IEC) is a form of ethics consultation identifying, analyzing, and facilitating the resolution of ethical concerns, uncertainties, and dilemmas in clinical ethics (American Society for Bioethics and Humanities [ASBH], 2011). In parallel with the flourishing of bioethics, ethics consultation has developed as a crucial mechanism to determine ethical breaches, appraise ethical conflicts, and produce ethically acceptable resolutions. As an institutional body, the IEC refers to the most comprehensive implementation of ethics consultation in healthcare institutions. Even though the initial focus in the emergence of IECs was on critical clinical decisions in the end-of-life and beginning-of-life issues, IECs have undertaken a broader role by providing ethics education and engaging in institutional policy development (American Academy of Pediatrics Committee on Bioethics, 2001). According to Post, Blustein, and Dubler (2007); case consultation, ethics education, and policy development are the three specific goals of ethics committees. The American Society for Bioethics and Humanities (2011) defines the overall goal of ethics consultation as enhancing "the quality of health care through the identification, analysis, and resolution of ethical questions or concerns" and specifies that general goal as supporting ethics-related practices, providing individuals and the institution with ethics education to deal with ethical challenges, and contributing to quality improvement, policy development, and resource utilization (p. 3).

Ethics education identified in the scholarly literature as a primary activity of IECs also has the potential to directly contribute to the other activities of committees as well. For instance, the availability of appropriate and adequate ethics education to all the pertinent parties, including healthcare professionals, patients, and families would facilitate reducing ethical challenges by generating a better therapeutic relationship. Ethics education transcends the intention to teach ethical norms, standards, and principles; it provides the parties with suitable tools to improve communication and build trust among the stakeholders and brings about a perspective that prioritizes patients' interests, values, and preferences (Lo, 2020). In this view, this chapter aims to examine IECs and elaborate on the significance of ethics education in IECs. Even though IEC points out a specific model of ethics consultation carried out by a multidisciplinary team, in this chapter, IEC and clinical ethics consultation are used interchangeably to refer to any ethics consultation services/models in hospitals.

Institutional Ethics Committees (IECs)

In terms of their birth and growth, IECs have been in an increasing trend in Europe, but their emergence and development have lagged behind IECs in the United States (Pfafflin et al., 2009). Janet E Fleetwood and her colleagues (1989) point out three

momentous occurrences as the driving force behind the development of IECs in the United States: The New Jersey Supreme Court's decision about the Karen Ann Quinlan case in 1976, the report *Deciding to Forego Life-Sustaining Treatment* of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research in 1983, and the Baby Doe Rules in 1984. In the conclusion of the Karen Ann Quinlan case, the Supreme Court of New Jersey – *In re Quinlan, 355 A.2d 647 (N.J. 1976)* – highlighted the role of the ethics committee as follows:

…the life-support apparatus now being administered to Karen should be discontinued, they shall consult with the hospital "Ethics Committee" or like body of the institution in which Karen is then hospitalized. If that consultative body agrees that there is no reasonable possibility of Karen's ever emerging from her present comatose condition to a cognitive, sapient state, the present life-support system may be withdrawn and said action shall be without any civil or criminal liability … (JUSTIA US Law, 2021, n.p.).

In the ruling, the court did not merely address the necessity of ethics committee consultation but also guaranteed free of any civil or criminal liability of the committee's decision. In particular, the former point is remarkable to encourage IECs to freely evaluate cases without any legal ramifications.

Similarly, in *Deciding to Forego Life-Sustaining Treatment*, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (1983) accentuated the need for ethics consultation when deciding for incapable patients by saying:

The medical staff, along with the trustees and administrators of health care institutions, should explore and evaluate various formal and informal administrative arrangements for review and consultation, such as "ethics committees," particularly for decisions that have life-or-death consequences for incompetent patients (p. 5).

Like the Supreme Court of New Jersey, the President's Commission underscores the availability of IECs based on their function in end-of-life decisions for incapable patients.

The discussion that started with the infant Baby Doe case in 1982 turned into a political and legal battle with the amendment to the Child Abuse Prevention and Treatment Act in 1984 (The Embryo Project Encyclopedia, 2021). As part of that discussion, the United States Department of Health and Human Services (HHS) urged healthcare institutions "to establish an Infant Care Review Committee (ICRC) to assist the provider in delivering health care and related services to infants" (Cornell Law School Legal Information Institute [CLSLII], 2021, n.p.). Contrary to the attention of the previous two cases to the life-sustaining treatments, the Baby Doe regulations request healthcare providers to institute ethics consultation to develop "standards, policies and procedures for providing treatment to handicapped infants and in making decisions concerning medically beneficial treatment in specific cases" (CLSLII, 2021, n.p.). Therefore, though carrying differences in their focus areas, these three instances have the common point of establishing IECs to analyze cases indicating serious ethical consequences.

In the United States, the Joint Commission on Accreditation of Healthcare Organizations (1992), which is the nation's oldest and largest standards-setting and accrediting organization in health care demands healthcare providers to "has in place a mechanism(s) for the consideration of ethical issues arising in the care of patients and to provide education to caregivers and patients on ethical issues in health care" (p. 104). According to the data collected between September 1999 and May 2000, in the United States, all hospitals with more than 400 beds and 81% of general hospitals have ethics consultation services (Fox et al., 2007). The percentage of general hospitals having ethics consultation increased to 86.3 in 2018 (Fox et al., 2021). Besides, the role of the above-mentioned occurrences and the Joint Commission's pushing, the Medicare and Medicaid programs' requirements for hospitals also plays a pivotal function in the prevalence of ethics consultation in American hospitals (Moon, 2019).

In regard to IECs in Europe, the study conducted by Steinkamp et al. (2007) examining IECs in Croatia, Lithuania, Poland, Slovakia, Belgium, France, the Netherlands, and the United Kingdom demonstrates that some regulations and practices of IECs have existed since the 1990s alongside research ethics committees (RECs), but RECs have more developed than IECs in these countries. Orzechowski et al.'s (2020) recent literature search-based scholarly work inquiring about IECs in Albania, Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Hungary, Kosovo, Latvia, Lithuania, Macedonia, Moldova, Montenegro, Poland, Romania, Serbia, Slovak Republic, Slovenia, and Ukraine reaches a similar conclusion by addressing the presence of IECs in most of the countries since the beginning of the 1990s with their primary focus on research ethics-related matters. Therefore, it may be stated that either as independent committees or as coexistent with RECs, IECs have been available in many European counties for three decades, but they are not as flourished as they are in the United States (Crico et al., 2021). For this reason, when people talk about IECs, they mostly point out clinical ethics consultation services in the United States (Slowther and Hope, 2000).

Clinical Ethics Consultation

Clinical ethics consultation is an institutional endeavor handling ethical issues at the clinical level. Ethics consultation is provided through individual consultants, consultation teams, or ethics committees. Different healthcare organizations may determine distinctive forms of ethics consultation in accordance with their needs. Each consultation model has some advantages as well as some disadvantages. Instead of suggesting a certain kind of ethics consultation to all healthcare organizations, paying attention to the ethical challenges they face, the institutional capacity they have, and the competencies the consultants carry might help them to choose the most appropriate type of ethics consultation (Post et al., 2007). The individual consultant model refers to either one consultant's or independent individual consultants' ethics consultation. Each consultant conducts the consultation independently. If a

consultant carries the required ethical knowledge, skills, and attitudes, his/her independent consultation may create more effective, active, and timely outcomes than group consultations. On the other hand, the consultant's shortcoming of experience and knowledge in ethics consultation might preclude generating productive consultation. The consultation team that consists of more than one consultant working as members of the same group is the second ethics consultation model. Though the burden of the consultation is not on one individual, each team member should continue enhancing his/her core ethical knowledge, skill, and attitudes to improve the competency of the team. The major advantage of this model is that despite the team that comprises a certain number of members with distinct experience, expertise, and knowledge, it can still act dynamically and timely. Additionally, having more than one member allows striking a balance among individual consultants' perspectives and judgements (ASBH, 2011; Post et al., 2007).

The third ethics consultation model is the ethics committee. An ethics committee is a group consultation model like the consultation team, but it consists of an interdisciplinary team with a greater number of members including physicians, nurses, social workers, and clergies. The ethics committee model may be beneficial especially for large hospitals, which have at least 400 beds. The committee's multidisciplinary nature may allow the organization to benefit from each member's experience and view. Nevertheless, due to working as a committee, which requires arranging meetings with the participation of all members, it is not as time-effective as the other two models. Moreover, patients, families, or surrogates may not feel comfortable enough to express themselves in front of such a crowded group. Additionally, the committee members' competencies, the committee's approach regarding whether encouraging the members to declare their opinions, and the members' desire to take responsibility would determine the efficiency of the ethics committee model (Lo, 2020; Post et al., 2007).

The success of these ethics consultation models mostly depends on certain internal factors, such as consultants' competencies and external elements like organizational considerations that positively or negatively influence the effort of ethics consultation. Guiding patients, families, caregivers, and other relevant parties through ethical uncertainties, challenges, dilemmas requires consultants' proficiency in core ethical knowledge, skills, attitudes, and behaviors. Furthermore, organizational elements and conditions in which the consultant works are decisive in the achievement of ethics consultation services. According to Post, Blustein, and Dubler (2007), "[e]thics consultation services need to have integration, leadership support, expertise, staff time, and other resources. Access, accountability, organizational learning, and evaluation are also essential" (p. 142). In many cases, organizational structure and factors may be more influential than employees' competencies in institutional success because the shortcomings of employees may be eliminated or reduced through well-structured organizational effort, such as training and mentoring. Nevertheless, it might be difficult or impossible to be able to fix institutional deficiencies only by a few well-skilled employees' endeavors. At that point, the relationship of ethics consultation services with other relevant departments and leadership approaches to ethics consultation are two substantial issues directly impacting the outcomes of ethics consultation.

A newly published study demonstrates that in the United States, the consultation team is still the most widespread model in case consultation within 65.1% of hospitals, while 18.6% of hospitals use the individual consultant model, and 16.3% of them employ the ethics committee model (Fox et al., 2021). Another interesting finding of the study is that the percentage of ethicists/bioethicists in the individuals who perform ethics consultation is 2.0., and only 8% of ethics consultation practitioners have a fellowship or graduate degree in bioethics (Fox et al., 2021).

Functions of Institutional Ethics Committees

Cranford and Doudera (1984) argue that IECs have three functions: consultation and case review to appraise specific ethical and social concerns and give advice to the pertinent parties about the relevant concerns; development of policies and guidelines in decision making regarding ethical dilemmas, conflicts, and problems; and education for IEC members and healthcare professionals. Garrison and Magnus (2012) name consultation, policy development, and education as "the traditional trinity of hospital ethics committees" (p. 1). The Joint Commission (1992) delineates the role of ethics consultation through two general functions: having a mechanism to address ethical considerations and providing caregivers and patients with ethics education. Explicitly requesting ethics education also for patients is an important aspect of the Commission's standard. In *Core Competencies for Healthcare Ethics Consultation*, the American Society for Bioethics and Humanities (2011) formulate the functions of ethics consultation more comprehensively by specifying five goals: identifying and analyzing ethical uncertainties or conflicts; facilitating the resolution of the uncertainties and conflicts; promoting practices consistent with ethical norms and standards; helping policy development, quality improvement, and resource utilization; and providing ethics education. In this view, it is possible to say that as a primary form of ethics consultation, IECs have various functions in healthcare, but they may be worded differently based on the institutional structure, focus, and needs of healthcare organizations.

We classify the functions of IECs under four categories: consultation, case analysis, policy development, and ethics education.

Consultation

In the therapeutic relationship or decision-making processes, either healthcare professionals or patients or their families may need to consult the IEC to get their opinion or advice about the issue at hand. Consultation refers to the situation where any party or parties is/are unsure how to address ethical challenges and seek/s the IEC's guidance and recommendation to cope with the ethical matter. Consultation is the easiest way for physicians and patients to get help for the ethical issues they

encounter in daily medical practices (Frenkel, 2011). For example, a patient with the decisional capacity requests to be discharged from the hospital, but the attending physician considers the discharge premature and risky. The physician is aware of the superiority of the patient's autonomy but also can foresee the possible consequences of the discharge. Both options (overriding the patient's autonomy for the sake of the patient's interest and honoring the patient's decision with likely detrimental effects on the patient) may overwhelmingly make the physician stressed out. However, the engagement of the IEC would help the physician to handle the situation by either giving some advice to the physician or having a constructive conversation with the patient and physician, which indicates a priceless resource both for healthcare professionals and patients to reach an agreeable solution (Mercurio, 2011). In this view, the role of the IEC in consultation is mediation between different parties.

Case Analysis

Many sources assess consultation and case analysis as a single task. However, differentiating consultation from case analysis would be a more proper approach because of the distinctions in their proceedings. Firstly, consultation may be given by individuals consultants, but case analysis should be done by IECs as a multidisciplinary team. Secondly, consultation is an instant advisory effort for ongoing processes or procedures mostly through a verbal dialogue between the consultant and pertinent party, which could facilitate reaching a reasonable conclusion or decision promptly. However, some issues may indicate serious ethical problems requiring more comprehensive, official, and written evaluations. Thirdly, people can retrospectively focus on medical matters largely while they experience any undesirable outcomes. In such situations, IECs should carry out a case analysis to explore a different aspect of the case. For instance, based on the example given above, the physician discharges the patient from the hospital in light of the patient's wish and with information about feasible consequences. However, a family member could dispute the discharge, or the patient may complain about it if he/she faces a harmful but foreseen medical condition by claiming that he/she was not sufficiently informed about the possible outcomes before the discharge. In such a situation, the IEC should transcend the role of mediation and function as an ethical analyzer to elaborate on all the arguments from the relevant parties and help them to find ethical resolutions.

Policy Development

IECs are essential components of healthcare organizations to achieve, maintain, and improve the quality of healthcare services by concentrating on ethical considerations (ASBH, 2011). In this context, IECs should take an active role in institutional

policy development, quality improvement, and resource allocation. Ethics does not only look at the relationship between physicians and patients, but also studies the fair distribution of scarce resources, moral acceptability of policies and their implementations, and ethical applicability of standards. For this reason, IECs should work with other departments and the leadership to produce ethically justifiable proposals regarding all institutional activities. Of course, IECs' members' competencies, their cooperation with other departments, and their relationship with the institutional leadership directly affect their role in these areas. As some examples demonstrate, IECs contribute to their institutions through a wide range of policy development works, while they are allowed or encouraged to take an active role in those activities (Garrison and Magnus, 2012). Additionally, close connection and communication with healthcare professionals, patients, and families enables IECs to obtain a valuable observation about each party's perceptions, expectations, and needs, identify institutional structure, and explore the areas causing ethical conflicts. Therefore, IECs' engagement in policy development, quality improvement, and resource allocation would allow healthcare institutions to benefit from that worthwhile experience and knowledge in order to proactively prevent ethical problems (Moon, 2019).

Ethics Education

Ethics education is the most substantial task of IECs. Laddrole (2009) underscores the magnitude of education by saying that the IEC "may be passive in that it may review policy only when asked and engage in consultation only when requested, but its role in education within the whole institution should be active and on-going" (p. 42). Education carries a direct impact on the other activities of IECs. In particular, the relationship between ethics education and consultation and case analysis is inverse proportional; increasing ethics education has the potential to decrease the demand for consultation and case analysis because the stakeholders will be more familiar with knowing how to act ethically and avoid ethical breaches. For example, giving ethics education to caregivers and families on end-of-life issues, such as brain death and do-not-resuscitate (DNR) may significantly reduce the risk of a conflict on these matters (Cranford and Doudera, 1984).

Ethics education in IECs is threefold: educating IECs members, educating healthcare professionals, and educating patients and their families. IECs is composed of staff from various disciplines, including ethicists, physicians, nurses, social workers, and clergies. While assigning people to the IECs, their ethical knowledge, skills, and attitudes should be taken into account to form a competent team. However, it may be difficult for institutions to find qualified personnel with core ethical competencies. Additionally, ethics is a dynamic field that requires updating ethical knowledge and exploring new ethical issues. Since the effectiveness of IECs chiefly depends on its members' proficiencies in ethics, IECs should plan continuing

educational programs for their members and encourage them to individually obtain ethics education (Jonsen et al., 2015).

Education is not an activity only carried out at school. Having in-service education programs is an effective method to internalize job-related skills, abilities, and knowledge. Healthcare institutions should provide educational opportunities to their personnel through periodic in-service educational programs. These programs may aim to refresh the staff's knowledge about specific areas, raise awareness of particular issues they mostly encounter, provide new knowledge regarding new developments in their professional area, address certain problems they have to deal with, and satisfy legal and institutional educational requirements. IECs should undertake this role to educate all employees about ethical challenges, dilemmas, and violations. Instead of providing the same education to all professionals, education programs and their contents and duration should be determined in accordance with each group's needs.

Furthermore, IECs should reach out to patients and their families through educational opportunities. Since patients and their families are the main stakeholders in healthcare as well as the focus of ethical concern in caring relationships, IECs should reflect a proactive approach by making ethics education available for them instead of waiting until ethical problems come out. IECs can specify most pertinent subjects, such as patients' rights, decision making, surrogate decision making, advance directives, confidentiality and privacy, and physician-patient relationship when organizing ethics education for patients and families.

Ethics Education

Aristotle (1999) classifies virtues as intellectual and moral, and argues that "intellectual virtue in the main owes both its birth and its growth to teaching (for which reason it requires experience and time), while moral virtue comes about as a result of habit" (p. 20). Based on this approach, many scholarly works in the literature inquire into the matter of whether ethics education creates moral individuals (Campbell et al., 2007; Gross, 1999). The discussion brings about various arguments but takes an inclination toward teaching ethics due to its favorable ramifications (Gordijn and ten Have, 2013; Wright, 1995). However, some believe that ethics education should not take the responsibility for creating virtuous individuals (also does not have such a role), but help individuals to perform their professions in a way consistent with ethical standards (Avci, 2017). In regard to IECs, ethics education may aim to contribute to establishing, maintaining, and encouraging ethically acceptable policies, guidelines, and practices by increasing ethical knowledge, improving ethical skills, developing ethical behavior, and promoting cultural competence through continuous educational activities for IECs members, healthcare professionals, and patients and their families (Avci, 2017).

The figures of the UNESCO Global Ethics Observatory (GEObs) 2021 reveal that bioethics education is a worldwide phenomenon with an abundance of experts,

institutions, centers, and teaching programs. However, alongside the birth and growth of bioethics, bioethics education has bloomed more in the United States than in other parts of the world. The study carried out by Lee and McCarty (2016) demonstrates that the number of educational institutions offering bachelor's degrees in bioethics and applied ethics in the United States increased from 1 to 10, master's degrees from 4 to 30, doctoral degrees from 2 to 6, and certificates from 1 to 14 in a decade between 2003 and 2013.

From this perspective, it is reasonable to expect a growing impact and presence of bioethics or any professionals with bioethics education. However, the numbers do not support that fair supposition. According to the study conducted by Fox et al. (2021) in the United States, 76.8% of ethics consultation is performed by physicians, nurses, social workers, chaplains, and administrators (24.0%, 23.0%, 10.9%, 9.6%, and 9.3% respectively). The percentage of ethicists/bioethicists in that is merely 2.0, and only 8% of practitioners who carry out ethics consultations possess a fellowship or graduate degree in bioethics. Furthermore, the study done by Hauschildt and De Vries (2020) indicates striking findings regarding the role of ethicists in ethics consultation: ethicists mostly undertake the function of improving communication among the parties; ethicists' recommendations and judgement chiefly rely on physicians' technical expertise; and ethicists' consultation does not sufficiently affect patients' decision-makings that are independent of physicians' authority.

All these findings and figures show that in parallel to the increase in the number of IECs, the number of bioethics experts, bioethics institutions, and bioethics teaching programs have been raising. However, the increase in ethics education does not proportionately impact ethics consultation and does not play a significant role in ethics consultation services. The matter of who should perform ethics consultation and which qualifications consultants should have has been an ongoing debate (Agich, 2001). Nevertheless, with the availability of sufficient bioethics experts and bioethics programs, it is feasible to encounter more bioethicists or other professionals having bioethics education in IECs. However, even in the United States, where bioethics, bioethics education, and IECs are most developed, the percentage of consultants carrying a fellowship or graduate degree in bioethics is only 8, which means that, in general, 92% of ethics consultation, case analysis, policy development, and ethics education are performed by people who do not have a degree in bioethics. The risk is that contributions of IECs have the character of professional second opinion rather than separate and critical ethical analysis.

At that point, we believe that there is a serious need for a paradigm shift in the relationship between IECs and ethics education. First of all, a well-designed framework should be formulated for IECs in the organizational structure; ethics consultation should not be considered a secondary activity carried out by any professionals with any education; it should be accepted as the main enterprise of institutions directly affecting the quality of their healthcare services. The role, position, and contribution of IECs should be recognized, supported, and promoted by the organizational leadership. Secondly, ethics consultation should be provided by individuals who formal education in bioethics. Especially, ethics committees are

multidisciplinary groups consisting of different professionals, including physicians, nurses, social workers, and clergies, work as team members. Now that numerous bioethics institutions and teaching programs are available, ethics consultants and committee members should be required to earn a degree, at least a certificate, in bioethics education. Thirdly, IECs should have continuing ethics education programs for their members because bioethics is a dynamic field facing rapid changes through social, medical, technological, and environmental developments. Finally, IECs should arrange ethics education and training programs and sessions for healthcare professionals, patients, and their families. The effectiveness of that education and training would positively shape the need for ethics consultation and case analysis. In short, quality ethics consultation, case analysis, and policy development can be achieved through well-educated individuals and teams. Therefore, the presence and magnitude of bioethicists and people with bioethics education in IECs would have proportionate influence on the quality of ethics consultation services.

Conclusion

Ethics consultation in healthcare has attracted more attention in the past few decades alongside the growth of bioethics and bioethics education. Even though ethics consultation is practiced in many countries, it has emerged and flourished in the United States as the result of certain legal cases and political initiatives. Ethics consultation services are provided through individual consultants, consultation teams, and ethics committees to fulfill ethics consultation, case analysis, policy development, and ethics education.

Ethics education is the most crucial task of IECs due to its expected positive impact on the other functions, which should be provided to IECs members, healthcare professionals, patients, and patients' families. The studies demonstrate that the numbers of bioethicists, bioethics institutions, and bioethics teaching programs have swiftly increased. However, even in the United States, the percentage of consultants who have a fellowship or degrees in bioethics is very limited, and IECs do not play a significant role in consultation, except for improving communication between the pertinent parties.

For more favorable outcomes of ethics consultation, healthcare institutions should acknowledge the function of ethics education in IECs. IECs should be constituted of bioethicists and other professionals having an education in bioethics. IECs should organize continuing ethics education for their members to promote their ethical knowledge, ethical skills, ethical behavior, and cultural competence. Furthermore, IECs should provide caregivers, patients, and families with educational and training opportunities in ethics to raise their awareness about ethical issues in order to reduce ethical uncertainties, concerns, and conflicts between healthcare professionals and patients/families.

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Chapter 22
The New Role of Ethics Committees in Emergency Use of Unproven Interventions Outside Research

Ignacio Mastroleo and Timothy Daly

Abstract Recent ethics guidelines from the World Health Organization (WHO) on monitored emergency use (MEURI) state that, during a public health emergency, prospective ethical review and oversight of the use of unproven interventions outside of the context of research is an ethical principle or criterion for its permissible use. In this chapter, we argue that this new role of ethics committees in the review, authorization and oversight of emergency use outside research is a developing conceptual innovation against the background of ethics documents such as the Declaration of Helsinki of the World Medical Association and the WHO earlier guidelines on "compassionate use" and MEURI. To support this claim, we offer definitions of key terms in this emerging literature and a clear methodological framework of practical analysis before presenting a literature review of relevant guidelines that focus on the presence or absence of the criterion of independent ethical review of emergency use of unproven interventions outside research. We close by discussing the future of the criterion of ethical review and oversight including questions around the greater normative complexity, both ethical and regulatory of monitored emergency use in comparison with research, the mutual influence between emergency and non-emergency use contexts, and questions of access pathways with and without committees as part of a rapidly-evolving emerging ethical literature.

Keywords Ethical review · Monitored emergency use (MEURI) · Compassionate use · Use of unproven interventions outside research · Public health emergency · World Health Organization (WHO) · Declaration of Helsinki · Literature review · Practical analysis

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Introduction

For serious or life-threatening diseases or conditions such as Ebola or COVID-19 that result in a public health emergency, where existing emergency control measures are insufficient and proven clinical interventions are absent or unsatisfactory, using unproven interventions outside the context of research has been considered permissible providing that such use follows appropriate ethical criteria designed to separate the wheat from the chaff (WHO, 2014a, 2016, 2022; Calain, 2018; PAHO, 2020). The use of unproven interventions outside research in such circumstances covers a wide spectrum of interventions with varying degrees of preliminary evidence and different risk benefit profiles, including first in-human uses with preclinical data such as Zmapp for Ebola Virus Disease (Qiu et al., 2014: 53; Shah et al., 2015), or "off-label" uses, that is, unproven modes of use of proven interventions, such as hydroxychloroquine for COVID-19 (Gould & Norris, 2021). In this chapter we will focus on one principle or criterion of ethically permissible use, namely, prospective review of an unproven intervention by an ethics committee. To do so, we will be guided by a fundamental question,

Fundamental question. What is the role of ethics committees in emergency use of unproven interventions outside research in recent ethical guidelines?

Recent guidelines for use of unproven interventions outside clinical trials during public health emergencies–also referred to as "compassionate use", a misleading term (Upshur, 2014; Calain, 2018: 6–7) – have assigned to ethics committees the responsibility of mandatory prospective review, authorization and oversight of such interventions within a larger regulatory system that includes qualified scientific committees, national regulatory authorities and other relevant health authorities (PAHO, 2020; WHO, 2016, 2022). However, ethical review has not always been considered an ethical criterion. To situate the reader, there are two historical developments worth comparing. First, consider a quick chronology of today's well-established ethical criterion or principle of "independent ethical review" of clinical research protocols (Emanuel et al., 2008: 130) that typically implies the mandatory prospective review, authorization and oversight of use of unproven interventions *within* clinical trials by research ethics committees (RECs), also known as Institutional Review Boards (IRBs) (London, 2012). This ethical principle or criterion was a novelty around the 1970s that had antecedents from the 1950s and 1960s in the US and the UK respectively (Hedgecoe, 2009, 2020) and was timidly introduced into global health ethics by the Declaration of Helsinki of the World Medical Association, the most influential international research ethics guideline (WMA, 1964a, first revision 1975; Schmidt et al., 2020). In turn, this implies that the ethical principle or criterion of mandatory prospective ethical review and authorization was absent in previous international ethical guidance such as the Nuremberg Code ([1947] 1949) or the first version of the Declaration (WMA, 1964c) as well as in previous influential literature on research ethics (Beecher, 1966 commented by Harkness et al., 2001). Second, now consider the ethical criterion of ethical review

and authorization for use of unproven interventions outside research during public health emergencies. As we will argue, ethical review was not present as an ethical criteria or principle in international ethical guidelines. Hence, this is an analogous novelty of international ethical guidelines of the mid 2010s and early 2020s still in the making that we believe is worthy of closer examination (Table 22.1).

The work in this chapter will be ordered as follows. In section "Introduction", we will introduce some definitions of basic terms and methodology that we believe will shed light on the ensuing arguments. We consider the explicit definition and methodology to be particularly necessary to avoid miss understandings due to the fact that the field of ethics of emergency use of unproven interventions outside research is still in an exploratory phase and lacking a well-established common language.

In section "Definitions of basic terms and methodology" we will argue that the role of ethics committees in emergency use is a recently introduced conceptual innovation. To justify this claim, we will first review and compare the role of ethics committees in a selection of recent and relevant ethical guidelines. A first set of documents includes the Declaration of Helsinki (WMA, 1964b, last revision 2013), the latest CIOMS-WHO (2016) research ethics guidelines and in the first WHO ethical documents on the topic. These ethical guidelines and documents do not mention ethics committees, and do not consider prospective ethical review and oversight by a committee among the ethical criteria for monitored emergency use – although they do not forbid such a role either. Then, we will review the ethical criteria, in more recent WHO ethics guidelines of monitored emergency use, (also known as MEURI), and WHO clinical management guidelines for COVID-19 that quote the former. It will be seen that in these guidelines, there is an explicit role of ethics committees recognized for prospective review, authorization and oversight.

Finally, in section "Literature review", we will recover our comparison between the role of ethics committees for research and for monitored emergency use and present some final considerations on its future development centered around complexity, the mutual influence between emergency and non-emergency use contexts, and questions of access pathways with and without committees.

Table 22.1 An analogy of the development of independent ethical review and oversight of the use of unproven interventions *within* and *outside* of research activities

Ethical review (prospective review by an ethics committee)	Use of unproven interventions *within* research	Emergency use of unproven interventions *outside* research
Required (*)	Declaration of Helsinki (WMA, 1964b, first revision 1975)	WHO (2016, 2022) and PAHO (2020)
Not required	Nuremberg Code ([1947] 1949), Declaration of Helsinki (WMA, 1964c) and Beecher (1966)	Declaration of Helsinki (WMA, 1964c, last revision 2013, para. 37) and WHO (2014a, b, 2015)

(*) *Required*: here we use the term to broadly capture any mention of ethical consideration, criterion, condition, principle, duty, obligation or else in the documents above

Definitions of Basic Terms and Methodology

Here we will present some basic definitions that we believe are needed for understanding the current work following the order of the fundamental question "What is the role of ethics committees in emergency use of unproven interventions outside research in recent ethical guidelines?". After that, we will make explicit the methodology for our tentative answer.

Definitions

Ethical review (also called, independent ethical review, independent review, ethical review and oversight). By ethical review we will mainly refer to the mechanism of prospective review, authorization and oversight by a group of diverse representations (i.e. ethics committee), different from the main agent responsible of the intervention or its recipient (i.e. independent review), within a governance system of emergency use of unproven interventions outside research. This is an operative definition for the purpose of our chapter and does not pretend to exhaust all the features of ethical review. For our definition, we have partly adapted and extended London's (2012, 2021: chapter 7) definition of research oversight and review by a research ethics committee (REC, also called institutional review board or IRB in the US). For London's analysis RECs' core function is prospective review and that is what we want to keep for our definition. However, here we use the term ethical review in a broader sense than research review. This definition can be fulfilled by either ethics committees whose main remit is to review unproven interventions within clinical trials or other research designs, including any type of international, national, regional or local RECs, or by ethics committees whose main remit is not to review unproven interventions within research but are sufficiently qualified to review use of unproven interventions for other purposes, including public health ethics committees, medical practice committees, clinical ethics committees, innovation or non-validated practice committees in all its various formats, as long as they retain the core functions of prospective review, authorization and oversight identified in our definition. In our definition, we explicitly add "authorization", that is, the capacity to grant permission (or not) for the use of unproven interventions. Although in London's analysis prospective or prior review implies the committee's capacity of authorization, we wanted to highlight "authorization" to distinguish *ethical review* from *ethical consultation* that would amount only to advice which does not imply the capacity of authorization of the consulted party. Finally, by "oversight" here we refer to its narrow meaning of subsequent review by the ethics committee of the initially reviewed emergency use, including its capacity to modify, stop and

terminate such use.[1] Again, this function might be presupposed in London's analysis but we wished to make it explicit.

It is noteworthy that the term "oversight" in the literature is used both in a narrow and broad sense. In a narrow sense, such as in "ethics committee oversight", it typically means "subsequent review" which implies the capacity to modify what was previously authorized in the light of new evidence, including to ask for modifications, suspension or termination (PAHO, 2020: 8). In a broader sense, such as in "independent oversight" (WHO, 2016) or "ethics and regulatory oversight" (PAHO, 2020), the term oversight refers to the whole function, that is, prospective review, authorization and subsequent review by an ethics committee and sometimes by other relevant health authorities as well. Finally, we believe that an ethics committee should not exercise this function in isolation but as part of a wider governance system of emergency use of unproven interventions outside research.

Governance system of emergency use of unproven interventions outside research. Here we will presuppose as a working hypothesis that the relevant national health authorities of each country, as well as international health authorities, such as the WHO, are ethically responsible for producing and maintaining a governance system coordinated within and between each country for the use of unproven interventions outside clinical trials or other research (Singh, 2015; PAHO, 2020; WHO, 2022).

For instance, in the US, different types of unproven interventions are covered by a complex set of regulations of what it is sometimes called non-trial pre-approval access (Kimberly et al., 2017) in which the national regulatory authority (e.g. the US Food and Drug Administration, FDA) and the national disaster management agency (e.g. the US Center of Disease Control, CDC) as well as the ministry of health (e.g. the US Department of Health & Human Services) typically have a central role, although this role varies depending on the type of pre-approval access. A non-exhaustive list of regulatory preapproval access pathways includes the expanded access program (associated to biomedical research regulations) (Lynch & Bateman-House, 2020), the emergency use authorization (associated to medical countermeasures regulations) (FDA, 2021), the "off-label" uses of proven interventions (associated to medical practice regulations, Gazarian et al., 2006; Largent et al., 2009), as well as access to unproven interventions through complementary or alternative medicine (associated to medical and non-medical practice and professional licenses regulations) (Wexler, 2019; Nagappan et al., 2021).[2] Meanwhile at the international level, WHO and PAHO (the regional office of WHO for the Americas), have developed the MEURI ethical framework for use of unproven interventions outside clinical trials (PAHO, 2020; WHO, 2016, 2022), including "off-label" uses of proven interventions (WHO, 2020a), as well as an Emergency Use Listing (EUL) (WHO, 2020b), a mechanism intended to provide a time-limited scientific and

[1] In the literature, subsequent review by the ethics committee sometimes is called "monitoring", a term that is also used to refer to the systematic collection of data of emergency use outside clinical trials. Both uses of "monitoring" activities should be distinguished because the agents and the activities are different in each case.

[2] For an alternative complementary list see Singh (2015).

quality evaluation of unproven interventions during public health emergencies and expedite its availability. However, to our knowledge, no single country has a unified and fully coordinated system to oversee all uses of unproven interventions outside clinical trials and consequently this also lacks at the international level. So, a coordinated system of monitored emergency use is at the moment an idea or working hypothesis to help unify ethical and legal considerations in different uses of unproven interventions outside clinical trials.[3]

Emergency use.[4] In this chapter, when using the term emergency use, we refer *to the use of interventions during a public health emergency* declared by a relevant national or international authority. It is important to distinguish this use of the term emergency, from the narrower use of unproven interventions for emergency care or a rescue treatment of last resort.

Unproven interventions.[5] Here, we define an unproven intervention as an intervention for which there is insufficient evidence of safety and/or efficacy for regular use in a healthcare system (Mastroleo & Holzer, 2020). Under this negative and ethically neutral definition, "unproven intervention" turns into an umbrella term for use of interventions with disparate preliminary evidence (e.g. Shah et al., 2015: Figure 1), risk–benefit profiles (e.g. Calain, 2018: Figure 1) and ethical status (e.g. ethically permissible or forbidden, responsible or irresponsible, etc.). However, it is useful to distinguish two sub-groups of unproven interventions with the same characteristics: "off-label" use, i.e. unproven modes of use of a proven intervention, and "completely unproven interventions", i.e. interventions for which there is no proven mode of use. Other terms often used to refer to unproven interventions or subgroups of unproven interventions in both ethics and regulatory documents can be partially ordered according to the main attribute of the intervention they typically highlight. A non-exhaustive list of terms reads as follows:

- *Lack of sufficient evidence*. This group of terms refer or imply lack of sufficient evidence for regular use of an intervention and includes the terms such as "unproven", "experimental", "investigational", "empirical", "untested", "unvalidated" and "non-validated".
- *Lack of full authorization*. A second group of terms refers to lack of full authorization by a relevant regulatory authority for regular use in a health system, such as "unregistered", "unlicensed", "unauthorized" and "unapproved".
- *Preauthorized*. An important subset is preauthorized interventions, which have not been fully authorized for regular health care. These include "accelerated approval (pathway)", "preapproved", "conditionally approved", "extended use", "emergency use authorization (pathway)".
- *Unauthorized modes of use of authorized interventions*. Another subset are not fully authorized modes of use of authorized interventions, such as "off-label",

[3] For a discussion on the importance of unification of ethical and legal considerations on the use of unproven interventions see Mastroleo and Daly (2021b) and Nagappan et al. (2021).

[4] Here we follow the glossary of WHO (2022) with minor edits.

[5] Here we follow the glossary of WHO (2022) with minor edits.

"used in unapproved ways", "repositioned" and "repurposed" (also known as "repositioning", "reprofiling", "redirecting" or "rediscovering").
- *Novelty*. An important group of terms associates unproven interventions with their novelty, such as "innovation", "innovative", "novel", "new non-validated" and "emergent".
- *Desperate situation*. A group of terms that refer to the desperate situations in which unproven interventions are often used, such as "compassionate use", "last chance", "last ditch", "rescue" and "emergency use".

The attributes of evidence, authorization, novelty and desperate situations are not logically equivalent, i.e. not all unproven interventions are unauthorized, novel or used in desperate situations. The same is true for the other possible combinations of attributes. The fundamental research question of this chapter uses the term "unproven interventions" because we believe lack of sufficient evidence for regular use is the core attribute of the interventions we want to analyze, while the others may or may not be present.

Outside clinical trials or outside research (capable of evaluating causal effects).[6] In the literature of ethics of monitored emergency use, the terms "outside clinical trials" and "outside research" are used interchangeably but without explicit definitions (e.g. WHO, 2016; PAHO, 2020). Hence, we follow WHO (2022) and use the terms "outside clinical trials" or "outside research" both as a shorthand for *use of unproven interventions in activities other than randomized controlled clinical trials (RCTs) or other research capable of evaluating the causal effects of such interventions*.

First, this definition of "outside clinical trials" or "outside research" is consistent with the principle that high quality evidence for public health decision making can come from different sources, not exclusively RCTs (Frieden, 2017; Deaton & Cartwright, 2018). Second, this definition restricts the term "clinical trials" or "research" to research designs capable of evaluating causal effects. This is because national regulatory authorities typically consider that research designs capable of evaluating causal effects, in conjunction with other relevant biomedical evidence and theories, are needed to provide sufficient evidence of the safety and efficacy of unproven interventions to give them full authorization for regular use in their healthcare systems. Finally, this definition implies that certain activities of systematic collection of data such as registries or other observational studies designs may fall under the category of "outside research" according to our definition even though they may be considered as "research with human beings" under some national or regional regulations (Leavy, 2018: 9). This apparent contradiction may be explained because of a lack of harmonized terminology and criteria for observational studies.[7] This is not necessarily a substantive ethical problem because monitored emergency

[6] Here we follow the glossary of WHO (2022) with minor edits.

[7] As Leavy notes "the definition of an observational study and the regulatory framework governing the conduct of such studies vary across countries and regions. In fact, even the terminology for an "observational study" is not harmonized at a global level." (Leavy, 2018: 9)

use has as a *main* aim benefit of patients, and as *secondary* aim (also an ethical obligation) systematic collection of data. Hence, both aims can be combined in the same complex activity – e.g. the Mayo Clinic expanded access program plus a national registry of convalescent plasma for COVID-19 (Joyner et al., 2021: 1016) – as long as the hierarchy of aims is respected by the design of the monitored emergency use protocol (e.g. the systematic collection of data does not unduly withdraw or restrain potential benefit to recipients) and by the application of the appropriate ethical framework (e.g. the MEURI or other equivalent ethical framework, instead of a less demanding or no ethical framework).

Methodology

The methodology employed in this chapter can be distinguished into two parts. Firstly, the identification of the main ethical guidelines in the research field of the use of unproven interventions outside clinical trials during public health emergencies. Secondly, a conceptual reconstruction and argumentation based on our reading of this literature using a philosophical framework of practical analysis (Mastroleo, 2021).

Our practical analysis framework (from the Greek *praxis* meaning action) interprets unproven interventions as actions between typically two responsible parties; where the action holds priority over the material and informational dimensions of an intervention.[8] Thus, it is important to stress that for practical analysis such as ethics or law, what comes first is the *use and main aim* of an unproven intervention; what the intervention in question *is and how it works* comes second. This priority of actions and aims has real world consequences and explains why the use of the same intervention (e.g. use of hydroxychloroquine for COVID-19) with different main aims (e.g. to develop generalizable knowledge; to enhance the well-being of a particular individual or group; to promote and protect the health of the public)[9] is a case of a different activity (respectively, research, clinical practice and public health practice)[10] and why the responsible agents involved are beholden to different ethical and legal requirements.

This responsibility also includes the agents in the role of authorities that are responsible for the governance (or lack of it) of such activities and its articulation in terms of *means and ends* (or its absence) as parts of a reasonable and unified

[8] The following analysis is an adaptation our discussion of ethics of unproven interventions in neuroscience (Mastroleo & Daly, 2021b).

[9] For an analysis of the definition of the main aims of research and practice, see Beauchamp and Saghai (2012); for public health practice see (Verweij & Dawson, 2007: 22).

[10] In our view, research and clinical practice should be considered part of the more complex activity of public health. For instance, research and clinical practice during a public health emergency should be considered part of the response and management of public health emergencies for ethical justification.

response to a public health emergency (Smith et al., 2021: lesson 2). In our regular use of language, we tend to identify interventions with their material dimension: a treatment *just is* a pill, or the *stuff* inside a syringe. But based on Kimmelman and London (2015)'s web of information model of clinical translation, we have previously argued (Daly et al., 2022) that a treatment can be usefully understood as a "setup:" safety (s) and efficacy (e) instructions used to make some thing (t, a drug or activity) useful (u) to a given endpoint (p). This endpoint can be understood in light of the aims of research (garnering generalizable knowledge) or practice (improving care for individuals or groups of patients or other recipients, e.g. prophylaxis for frontline workers).

Conflict of Interests

It must be disclosed that one of the authors (Mastroleo) is an active participant in the recent development of ethics guidelines for monitored emergency use that recognize this new role for ethics committees (PAHO, 2020; WHO, 2022, commentator and leading writer respectively). However, the views and interpretations presented in this work are personal to the authors and do not necessarily reflect the policies of the institutions mentioned above or other institutions involved.

Literature Review[11]

The following is a non-exhaustive review of the literature on ethical guidelines with the main aim of highlighting the recent and unfinished development of the role of ethics committees as responsible agents for prospective review, authorization and oversight of monitored emergency use of unproven interventions outside research. It does not pretend to be neither a systematic review nor a needed in-depth historical analysis of such a development.

The Declaration of Helsinki: No Role for Ethics Committees

Among the international human health research ethics guidelines, the Declaration of Helsinki of the World Medical Association (hereinafter the Declaration) *Ethical Principles for Medical Research Involving Human Subjects* (WMA, 1964b, last revision 2013) has the greatest normative weight. This is because of its history and

[11] This section is based on the literature review of Mastroleo (2021), partly present in WHO (2022) of which Mastroleo was its leading writer.

the international legitimacy given to it by the democratic representation of the World Medical Association (Schuklenk, 2004). The normative authority of the Declaration comes also from the recognition by other important international documents including CIOMS-WHO (2016) guidelines and the Good Clinical Practice Guidelines (GCP) of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (ICH, 2016).[12] The content of the Declaration has been incorporated worldwide to national regulations and laws in various forms.

Hence, the Declaration's paragraph 37 is perhaps the most popular and accessible reference to the ethics of use of unproven clinical interventions outside research during public health emergencies:

> *Unproven Interventions in Clinical Practice*. 37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available. (WMA, 1964b, last revision 2013)

Given that there is no explicit mention of emergencies, the first fundamental question is: does the Declaration support the use of paragraph 37 as ethical guidance during public health emergencies? The short answer is yes, at least for one public health emergency of international concern (PHEIC).[13] In 2014, the WMA issued a *Resolution on Unproven Therapy and the Ebola Virus* explicitly stating that "In the case of Ebola virus, the WMA strongly supports the intention of Paragraph 37 of the 2013 revision of the Declaration of Helsinki" (WMA, 2014). No analogous resolution was found for the COVID-19 pandemic, but even without an official resolution many agents from the biomedical community used paragraph 37 to justify the ethical permissibility of the use of unproven interventions outside research (Mastroleo, 2021).[14]

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[12] "Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible." (ICH, 2016)

[13] According to WHO a "PHEIC is defined in the [International Health Regulations] IHR (2005) as, 'an extraordinary event which is determined to constitute a public health risk to other States through the international spread of disease and to potentially require a coordinated international response'. This definition implies a situation that is: serious, sudden, unusual or unexpected; carries implications for public health beyond the affected State's national border; and may require immediate international action" WHO (2019).

[14] Given the breadth of ethical issues raised by use of unproven interventions outside clinical trials, recent academic literature has considered that the paragraph 37 should be revised for the context of non-public health emergency situations (Asplund & Hermerén, 2017; Daly et al., 2020: table 2; Helgesson, 2021). We believe that a similar strong suggestion should be made for its use during public health emergencies.

A second fundamental question related with the role of ethics committees is: Do the ethical requirements identified in paragraph 37 include a mention of ethics committees or independent ethical review? We believe this not to be the case. As the analysis of paragraph 37 shows (see Box 22.1), there is identification of the relevant action (use of an unproven intervention), the relevant agents (the individual patient, the physician) and the exceptional circumstances ("where proven interventions do not exist or other known interventions have been ineffective"), but there is no mention of ethics committee in the ethical requirements for such action. The closest it gets to giving some role to an ethics committee is when it states "[…] after seeking expert advice". How should the requirement of "seeking expert advice" be understood? Here, we have interpreted it as both the ethical requirements of preliminary scientific support based on favorable risk–benefit ratio (Box 22.1, req. 1) and of prior consultation (Box 22.1, req. 2).

Box 22.1: Analysis of the Declaration of Helsinki's Actions and Ethical Requirements for Use of Unproven Intervention in Clinical Practice (Non-research Activity) During or Outside a Public Health Emergency (WMA, 2013, para. 37)

A. **Identification of main agents, relevant action and circumstances**
"In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician […] may use an unproven intervention […]"

B. **Ethical requirements**

1. *Preliminary scientific support based on a favorable risk-benefit analysis*. "[…] after seeking *expert* advice […]" (emphasis added)
2. *Prior consultation*. "[…] after seeking expert *advice* […]" (emphasis added)
3. *Informed consent (by patient or LAR)*. "with informed consent from the patient or a legally authorised representative"
4. *Social aim of individual patient well-being*. "[…] if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering"
5. *Avoid individual and public health harm by validation through research*. "This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy."
6. *Contribute to the generation of evidence (monitored use; collection and sharing of results)*. "In all cases, new information must be recorded and, where appropriate, made publicly available"

Helgesson suggests that "reading a couple of papers" may satisfy the requirement of seeking expert advice in the Declaration of Helsinki (Helgesson, 2021). Here we argue that consultation with peers adheres to a more robust standard. If our argument holds for this stronger standard, it will also hold for a weaker one. In turn, in the light of the MEURI ethical framework (e.g. WHO, 2016; PAHO, 2020), we interpret this short sentence as an antecedent to the role of a qualified ethics committee and the consequent ethical requirement of prospective review, authorization and oversight.[15] However, though an antecedent, the requirement of "prior consultation" is much less demanding. As Miola (2015) explains, the requirement or duty of physicians to ask for prior consultation with experts ("expert advice") does not imply the duty to reach consensus, nor to follow such advice.[16]

As Miola explains, consultation must satisfy four principles to be proper: (1) the consultation process must be taken at a formative stage; (2) the consultants must be provided with sufficient reasons [and information] for intelligent consideration and response; (3) the consultants must be given adequate time for intelligent consideration and response; and (4) the consultants' advice must be conscientiously taken into account when the final decision is made. These four principles presuppose that the party consulted is an expert on the matter (Miola, 2015: 145). As long as consultation is done in good faith and following these four principles a physician may listen to the expert advice of a colleague against using an unproven intervention outside a clinical trial, including "off-label" uses, and still carry on with it. Hence, "a duty to consult does not provide a consultee with a veto" (Miola, 2015: 145). Furthermore, regarding the fourth principle, taking consultation's advice consciously does not imply not having a prior preference about what to do, that is, an open mind is not an empty mind (Miola, 2015: 145). In comparison, a duty to ask for prior review and authorization to a qualified ethics committee does provide a veto power to the ethics committee. Here, the situation is of the physician asking for permission from a third party to use such interventions, not of asking for advice. Even if it takes into account the requirement of prior consultation with experts, we count the Declaration of Helsinki as not assigning the role to an ethics committee of prior review and authorization for the use of unproven interventions outside research during public health emergencies.

[15] "data providing preliminary support of the intervention's efficacy and safety are available, at least from laboratory or animal studies, and use of the intervention outside clinical trials has been suggested by an *appropriately qualified scientific advisory committee* on the basis of a favourable risk–benefit analysis" (WHO, 2016; PAHO, 2020); "the relevant country authorities, as well as an appropriately *qualified ethics committee*, have approved such use" (WHO, 2016; PAHO, 2020).

[16] We argue for more stringent language around the need for expert consensus and transparency in Daly et al. (2020).

The CIOMS-WHO International Research Ethics Guidelines: No Role for Ethics Committees

There is no mention of the role of ethics committees or independent ethical review in CIOMS-WHO (2016) ethics guidelines for use of unproven interventions outside research during public health emergencies. However, we believe it is still important to comment on the CIOMS-WHO guidelines because of its normative weight, especially in developing countries. Originally drafted in the 1980, the CIOMS-WHO guidelines are considered an excellent complement to the Declaration of Helsinki and explicitly acknowledge the Declaration as a source of normative authority. Since the WHO did not have the appropriate expertise at the time, the Council for International Organizations of Medical Sciences (CIOMS) was created with the task to counsel WHO representative countries on the application of the ethical principles of research ethics laid down in the Declaration. The fact that CIOMS presents ethical "guidelines" followed by detailed paragraphs explaining each guideline is a virtue of this document. This latest revision introduced very important changes from the previous one, among them, unifying several previous guidelines.

The latest version of CIOMS-WHO (2016), revised after the West Africa Ebola pandemic in 2014–2016, includes only an indirect reference and commentary on emergency use of unproven interventions outside research in its guideline 20 on "Research in Disasters and Disease Outbreaks"[17],[18] That is, unlike the Declaration of Helsinki, the CIOMS-WHO guideline 20 does not explicitly provide a list of ethical criteria for when it is ethically permissible.

Although the MEURI ethical framework (WHO, 2014b, 2016) is not explicitly quoted in CIOMS-WHO (2016), the guideline refers to "emergency use [of investigational interventions] outside clinical trials" (CIOMS-WHO, 2016: 77). Dr. Aissatou Touré, member of the CIOM-WHO Working Group, was also member of the WHO (2014a) Working Group and one of the leading writers of the "Green Book" (WHO, 2016: 5) that includes the first extensive formulation of the MEURI ethical framework.

[17] Although this guideline takes the concept of disasters and disease outbreaks as central, they can be associated with the ethics of public health emergency ethics since both types of events are associated with the declaration of PHEICs by WHO. To our knowledge, research in disasters and disease outbreaks was a novel topic not included in previous versions of the CIOMS-WHO guidelines.

[18] We have previously studied (Daly et al., 2020) a case of problematic use of unproven interventions outside research in the context of Alzheimer's disease (AD), thought to be the leading cause of 55 million cases of dementia worldwide (WHO, 2021b). Racine (2010) argues that neurodegenerative diseases like AD are appropriately described as "burdens," since they represent a major source of financial loss and need for constant care that healthcare systems are unable to respond to. Thus, this burden is mostly carried by informal caregivers. Given the rapid rise in dementia cases expected for the aging world population, dementia is referred to by the WHO as a public health "priority" but not an emergency (WHO, 2012). We argue that ethics should use a language of proportionality rather than exceptionalism in the ethical analysis of research into conditions like dementia (Mastroleo & Daly, 2021a).

According to London the CIOMS-WHO guideline 20 states that "health-related research should form an integral part of disaster response" and that, "widespread emergency use [of unproven interventions] with inadequate data collection about patient outcomes must therefore be avoided" (CIOMS-WHO, Guideline 20 in London, 2018). The primary aim of the guideline 20 is therefore to establish as a duty to conduct research during disasters and outbreaks and secondly, to forbid widespread use of unproven interventions outside clinical trials with inadequate data collection.[19] This last ethical prohibition does not forbid the use of monitored emergency use as understood in the text of the Declaration of Helsinki (WMA 1964c, last revision 2013, para. 37) or in the MEURI ethical framework since both refer to a controlled process for using and accessing unproven interventions outside research that includes, among other criteria, relevant data collection and sharing.

WHO Early Guidance and Documents (2014–2015) on the Ethics of Emergency Use of Unproven Interventions Outside Research: No Role for Ethics Committees

On 11 August 2014, in the context of the West Africa Ebola outbreak, WHO convened a panel of experts to answer five questions (WHO, 2014a: 3) that were summarized by a second Working Group with the following fundamental question:

> Fundamental question. "Is it ethically permissible to use scientifically promising but unproven interventions (outside research) for treatment and prevention? And if this is the case, what are the conditions and criteria before they can be used?" (WHO, 2014b: 3)

In the report of the first Working Group "*Ethical considerations for use of unregistered interventions for Ebola viral disease*" the panel reached consensus that there was a "moral duty" to evaluate unproven interventions in "clinical trials" even during a public health emergency. However, in the exceptional circumstances of the 2014 Ebola outbreak they "agreed unanimously" it was ethical to offer unproven interventions outside research "to patients and people at high risk of developing the disease", with the condition these interventions followed a set of prior ethical considerations and criteria including but not limited to: effective use of resources for a public health response,[20] transparency about all aspects of care, trust, fair distribution in the face of scarcity, promotion of cosmopolitan solidarity, informed consent,

[19] According to London "This position is defended against two lines of criticism that emerged during the 2014 Ebola outbreak. One holds that desperately ill patients have a moral right to try unvalidated medical interventions (UMIs) and that it is therefore unethical to restrict access to UMIs to the clinical trial context. The second holds that clinical trials in contexts of high-mortality diseases are morally suspect because equipoise does not exist between a standard of care that offers little prospect of clinical benefit and a UMI that might offer some clinical advantage." (London, 2018)

[20] "Investigational therapeutic or prophylactic options should not divert attention or resources from the public health measures that remain the main priority in outbreak control." (WHO, 2014a)

freedom of choice, confidentiality, respect for the person, preservation of dignity, involvement of the community, risk-benefit assessment, sufficient preliminary scientific evidence, capacity for risk minimization and monitoring [side effects and the progress of treatment], collecting and sharing relevant data, avoid precluding or delaying research of unproven interventions (WHO, 2014a). Also, in order to understand the safety and efficacy of these interventions, the panel advised that "if and when they are used to treat patients, there is a moral obligation to collect and share all data generated, including from treatments provided for 'compassionate use' (access to an unapproved drug outside of a clinical trial)" (WHO, 2014c). However, this first Working Group did not mention prospective review, authorization and oversight by a qualified ethics committee among the ethical considerations, conditions or criteria to use unproven interventions outside clinical trials.

On the 20th–21st October 2014, during the Ebola virus disease outbreak in West Africa, a second advisory panel to the World Health Organization (WHO) was convened due to criticism of the first working group.[21] This second Working Group coined the term MEURI (WHO, 2014b) to avoid the misleading designation of "compassionate use" (Upshur, 2014; Calain, 2018: 6).[22] Beyond that, there was no substantive change from the ethical criteria and conditions recognized by the first Working Group, nor a mention of prospective review, authorization and oversight by an ethics committee.

On 5 November 2014, an Interim Guidance for "Potential Ebola therapies and vaccines" was published. To note, the Interim Guidance referred to the work of the first Working Group (WHO, 2014a) but not to the second (WHO, 2014b). This has as a result that the term MEURI was not employed in the guidance. This guidance included a rich and detailed third section on "Evaluation and emergency/compassionate use of unproven interventions". However, there was no mention of

[21] "The [first] panel [(WHO, 2014a)] has been criticized for the haste in which it was brought together and the lack of representativeness of the panel. These shortcomings have been acknowledged; however, there has been little disagreement with the substantive decision. The subsequent larger panel [(WHO, 2014b)] is well represented by ethicists and social scientists from West Africa and the report of their deliberations will be released sometime in late September 2014." (Upshur, 2014: 422, edited)

[22] "Some ethicists noted that the word 'compassionate' is misleading in the EVD situation, for at least two reasons. Firstly, compassionate use typically refers to agents evaluated in clinical trials, and for which some prior data on safety in humans exist. Secondly, compassionate use does not necessarily entail moral obligations to contribute to evaluating effectiveness. Accordingly, and to reflect the fact that emergency trials considered for EVD can carry as many risks as benefits, it became clear that a more precise concept had to be defined. To reflect such considerations, a WHO Ebola ethics working group has coined the qualifier of monitored emergency use of unregistered and experimental intervention' (MEURI). MEURI protocols would thus commit their promoters to the systematic documentation of clinical outcomes and other effects. This approach reflects one of the recommendations of the WHO panel saying that: 'Capacity should be available to administer the experimental therapy in conjunction with the necessary supportive treatment, to monitor and manage any side effects and to monitor the progress of treatment, including, at a minimum, measuring when possible appropriate surrogate outcomes, such as disease and immune response markers'". (WHO, 2014a, quoted by Calain, 2018: 7)

prospective review and oversight by an ethics committee as an ethical consideration, condition or criterion.

In 2015, WHO published a training manual for ethics of epidemics, emergencies and disasters (WHO, 2015). This manual was divided into two big sections: "Research and surveillance" and "Patient care". Within the latter section, there was a chapter dedicated to "Identify issues of equity of access to unproven treatments during research in the course of emergency response". This chapter still used the language of "compassionate use" and not MEURI. Consistently with the previous guidance, there was no mention to ethics committees related to the use of unproven interventions outside clinical trials.

WHO Latest Guidance (2016–2022) on Ethics of Emergency Use of Unproven Interventions Outside Research: A New Role for Ethics Committees

The *Guidance for Managing Ethical Issues in Infectious Disease Outbreaks* (WHO, 2016), also known as the "Green Book" for its cover, is one of the most authoritative guidance for ethics of pandemic preparedness and response (Smith & Upshur, 2020, Saxena et al., 2021). Guideline 9 "Emergency use of unproven interventions outside of research" (and its cross-references from guideline 4 "Allocating scarce resources", 10 "Rapid data sharing" and 13 "Frontline response workers' rights and obligations") is what we would regard as the first well-developed version of the MEURI ethical framework. Guideline 9 argues that use unproven interventions outside research during a public health emergency is ethically permissible,[23] provided that the following seven conditions were satisfied:

> (1) no proven effective treatment exists; (2) it is not possible to initiate clinical studies immediately; (3) data providing preliminary support of the intervention's efficacy and safety are available, at least from laboratory or animal studies, and use of the intervention outside clinical trials has been suggested by an appropriately qualified scientific advisory committee on the basis of a favourable risk–benefit analysis; (4) the relevant country authorities, as well as an appropriately qualified ethics committee, have approved such use; (5) adequate resources are available to ensure that risks can be minimized; (6) the patient's

[23] Not an "imperative" as supposedly stated by the report of the first Working Group (WHO, 2014a), according to Landry et al. (2015). Against Landry et al.'s interpretation, it might be the case that the first Working Group meant that it was an imperative, to use unproven interventions during a public health emergency *within research,* that is, there's a duty to conduct research of unproven interventions during a public health emergency under certain conditions, while it was only ethically permissible to use unproven interventions *outside research*. As Calain states "The WHO panel did not take any position to encourage or discourage the compassionate use of experimental products during the course of the Ebola epidemic. It simply declared a moral obligation to share 'transparently and rapidly' all scientific data generated by any sort of use of investigational products." (Calain, 2018: 6)

> informed consent is obtained; and (7) the emergency use of the intervention is monitored and the results are documented and shared in a timely manner with the wider medical and scientific community. (WHO, 2016: guideline 9)

Besides these seven considerations, guideline 9 included a set of fundamental questions and added that emergency use of unproven interventions outside research should be guided by a set of seven ethical principles that "guide use of unproven compounds in clinical trials", namely, independent oversight, effective resource allocation, minimizing risk, collection and sharing of meaningful data, informed consent, need for community engagement, and fair distribution in the face of scarcity (WHO, 2016: 36–7). This guidance has relevant continuities but also differences in the ethical considerations with previous ethics guidance. For the aims of the current literature review, we should only pay attention to the third fundamental question addressed by guideline 9 ("What type of ethical oversight should be conducted when unproven interventions are offered outside clinical trials during infectious disease outbreaks?"), the fourth condition or criterion (that "the relevant country authorities, as well as an appropriately qualified ethics committee, have approved such use"), and the first principle of independent oversight:

> *Independent oversight.* MEURI is intended to be an exceptional measure for situations in which initiating a clinical trial is not feasible, not as a means to circumvent ethical oversight of the use of unproven interventions. Thus, mechanisms should be established to ensure that MEURI is subject to ethical oversight. (WHO, 2016: 36, original emphasis)

In our view, these references amount to sufficient evidence for the role of ethics committees as a mechanism for prospective review, authorization and oversight of unproven interventions outside clinical trials during public health emergencies. However, in this document there is no explicit answer of the fundamental question on the type of ethical oversight beyond mentioning a "qualified ethics committee" nor about its implementation in the real world.

Fast forwarding to the context of the COVID-19 pandemic, at least three important documents related to the MEURI ethical framework were published within WHO's remit.

On 28 January 2020, WHO's interim clinical management guidelines recommended that unproven interventions for COVID should be used either in ethically approved clinical trials or monitored emergency use (WHO, 2020c: 8).[24] The 21 January 2021 living version of WHO's clinical management guidelines also quotes the seven MEURI ethical criteria for access to unproven interventions outside clinical trials (WHO, 2021a: 45) from guideline 9 of the "Green Book" (WHO, 2016), which includes the fourth criterion of ethical review.

On 31 March 2020, a press release named "Off-label use of medicines for COVID-19" was the first document published on MEURI or "compassionate use" by WHO for the COVID-19 pandemic (WHO, 2020a). The publication came during

[24] "Unlicensed treatments should be administered only in the context of ethically-approved clinical trials or the Monitored Emergency Use of Unregistered Interventions Framework (MEURI), with strict monitoring." (WHO, 2020c: 8)

a surge of "off label" use of interventions for COVID-19, that is unproven modes of use of proven interventions for other conditions, such as the US Food and Drug Administration (FDA) Emergency Use Authorization (EUA) for Chloroquine and Hydroxychloroquine (authorized for emergency use, March 28 – revoked authorization for lack of evidence, June 15) (FDA, 2020). This press release made explicit reference to "national laws and regulations" and spelled out some of the seven ethical criteria of the MEURI ethical framework (WHO, 2016), but did not explicitly mention (nor forbid) the principle of "independent [ethical] oversight".

On June 25, the Pan American Health Organization (PAHO), the Regional Office for the Americas of WHO, further advanced the MEURI ethical framework spelled in WHO (2016) with an elucidation of the seven ethical criteria by four ethical categories, namely, justification (criteria 1–3), ethical and regulatory oversight (criteria 4–5), consent process (criterion 6) and contribution to the generation of evidence (criterion 7) (PAHO, 2020: 3–4). Moreover, it clarified the MEURI ethical framework with additional guidance, the identification of challenges that might stem from not using the MEURI framework, explicit comments to the new ethical categories of the framework, and general and operational recommendations for its implementation (PAHO, 2020). For our purposes, the 4th criterion of the second category, "ethical and regulatory oversight", and its comments is of great importance. A first comment states that:

> MEURI [that is, monitored emergency use of unproven interventions outside a clinical trial] requires the review and approval of an ethics committee and the NRA [national regulatory authority], along with other relevant national authorities, which will vary based on the local norms and the type of intervention at stake. (PAHO, 2020: 3, edited)

This comment adds to the explicit and straightforward recognition that ethics committees should have a shared role of prospective review and authorization of unproven interventions outside research, together with other relevant authorities including national regulatory authorities. A second comment will be useful as a bridge to the topic of implementation of this role and the following section of this chapter:

> While MEURI [that is, monitored emergency use of unproven interventions outside a clinical trial] does not constitute research but rather access to an unproven intervention outside of research, it should be guided by the same ethical principles that govern the use of unproven interventions in clinical trials. A research ethics committee (REC) must thus conduct the review. Only investigational products manufactured according to good manufacturing practices should be used for MEURI. (PAHO, 2020: 3, edited)

Here, we will comment on three points. First, the authors of the PAHO document explicitly recognize that monitored emergency use is not a research activity, from which we interpret based on an important part of the literature and our methodological framework (see section "Methodology") that the main aim of monitored emergency use is not to "develop generalizable [scientific] knowledge" (National Commission, 1978, quoted in Beauchamp & Saghai, 2012: 52). In our understanding, the main aim of emergency use of unproven interventions outside research is to benefit its recipients, it is thus usually a form of medical practice or care, and we found it could be better understood as a form of new or long(er)-standing

non-validated practices (Mastroleo & Holzer, 2020) during public health emergencies.[25] This interpretation is also consistent with WHO (2015) that considers problems of "compassionate use" as practice rather than research or surveillance.

Second, that PAHO in its comments departs from the general language of a "qualified ethics committee" of ethical guidelines and explicitly defends that the research ethics committee (RECs) should conduct the review of monitored emergency use. This point is later developed in the section of the document devoted to implementation. Third, the section on implementation includes useful recommendations, not ethical principles, conditions or criteria, on how to operationalize ethical review. We believe such recommendations are useful whether one decides to follow the RECs model or another type of qualified ethics committee model. It spells out the tasks of an ethics committee ordered into two functions, namely, review and oversight (see Box 22.2).

Box 22.2: Two Functions of a Qualified Ethics Committee for Emergency Use of Unproven Interventions Outside Clinical Trials (PAHO, 2020: 7, edited)

What does the REC [research ethics committee] review?

(a) Whether or not the proposed intervention adheres to the seven criteria for MEURI […]. (b) The ethical and scientific basis for the protocol, taking into account among other things the following: [1] the available scientific evidence justifies the intervention based on its risk-benefit balance; [2] the intervention is offered to the appropriate population; [3] the informed consent process is adequate and pertinent in the context of the pandemic; [4] the consent document specifies the details about the interventions and the data that will be collected, along with the risks and potential benefits of the unproven intervention; [5] the confidentiality of the data is guaranteed; [6] the data to be collected are relevant to provide information on the safety and efficacy of the intervention; [7] procedure to share data quickly with health authorities and the national and international scientific community has been established.

What does the REC [research ethics committee] oversee?

Through the reports provided by the health care professional responsible for the intervention, the REC oversees that the intervention is still justified in light of new available evidence. The REC can require modifications in the intervention or the way it is offered, its suspension or termination.

[25] Independent support for our interpretation that the main aim of monitored emergency use is to benefit patients or other recipients comes from the "ethical basis" or justification of MEURI, in particular its considerations of beneficence, that is: "providing patients with available and reasonable opportunities to improve their condition, including measures that can plausibly mitigate extreme suffering and enhance survival" (WHO, 2016). This consideration is very close to the requirement of justification in the Declaration of Helsinki of "use of unproven interventions in clinical practice", namely "[…] if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering" (WMA, 1964b, last revision 2013).

The implementation section also recommends unproven interventions to be provided under a protocol and states what should be regarded as its minimal content:

Development of the MEURI protocol: The intervention must be proposed as a protocol that, at the minimum, must include the following: (a) background; (b) scientific justification on the basis of the recommendations of a scientific committee; (c) objectives; (d) population to be offered the intervention; (e) risks and potential benefits; (f) scientific data to be collected to provide information on the intervention's safety and efficacy; (g) plan to offer the intervention to patients; (h) informed consent documents and details about the process; (i) data sharing plan; and (j) measures to protect confidentiality. The protocol must also indicate the planned time frame for offering the intervention under MEURI and presenting it to be evaluated as part of a research protocol (ideally a randomized clinical trial) (PAHO, 2020: 7).

Other operational recommendations for the implementation of the MEURI framework complement the previous ones, but these two in particular play a central role fleshing out the bare bones of the fourth ethical criteria or independent ethical review in the WHO (2016) ethical framework.

Finally, we should also mention that it is plausible to interpret PAHO's ethical guidance as explicitly extended ethics review to "off-label" use of proven interventions when it explicitly included under the scope of the document "interventions that have been proven safe and efficacious for a condition other than COVID-19 and thus authorized", that is "off-label" use, and "interventions that have not been proven effective nor authorized for another condition". This is itself a novelty in comparison with the previous WHO document (WHO, 2020a) that has been continued in the latest version of the MEURI framework (WHO, 2022).

Since April 2020, there has been significant work on a revised version of the MEURI ethical framework. This ethical guidance includes the collaboration undertaken by the WHO Working Group on MEURI as well as members of the WHO Clinical Management Working Group and is still a work in progress (WHO, 2022) and one of the authors of this chapter (Mastroleo) is the leading writer. This document is intended to provide policy-makers, national regulatory authorities (NRAs), healthcare workers, ethics committees and other stakeholders with an updated version of the ethical framework for use of unproven clinical interventions outside research during public health emergencies (also known as the MEURI ethical framework), following the previous developments. In its current form, it includes a reference to the criterion of ethical review. However, since it is still a late-stage work in progress at the moment of writing this chapter, we feel it would not be appropriate to make a more detailed comment on its content.

Final Considerations: The Future of Ethical Review in Emergency Use of Unproven Interventions Outside Research

If our previous literature review is sound, there is clearly a new role for ethics committees in the review, authorization and oversight of unproven interventions outside clinical trials during public health emergencies, at least in what it regards to the ethical guidelines that may or may not translate into effective practice. In this final section, we want to revisit the analogy of the development of independent ethical review and oversight of the use of unproven interventions *within* and *outside* of research activities (see section "Introduction", Table 22.1) for further insights into the future of such ethical requirement.

The role of ethics committees as a mechanism of prospective review, authorization and oversight of the use of unproven interventions *within* clinical trials and other research activities by regular RECs, IRBs or other specialized committees has been more or less established in international documents and national regulations since the 1970s. It has a solid conceptual foundation (London, 2012, 2021: chapter 7) and its many challenges are those of the differential designs of prospective review systems, including their quality and expeditiousness (e.g. Lynch et al., 2019, 2020). One forward-looking question is: will something similar happen for ethics committees for the use of unproven interventions outside clinical trials during public health emergencies? Based on the place of the mechanism of prospective review in current guidelines (e.g. WHO, 2016, 2022; PAHO, 2020) this does seem possible. However, in spite of the recent developments, this possibility coexists with the reality that most countries lack well-developed regulatory frameworks and/or the capacity to devise and enforce monitored emergency use of unproven interventions outside research (Singh, 2015: 2; Singh & Upshur, 2021). This has made for an active movement, with important political and economic support in developed countries, for earlier and more readily available access to unproven interventions outside clinical trials in which the role of ethics committees as a mechanism for review, initial authorization and overview is not at all present (Miola, 2015; Bateman-House et al., 2015; Lynch & Bateman-House, 2020).

We will not attempt to answer this question here, but there seems to be some general considerations one should take into account if trying to think about the future of the role of ethics committees for monitored emergency use.

First, it would be important to compare the complexity of emergency use of unproven interventions outside clinical trials to the activity of biomedical research. Biomedical research, especially clinical trials, is a comparatively less complex and better-established field with national regulatory agencies, a system of research ethics committees, and well-established international guidelines in spite of shortfalls and inequity in low- and middle-resource settings and contexts (CIOMS, 2016, guideline 2). This relative simplicity stands in contrast to the heterogeneous scope of the use of unproven interventions outside clinical trials that includes different authorities and access pathways for unproven interventions, some of them related

with research activity while others with traditional clinical practice (including "off-label" uses), or even with complementary and alternative medicine (Wexler, 2019). We believe the different complexity between both activities is a good reason to refrain from making any too straightforward an analogy between the development of the role of ethics committees in research and in monitored emergency use.

Second, it is important to recognize that the ethical literature on use of unproven interventions outside clinical trials during and outside public health emergencies mirrors and pollinizes each other in similar, yet not identical, ethical problems and considerations.[26] For example, during the West Africa Ebola outbreak, ethical and legal analysis of regulations of innovation (non-emergency use of unproven interventions outside clinical trials) quoted cases of Ebola (Miola, 2015: 150), literature on monitored emergency use for Ebola also refer to ethics guidance and regulations of innovation (WHO, 2015: 192). This mutual influence of regulatory developments in emergency and non-emergency contexts has also been explicitly recognized during the COVID-19 pandemic (Lynch et al., 2021; Mastroleo & Daly, 2021a). So, when looking for ethical reasons for or against the role of ethics committees for emergency use it is useful also to have a broader look at the literature on non-emergency use. Under this broader view, the dangers of use of unproven interventions outside clinical trials have clearly been recognized in the US at least since the 1970s in non-emergency use (Beauchamp & Saghai, 2012) and several sound justifications of the mechanism of prospective review, authorization and oversight by ethics committees (Taylor, 2010; Borysowski et al., 2017). In turn, this makes the criterion of ethical review and oversight in recent ethical guidance look less like an outlier.

A third related consideration to take into account is that whatever is the future of ethics committees it would be part of a broader change in national and international health systems. Authoritative literature defends the improvement and flexibilization of pre-approval access pathways (e.g. expanded use program) that include as a requirement prospective review, authorization and overview by some form of an ethics committee, both during and outside public health emergencies (Lynch & Bateman-House, 2020; Lynch et al., 2021) over pre-approval pathways without this role for ethics committees. Yet this literature also accounts for the presence of current (e.g. Emergency Use Authorization and Right to Try in the US) and future (e.g. Promising Pathway Act in the US) mechanisms in which ethics committees review and oversight are not required for access to unproven interventions outside clinical trials. To make matters more complex, it would be logically possible to articulate pre-approval access mechanisms with and without a role of ethics committees, such as a combination of early expanded access-like programs (with a role for ethics committee) and later emergency use authorization-like programs (without a role for

[26] These features of mutual mirroring and pollination and its similarity yet not identity of the ethics literature are easily explained by our practical framework. Both activities or uses of unproven interventions outside clinical trials share the same genus in our taxonomy yet diverge in its being part or not of the larger activity of a public health response and management to a public health emergency (Mastroleo & Holzer, 2020).

ethics committee) depending on the level of evidence, uncertainty and risk-benefit analysis of each particular situation.

Summing up, higher complexity than research, mutual influence between emergency and non-emergency use contexts as well as change of current forms and articulation of access pathways with and without committees are broad considerations to bear in mind when thinking about the future role of ethics committees for monitored emergency use.

Finally, we would like to restate the exploratory nature of our work. We believe we are at the dawn of a new field of ethics of monitored emergency use but also that monitored emergency use is just one part of a larger activity (and hence ethics) of prevention, response and management of public health emergencies. We hope this modest contribution to the literature can be of help to improve understanding of emergency use of unproven interventions outside clinical trials, and that with such understanding, greater collective practical wisdom might be attained.

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Chapter 23
The Ethics of Resource Allocation in Pandemics: A Bayesian Model

Erick Valdés

Abstract How to allocate scarce resources in pandemics is still a challenging issue. Several proposals are plenty of subjective criteria, based upon traditional ethical principles, such as dignity and integrity, among others. I will offer a Bayesian model for resource allocation, free from ideological basis, and as such, it is impartial. In this fashion, I seek to decontaminate reasoning and decision-making process from abstract principles and prevent the model from a paralyzing deliberative effect like natural law or natural ethics often do. In this fashion, it will be concluded that a decision-making process is more likely to be effective if it uses objective criteria, and it is not diverted by personal values, intuition, moral conscience, religion, tradition or idiosyncrasy.

Keywords Resource allocation · Pandemics · Bayesian model · COVID-19 · Ethical cognitivism

Moral Disagreement

Since the first case of SARS-CoV-2 was reported in Wuhan, China back in December 2019, the virus spread out with frightening speed to practically the entire world, by triggering a pandemic of disastrous dimensions, whose scope and definitive consequences are still unknown.

The latent danger that lurked in this new scenario compelled countries to take extraordinary measures not only to protect the health of population and avoid an unmanageable number of deaths, but also to ensure that health systems were able to deal with a massive demand for beds and ventilators.

People all over the world suddenly changed their way of living and understanding concepts such as closeness and remoteness. Apocalyptic stories started

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colonizing the media. Metaphysical solutions were suggested as praying and waiting could also be an option. However, beyond the ontological and onto-theological questions that COVID-19 engendered, a constellation of practical problems that governments, health centers, physicians, health staff and ordinary people have had to deal with emerged. One of those controversies is what distributive criteria should be considered to allocate scarce resources, such as ventilators, for example. Once this problematic environment of the pandemic displayed itself it inaugurated a new universe of excruciating conflicts, dangerous legal slopes, and diffuse ethical atmospheres.

More specifically, a hostile ethical question that has been raised in the context of the COVID-19 pandemic is how to deal fairly with a large number of patients who evolve into a critically ill state. This has pointed out that, in both developed and developing countries, health systems must handle a scenario where the demand for intensive medical care exceeds resources available. There is a need for ethical and policy guidelines on how to allocate treatment and resources when two or more patients strive for it, yet such guidelines may be highly controversial.

When decision makers both in policy settings and priorization bioethics committees have to make difficult choices regarding scarce resources allocation and pandemic response, potential strategies may include: reduction of demand for healthcare services through medical countermeasures (e.g., mass vaccination) or non-pharmaceutical interventions (e.g., social distancing); optimization of existing resources (e.g., central command structure); augmenting resources (e.g., adding temporary facilities or staff); and implementation of crisis standards of care (Hempel et al., 2020: 1).

In current pandemic, the need for medical resources, including staff, supplies, equipment, and space or infrastructure quickly outstripped the available resources. Decision makers need information and compelling strategies to inform crucial decisions about how to respond and make the most efficient use of scarce resources. It has been stated that potential strategies seek to boost the overall quantity of resources, stretch existing resources, and offer guidance about how to determine which patients should receive such resources. These strategies focused on the healthcare delivery system should be complemented by population-based strategies in order to reduce the spread of the disease and the demand for health care services (Hempel et al., 2020: 2).

The conflictive scenario of scarce resources allocation is crossed by at least four types of moral disagreement, which analogically can be extended to policy field. Such discrepancy engenders relativism in deliberation so it needs to be overcome procedurally to guarantee successful reasoning and decision-making processes. As resource allocation can be a source of disagreement at multiple levels, it shows how lacking common morality is to achieve plausible consensus regarding: 1. Disagreements on facts; 2. Disagreements due to lack of information or data; 3. Disagreements about rules and their applicability; and 4. Disagreements about key moral notions. As Beauchamp and Childress (2019: 1–30) argue, common morality

is *prima facie*, and such vague and general norms must be specified in order to limit their scope and add content to them. If competing specifications exist, moral balance models must be applied and it must be deliberately determined which norms should prevail over others.

However, identifying and determining courses of action within a process of moral deliberation is not uniquely related to common sense or *prima facie* principles of morality, since these are only formally shared. Rather, any deliberative process is related to the relative weight and binding force of norms. In addition, as an eventual balance might also be intuitive, partial or arbitrary, it is possible to build criteria to reduce intuition, partiality and arbitrariness in moral balance of substantive and procedural rules for resources allocation.

According to WHO Group (2020: 3–4) some key principles to be considered when making crucial decisions are: (i) Transparency: decisions and their justifications should be public. In other words, population should be informed about the criteria to guide decision-making; (ii) Inclusiveness: those affected by allocation decisions should be able to display some influence over the decision-making process as well as the decision itself; (iii) Consistency: decisions should be consistent to guarantee that people in the same categories are treated in the same way; (iv) Accountability: those making decisions about allocation must be accountable for those decisions by justifying their decisions and being responsible for them. In this sense, a fair allocation system generates solidarity and trust, key elements to ensure successful and sustained collective response needed for dealing effectively with any outbreak (WHO, 2020: 4).

Nevertheless, how to allocate scarce resources in pandemics is still a challenging issue. Several proposals are plenty of subjective criteria, based upon traditional ethical principles, such as dignity and integrity, among others. I will offer a Bayesian model for resource allocation, free from ideological basis, and as such, it is impartial. In this fashion, I seek to decontaminate reasoning and decision-making process from abstract principles and prevent the model from a paralyzing deliberative effect like natural law or natural ethics often do. My analysis, for reasons of space, is synoptic, but aims for precision. My approach is original in the least equivocal sense of the concept, so citation and references are not profuse.

A Bayesian Model for Resource Allocation

Bayes' theorem, in probability theory, is a proposition put forward by the English mathematician Thomas Bayes (1702–1761) and published posthumously (Bayes, 1763), which expresses the conditional probability of a random event A given B, in terms of the distribution of conditional probability of the event B given A, and the distribution of marginal probability of only A (Bernardo & Smith, 2000).

In more general and less mathematical terms, Bayes' theorem has enormous relevance as it links the probability of *A* given *B* with the probability of *B* given *A*. In other words, knowing the probability of having a headache given that you have SARS-CoV-2, you could know (if you have any more information) the probability of having SARS-CoV-2 if you have a headache. This simple example shows the high relevance of the theorem for science in all its branches, since it is closely linked to the understanding of the probability of causal aspects given the observed effects (Gelman et al., 2013).

Let {*A*1, *A*2,…, *Ai*,…, *An*} be a set of mutually exclusive and exhaustive events such that the probability of each of them is nonzero

$$\left(\mathrm{P}\left[A_i\right] \neq 0 \text{for} i = 1,2,\ldots,n\right)$$

If *B* is any event whose conditional probabilities are known $P(B \mid Ai)$ then the probability $P(Ai \mid B)$ comes given by the expression:

$$P\left(A_i|B\right) = \frac{P\left(B|A_i\right)P\left(A_i\right)}{P\left(B\right)}$$

Where:

$P(Ai)$ are a priori probabilities
$P(B \mid Ai)$ is probability of B in hypothesis Ai
$P(Ai \mid B)$ are a posteriori probabilities

Therefore, based on the definition of conditional probability, Bayes Formula, also known as Bayes Rule, is obtained:

$$P\left(A_i|B\right) = \frac{P\left(B|A_i\right)P\left(A_i\right)}{\sum_{k=1}^{n} P\left(B|A_k\right)P\left(A_k\right)} \tag{1}$$

This formula allows to calculate the conditional probability $P(Ai \mid B)$ of any of events *Ai* given *B*.

Bayes' theorem is valid in all applications of probability theory. However, there is a controversy about the type of probabilities that it uses. In essence, supporters of traditional statistics only allow probabilities based on repeatable experiments having an empirical confirmation, whereas the so-called Bayesian statistics allow subjective probabilities. The theorem can then serve to point out how we should modify our subjective probabilities when we receive additional information from an experiment. Bayesian statistics is proving its usefulness in certain estimations based on subjective a priori knowledge. The fact of allowing such estimations to be revised based upon empirical evidence is opening up new ways of making knowledge. One application of this is Bayesian classifiers, which are often used in spam filter

implementations, which adapt themselves with use. Another application is found in data fusion, by combining information expressed in terms of probability's density coming from different sensors (McGrayne, 2011).

Thus, Bayesian inference is a type of statistical inference in which evidence or observations are used to update or infer the probability that a hypothesis might be true. Nowadays, one of the fields of application is in decision theory (Berger, 1985), artificial vision (Kopparapu & Desai, 2001), simulation of perception in general (Knill & Richards, 1996), and pattern recognition by computer (Duda et al., 2001).

Uncertainty and imprecision are inherent to reasoning process (MacAskill et al., 2020). Logic establishes rules of inference the deductive reasoning system is built from, where a given proposition is considered true or false, that is, a system of only two possible states, without admitting degrees between those two ends (Jaynes, 1998). Approximate reasoning methods, including Bayesian methods, provide theoretical models that simulate reasoning ability under (i) uncertainty conditions, when the truth or falsity of a statement or hypothesis is not compellingly known, and (ii) imprecision, when a range of variation is allowed in statements.

Bayesian methods are among approximate reasoning methods. All of them share the assignment of a probability as a measure of hypotheses credibility (Bolstad, 2004). In this context, inference is understood as a process of updating credibility measures when new evidence becomes known. Bayes' Theorem is aimed at obtaining the probabilities of conditional hypotheses upon known evidence. Divergences between different Bayesian methods (causal models and Bayesian networks) lie on the conditional independence hypotheses between hypotheses and evidence. Such relationships are commonly expressed by a directed acyclic graph (Jaynes, 1998).

Bayesian inference uses aspects of the scientific method, which involves collecting evidence that is considered to be consistent or inconsistent with a given hypothesis. As evidence accumulates, the degree of belief in a hypothesis changes, which with enough evidence, it may often be very high or very low. Thus, supporters of Bayesian inference state that it can be used to discriminate between conflicting hypotheses: hypotheses with a very high degree of belief should be accepted as true, and those with a very low degree of belief should be rejected as false. However, critics say this method of inference may be affected by bias due to initial beliefs that must be held before beginning to collect any evidence (Robert, 2001).

Bayesian inference works with a numerical estimator of the degree of belief in a hypothesis even before the evidence is observed, and computes a numerical estimator of the degree of belief in the hypothesis after the evidence has been observed. Bayesian inference generally relies on degrees of belief, or subjective probabilities, in the induction process and does not necessarily claim to provide an objective method of induction.

As pandemic goes by, important evidence on scarce resource allocation has been collected, and beyond subjective probabilities that need to be considered as part of an inductive process, a Bayesian model can be applied to calculate which rules or which criteria for allocating scarce resources in pandemics are more likely to be

successful. Some authors have already proposed algorithms by including principles taken as essential guidelines for resource allocation (Savulescu et al., 2020: 253–258). Among them, we see autonomy, urgency, and resource availability, as well as other more specific rules, such as saving the most lives possible, and selection of patients to save. However, while is not clear that urgency and resource availability are principles or common morality norms (they seem to be more like criteria without imperative content), the authors end up asserting that: "As events such as the COVID-19 pandemic befall us, our values and choices play a significant role in determining who lives and who dies." (Savulescu et al., 2020: 258). I agree with that statement only in the case of substantial and competent self-determination of the patient. In any other case, I sustain that a decision-making process must be arithmetical instead of axiological.

Moreover, using autonomy as a principle in decision-making can tyrannize the process, since understanding it as a common moral norm would make impossible agree on its epistemological density, and would open a hermeneutical abyss that would prevent agreement from being made about autonomy's content and scope. In other words, everyone would understand it from personal and subjective values, which is precisely what my proposal intends to avoid.

Therefore, I will propose some allocation rules and justify them in light of Bayes' Theorem. I argue that this mathematical model of probabilities is ethically defensible in the context of scarce resource allocation in pandemic scenarios.

First Rule: Substantial Competence

When a competent patient presents a critical diagnosis, he or she should be fully and objectively informed about the available treatments and their likely effectiveness. In the case of unpromising prognoses, a space is opened for the patient to express their wishes, priorities and personal values in a scenario that can be definitive. Many patients, faced with the obvious and proven futility of a ventilator, for example, can have the possibility of rejecting, informedly, voluntarily and consciously, a futile treatment, by displaying a competent refusal. Such rejection may not necessarily be contemporaneous (Savulescu et al., 2020: 254), but rather, through a valid advance directive, or through a surrogated decision. It is essential, to optimize the allocation of scarce resources, to grant decision-making room enough to the patient, who can judge the status of the resulting quality of life after an intensive treatment close to futility. The procedural effect of this first rule is that it optimizes not only scarce resources allocation, but also the time and opportunity they are available for others.

Therefore, specifying the principle of respect for autonomy into the rule of substantial competence reinforces the methodological power of the principle and optimizes its decisional effects in specific scenarios.

Second Rule: Priority to the Most Urgent Cases

This rule orders non-urgent treatment to be delayed, which clearly reduces demand in critical hospital situations. To do this, health centers must design a clinical protocol for the evaluation of mild, severe and urgent cases, giving priority to the latter. Applying this rule not only refines the demand for treatment in the waiting room, but also mathematically improves the need-attention relationship.

Indeed, if it is quickly determined who presents the most serious symptoms, the relevance of clinical efforts is optimized as it is possible to detect which patients should be treated before and which after, without increasing the mortality rate. There is no fatal effect in the delay that impacts less severe patients, which would occur if urgent care was delayed, because none protocol was deployed to identify the most critical cases.

Therefore, the probability measure used to calculate the expected utility of delaying the treatment of less urgent cases is considered a representation of the degree of rationality of those who make the decisions conditioned to the total information available. Using an extended notation $P\,(Eij \mid ai, G, M0)$, instead of a more compressed $P\,(Ej \mid G$, I emphasize that: (i) the real variables (and events) considered can depend on a particular action already foreseen, (ii) the available information already includes the initial information together with $G > \emptyset$, and (iii) the degrees of prediction of the occurrence of an event such as *Eij* are understood as conditional of the action *ai*, so that the possible influence of the decision maker on the real world is taken into account as a relevant calculation factor.

Thus, for any action *ai* it is preferable, to ensure the clarity of the mathematical proof, to describe the relevant events Eij, $j \in J$, sequentially. For example, to consider whether the mortality rate will decrease and the use of scarce resources will be optimized, one must first consider whether the most seriously ill patient will survive and then, conditioned on that survival, whether the survival rate and resources allocation will be optimized or not.

In this way, if each stage or event *m* is considered; also, if *Gm* is the most relevant information available, and *u* (.) is the expected utility function, the proof can be written as follows:

$$\overset{(m)}{a_i} = G_m \overset{(m)}{a_j} \Big| u\left\{\overset{(m)}{a_i}\Big| G_m\right\} = u\left\{\overset{(m)}{a_j}\Big| G_m\right\},$$

Donde:

$$u\left\{\overset{(n)}{a_i}\Big| G_n\right\} = \sum_{j\in J_i}^{(n)} u\left(c_{ij}\right) P\left(E_{ij}\Big| G_n\right).$$

However, this is only one of the elements that must be considered in the equation to determine which patients to see first. There are cases where not only severity, but also resource availability plays a critical role in decision making. Therefore, another rule is needed.

Third Rule: Effectiveness

When the availability of resources is overcome by demand, this rule requires determining whether ventilator treatment is an equally effective resource for all clinically relevant patients, that is, whether a ventilator will cause the same results for the entire universe of patients who urgently need it.

If this scenario is consolidated, Savulescu et al. (2020, 254) recommend using a rule of equal treatment for the same need, namely, applying the queuing rule, that is, first come, first served. Theoretically, the criterion would be objective and, therefore, ethically defensible, as there would be no other elements of axiological judgment to determine ventilators allocation.

However, such proposal encompasses an important fissure. As the equation "same resource-same need," has too much hypothetical content, the criterion of "first come, first served," becomes fickle and arbitrary. Strictly speaking, it means that patients with a poor prognosis, requiring long periods of treatment, receive care at the expense of patients who arrive later, but with a much better prognosis. This inevitably leads to a reduction in the number of lives saved.

Simple risks chain models of biorisk can analogically be applied to calculate the effectiveness of the presented criterion. As these models' results have implications for biosecurity risk assessment and health security, they work in other risky settings such as pandemic ones. Applied on resource allocation in pandemics, the criterion can be stated mathematically as follows (Model taken from Sandberg & Nelson, 2020: 156–159):

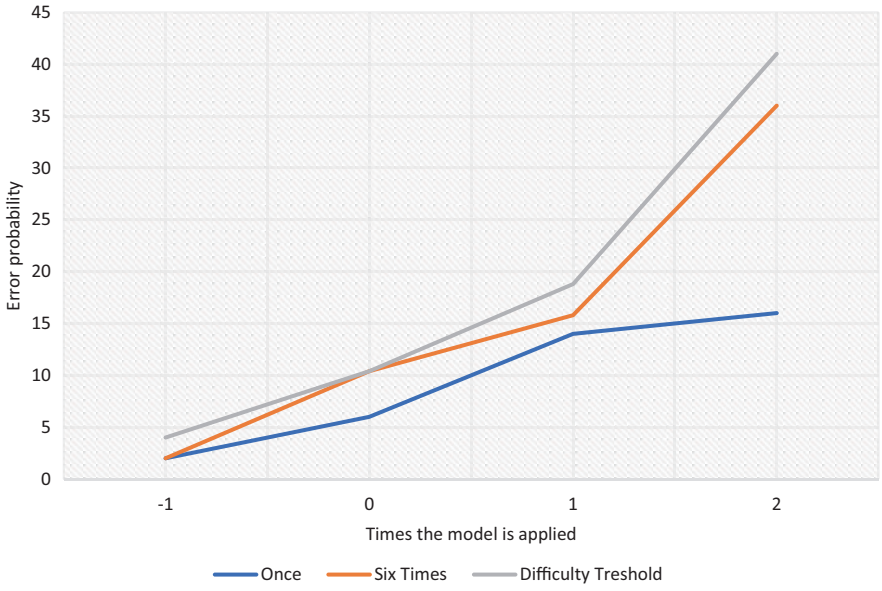
$$p(x) = 0.5 + 0.5 \tanh\left(g\left(x - x_0\right)\right)$$

Where *X0* represents the probability of error of the model and *g* indicates the purity of the deductive transition. Clearly, a higher value is seen, indicating that the probability of error (wrong allocation) rapidly rises from near 0 to near 1.

This function provides a robust basis for concluding the need to complement the model, since it can be reasonably assumed that a wrong allocation threshold, without this complement, boosts with a marginal success rate. Therefore, for this expression, it is evident that, as the number of times the model *N* is applied, the chances of failure grow logarithmically (Sandberg & Nelson, 2020: 157):

$$x = x_0 + (1/g)\tanh^{-1}\left(2^{1-1/N} - 1\right)$$

The above can be graphed as follows, where it is observed that, the more the defective model is applied, the more times it engenders an error when resources are allocated:

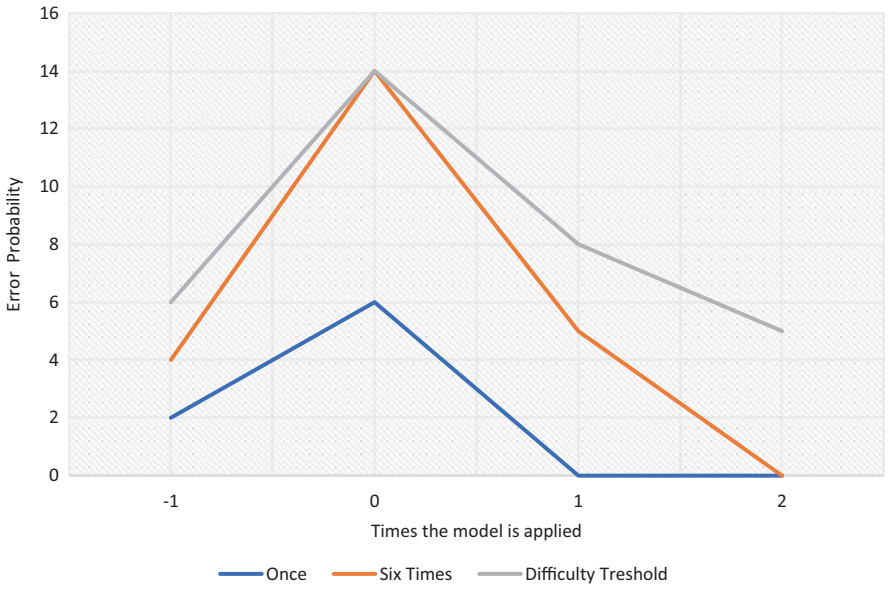


Now, if the effectiveness rule is complemented with another that perfects it, the function can be expressed as follows (Sandberg & Nelson, 2020: 157):

$$P(X = x|success) = \frac{P(success|X = x)P(X = x)}{P(success)}.$$
$$= Kp(x)^N f(x)$$

Where K is a normalization factor (a complementation rule). In this way, it is observed that the general effect is that the error probabilities dwindle.

When graphing it:



Therefore, treating that who gets sick sooner or later cannot become an overriding criterion allocate resources when these are equally effective for all those in need. Therefore, the effectiveness rule must be complemented with another one that I will call maximization.

Fourth Rule: Maximization

Savulescu et al. (2020: 254) assert that if, in the context of scarce resource allocation in pandemic, we choose behind a "veil of ignorance" (Rawls, 1999), a rational self-interest would lead us to choose a course of action that gives us the greatest chance of survival. In this way, reflective equilibrium, as a notion of epistemic justification, would make us decide to save more lives instead of fewer, all other things being equal.

In fact, a set of principles and intuitions are in reflective equilibrium when principles and intuitions coincide and the individual knows how judgments that intuitions encode can be derived from such principles. As reflective equilibrium is not a permanent state of stability, a set of principles and intuitions can be derived from equilibrium by reconsidering new information, new principles, and/or insights about new cases. Therefore, a rational agreement on a principle (or a rule), fruitful in promoting criteria to save lives in emergencies, would imply the aim to save as many lives as possible. In practice, saving the greatest number of lives logically entails saving those patients with better surviving's odds.

Savulescu et al. (2020: 254) propose to imagine that one group, A, has a 90% chance of surviving with treatment, and another group, B, has a 10% chance of surviving. For every 10 people treated in group A, 9 will survive, but only one will survive from group B. Therefore, the maximization of saved lives should be a universal decision-making requirement in pandemic or analogous scenarios.

However, saving the greatest number of lives also requires estimating the duration of treatment of patients and the use of resources, since a longer duration of therapy means that fewer patients can be treated. Let's imagine that patients in group A take 1 week to recover and patients in group B take 2 weeks. We can save two patients in group A for every patient in group B. Therefore, patients in group A, being those with the highest probability of survival, should have priority. Following this criterion, the survival rate boosts in 100%.

So, the maximization rule translates into the following operation (Savulescu et al., 2020: 254).

$$\frac{\text{Probability of Survival}}{\text{Expected Resource Demand}\left(\begin{array}{l}\text{Estimated Duration of Treatment /}\\ \text{Average Duration of Treatment}\end{array}\right)}$$

Therefore, any factor that reduces the probability of survival and, at the same time, optimizes the use of resources is relevant at this stage. I think that this model also provides a plausible ethical justification for considering not providing intensive care to patients with high morbidity scores and poor chances of survival.

$$u\left\{{}^{(n)}a_i \middle| G_n\right\} = \sum_{j\in J_i}^{(n)} u\left(c_{ij}\right) P\left(E_{ij} \middle| G_n\right).$$

Proving the above is not very complex. If we go back to:

It means that the final stage (*n*th) must be solved first, maximizing the expected utility; then, the (*n*-1)th stage must be solved, maximizing the conditional expected utility, looking for the optimal choice in the *n*th stage. Thus, continue progressively backwards, until the first optimal stage of choice has been obtained, through a procedure known as dynamic programming (Bernardo & Smith, 2000).

This inverse induction process satisfies the requirement that, at any stage of the procedure, its continuation at *m*th must be identical to the optimal procedure started at *m*th with the available information *Gm*. Therefore, it is not necessary to consider the maximization of the expected utility as a "principle" of the formulation, since it is simply a consequence of another tacit principle, which I will call quantitative coherence.

Therefore, the expected utility of an optimal application of the model establishes that:

$$u_0(x,r) = \max\left\{u_s(x,r), 1/r + 1\sum_{y=1}^{r+1} u_0(y,r+1)\right\},$$

Where:

$$us(x,r) = \sum_{z=x}^{n-r+x} u(z)\frac{(z-1)(n-z)}{(x-1)(r-x)}{(n,r)}$$

Values for $u0\ (x,\ r)$ can be found to establish a final condition in the application of inverse induction. The optimal procedure is:

(i) Continue if $u0\ (x,\ r) > us\ (x,\ r)$,
(ii) Stop if $u0\ (x,\ r) = us\ (x,\ r)$

Therefore:

(i) Continue if at least r^* options have been analyzed;
(ii) Stop if the r^*th option is the best so far;
(iii) Otherwise, continue until the tested option is the best so far, then stop (stop in any case where the nth option has been reached).

Is it discriminatory to apply the maximization rule? No. It would be discriminatory to include assignment criteria such as age, race, sexuality, religion or political beliefs. However, it is not discriminatory to use a patient's clinical data to estimate prognosis, unless a feature is used to systematically disadvantage a certain group (Savulescu et al., 2020: 257). Therefore, using the probability of survival vs. the expected demand for resources for maximization calculus is ethically defensible.

Fifth Rule: Selection

The maximization rule is very efficient at the first assignment level where the goal is to save the greatest number of lives. It is clear that, in these cases, patients with a high survival rate should receive the resource first. However, there may be more patients with high survival rate than ventilators available. In this case, a different assignment procedure is needed for this group. The selection rule must conform, then, to an ethically defensible criterion.

There are a number of possible policy options (Savulescu et al., 2020: 257):

Option 1: Lottery
The "first come, first served" approach can work in less complex scenarios. However, I have already shown that, in more complex cases, it becomes arbitrary. Furthermore, since high-priority patients have already been selected for treatment in detriment of

low-priority patients, such a lottery would have a marginal impact on overall survival.

Option 2: Desert
This criterion is based on an idea of poetic justice. It would be plausible, then, to grant resources to those who most deserve them. However, what sub criterion would determine who deserves more and who deserves less? Does that who needs more deserve more? Does that who contributes the most to society deserve more? Does that who has lived less deserve the resource as he has a greater life desert than others who have lived more? Clearly, taking this criterion as the main one, may lead to arbitrary decisions, such as giving priority to younger over older ones without considering other important elements for allocation.

Option 3: Utility
This criterion involves the expected duration of post-treatment life and the expected quality of life. If applied correctly, a rule of utility can maximize the quality of remaining years of life and, in turn, optimize resources allocation and decision-making process.

Final Remarks

A decision-making process is more likely to be effective if it uses objective criteria, and it is not diverted by personal values, intuition, moral conscience, religion, tradition or idiosyncrasy.

Second, efficiency does not only refer to resource optimization, which is central in this scenario, but also, it points to the ability to make decisions, in the most effective and least burdensome way possible, regarding how allocate scarce resources when highly demanded.

Third, this proposal implies an explicit defense of a non-naturalistic form of ethical realism. He is committed to what I would call an ethical cognitivism. In other words, ethical language is solidly apt for truth, as long as moral categories are not reducible into any natural property.

Finally, in these life and death scenarios we should avoid searching for moral differences where there are only factual ones (Valdés & Rendtorff, 2022).

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Part IV
Bioethical Issues in Institutional Ethics: *Social Responsibility and Institutional Liability*

Chapter 24
Scientific Knowledge and Social Responsibility

Amedeo Santosuosso and Marta Tomasi

Abstract This Chapter aims to present a very preliminary exploration of the role and functioning of some 'leading ideas' that represent the most consistent attempts to balance freedom of scientific research with the need to protect participants and the community as a whole. To this end, we searched two databases, a scientific and a legal one, for some keywords (Freedom of research, Precautionary principle, Risk-based approach, Responsible research and innovation), to check the consistency of their presence and evolution over time. Without aiming to in-depth investigate the precise connotations of each term and the context in which they are used from time to time, the core idea is to provide a very first quantitative exploration, which lays the foundations for further future investigation.

Keywords Freedom of research · Research regulation · Law and innovation · Precautionary principle · Risk based-approach

Science and Technology Between Promises and Risks

The dilemma about how to deal with science and technology in our societies and how to enjoy the benefits of their achievements while avoiding undesirable consequences is at the core of international political agenda and one of the main concerns in society and in academic enquiry.

On the one hand, the International Covenant on Economic, Social and Cultural Rights (1966) gives everyone the right to "enjoy the benefits of scientific progress and its applications" and still commits States parties to "respect the freedom

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essential to scientific research and creative activity".[1] On the other hand, in recent decades there has been growing concern about some (assumed) excesses of science, so fast and invasive of the natural order (emblematic the case of DNA manipulation), and its practical applications, which cause environmental damage sometimes irreversible (for example, climate change). In addition, there has been a growing criticism to the anthropocentric attitude traditionally underlying scientific culture, and the claim to take the point of view of nature, the earth, and the environment in its broadest sense (and not only of humans) has been strengthened.

In a relatively short period of time, we have moved from a strong recognition and reaffirmation of the importance of science and its freedom (after World War II) to an attitude of caution (which is reasonable) till to suspicion or even rejection of the scientific approach to reality. According to some tendencies, the distinction between science (as an investigation of the natural and social world) and innovation (as the practical social application of scientific knowledge) has been denied and, consequently, so has the need to preserve the Freedom of scientific research as a value. This change came about through the affirmation of certain ideas and concepts that sometimes became formulas and even slogans in the public debate and political arena.

The reasons for this change of attitude represent a huge cultural and scientific issue that would require extensive and deep research. We have no such ambition. In this paper, more modestly, we present a very preliminary exploration of the most important "ideas," "concepts," formulas, and some of their dynamics across the decades. In other words, we aim to chart the field for future research on how the role of science and technology has been discussed in our society, possibly contributing to the advancement of a fruitful debate. We do not explore these guiding ideas in depth, in their meaning and according to the doctrinal comments and elaborations. This will be a necessary second step. Our first step is purely quantitative and aims to show the distribution over time of publications centered on these ideas in the scientific and non-scientific (i.e. legal) literature.

Four Steps and Four Leading Ideas

We have considered four leading ideas and explored their evolutions in different time periods (see par. 3): **firstly**, the proclamation of the Freedom of scientific research in many of the European countries constitutions starting from the post-World War II; **secondly**, the Precautionary approach as a guidance for all the member states, listed under Principle 15 of the Rio Declaration on Environment and Development, proclaimed at the end of the United Nations Conference on Environment and Development (Rio de Janeiro, 1992); **thirdly**, Responsible

[1] United Nations, International Covenant on Economic, Social and Cultural Rights (1966; into force 3 January 1976), Article 15.

research and innovation, an approach that was tested and promoted during the last years of EU Framework Research Programme 2007–2013 (FP7); **fourthly**, the Sustainable Development Goals (SDGs, 2012), a proposed set of universal goals that meet the urgent environmental, political and economic challenges facing our world.[2]

In the following, we present very brief descriptions of these main ideas, with no claim to completeness. We have emphasized the main differences between them for the purpose of clarity, although in some cases the boundaries may be blurred. We reserve any further specification as the research develops.

Why to Start with the Post-World War II: Science as a Value Per Se

We start with the Freedom of scientific research in the post-World War II because it is the first time in modern history that science acquires an explicit consideration in national Constitutions.

The Bill of rights of Canada and the US have no specific provisions explicitly protecting Freedom of scientific research, and such freedom is considered as protected under the umbrella of the wider freedom of thought and expression (see, e.g., the First Amendment of the US Constitution).

Differently, several post WWII European constitutions and Bill of rights expressly recognize freedom of research and teaching arts and science.[3] For instance, article 5 of the German Constitution states that "Art and science, research and teaching are free", article 33 of the Italian Constitution establishes that "The arts and sciences as well as their teaching are free" and article 59 of the Slovenian Constitution states that "Freedom of scientific research and artistic endeavor shall be guaranteed".

Within this group, some constitutions do not limit their protection to the provision of Freedom of scientific research and engage governments in promoting and supporting it. This is the case, for example, of the Italian Constitution, which states that "The Republic promotes cultural development and scientific and technical research" (article 9), the Spanish Constitution, according to which "public authorities shall promote science and scientific and technical research for the benefit of general interest" (article 44) and, also, the Greek Constitution, whose article 16 establishes that art, science, research and their teaching are free, and their promotion is mandatory for the State.

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[2] United Nations Conference on Sustainable Development in Rio de Janeiro in 2012, replacing the Millennium Development Goals (MDGs), which started a global effort in 2000 to tackle the indignity of poverty: https://www.africa.undp.org/content/rba/en/home/sustainable-development-goals/background/

[3] However, freedom of science is a considerably older legal construct, which had one of its first expressions in the Constitution of the German Empire (28 March 1849), whose Article VI, paragraph 152 proclaimed: "Science and teaching are free" (*Die Wissenschaft und Lehre ist frei*).

Thinking about the difference between European and North American countries, the case of Italy is of particular interest. Between 1946 and 1947 the *Assemblea Costituente* discussed the opportunity to introduce an explicit provision to protect Freedom of scientific research. Some were critical about the possibility of dedicating a part of the constitutional text to liberties of culture and thought, considered different from the traditional constitutional rights. Others doubted the need of consecrating too gravely such an activity that is free in itself, and whose value might be diminished because of an explicit formal recognition in the bill of rights. At last, the importance of letting the social community be free from the fascist cultural subjection prevailed, and article 33 of the Italian Constitution was introduced, protecting freedom of art and science and their teaching as a means of assuring human cultural and spiritual growth.

In this light, we might say that in a historical perspective, constitutional provisions explicitly protecting Freedom of research in several European countries in the post-World War II look like a typical example of "rights emerging from wrongs" of Nazism, a reaction to the "error" of experimental practice carried out by Nazi doctors in concentration camps (Dershowitz, 2004). This is also particularly evident from the analysis of the limitations set by constitutional law to scientific research and the recognition of states' obligation to protect against the adverse effects of science. Except for some specific provisions,[4] these typically take the form of prohibitions against being subjected to medical or scientific experimentation (i.e., no one may be subjected to scientific or medical experimentation without knowledge/consent). In the following decades the citation of science in the constitutions became more and more frequent: currently scientific research and some its equivalent[5] can be found in more than 130 Constitutions around the world. However, there are also cases in which constitutional references to science turn into the opposite of Freedom of research: emblematic is the South Sudan Constitution (2011), which protects the freedom of scientific research but only within the ethical parameters of research and regulated by law, i.e., something completely different from the freedom of speech (art. 38).

Finally, on this point, it is worth noting that the centrality of the value of Freedom of research has recently been reaffirmed in Europe with the "Bonn declaration". On 20 October 2020, Ministers from the European Research Area have adopted a declaration asserting the "relevance of the freedom of scientific research for the progress of our societies" and defining it as a "universal right and public good", a core

[4] See, for instance, Article 66 of the Constitution of the Republic of Ecuador which prohibits "the use of genetic material and scientific experimentation that undermines human rights" and Article 25.3 of the Constitution of the Republic of Armenia which outlaws "eugenic experiments making human organs and tissues a source of financial gain" and "reproductive cloning".

[5] Such as right to academic freedom, right to enjoy the benefits of science. Source https://www.constituteproject.org/?lang=en

principle of the European Union, anchored in the Charter of the Fundamental Rights of the EU, and, therefore, "a pillar of any democracy."[6]

Rio Declaration and Precaution: Science and Uncertainty

The 1992 Rio Declaration on Environment and Development, states that: "In order to protect the environment, the precautionary *approach* [emphasis added] shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation".

From the outset, the statement is affected by linguistic uncertainty. The whole document is divided into "principles", of which the 15th introduces the concept of precaution, but if one reads the text the word used is not "principle" of precaution but "approach" (Precautionary approach).

The oscillation between "principle" and "approach" has fueled two main positions: the one that, by force of the "principle", has supported stricter policies of "do not do" if there is no scientific certainty of non-damage to the environment and the one that has maintained that a precautionary "approach" is no other than an invitation to a prudent attitude. In short, principles are hardly negotiable entities and can therefore have a paralyzing effect, while prudence does not exclude the possibility of doing things while verifying their harm *in fieri*.

Interestingly, the European Union has introduced precaution as a principle in the Treaty on the Functioning of The European Union, which has a substantial constitutional value: "Union policy on the environment [...] shall be based on the precautionary principle and on the principles that preventive action should be taken [...]".[7]

As a matter of fact, even in the EU the principle has proven to be not very manageable and in more recent times there seems to be an attitude that softens the rigidity of the principle, affirming that even "doing nothing" can be risky and that the Precautionary principle can change over time, in short, a sort of weak principle, or at a lower level, something that ends up being similar to an approach (Science for Environment Policy, 2017). At the same time, in the same EU a Risk-based approach (rather than a Precautionary approach) has gained the forefront in some critical areas, such as the applications of Artificial intelligence.[8]

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[6] Available at https://bmbf.bmbfcluster.de/files/_DRP-EFR-Bonner_Erkl%C3%A4rung_EN_with%20signatures_M%C3%A4rz_2021.pdf

[7] Article 191 (2) of the Treaty on the Functioning of the EU, 26.10.2012 Official Journal of the European Union C 326/47: CONSOLIDATED VERSION OF THE TREATY ON THE FUNCTIONING OF THE EUROPEAN UNION.

[8] Proposal for a *Regulation Of The European Parliament And Of The Council Laying Down Harmonised Rules On Artificial Intelligence (Artificial Intelligence Act) And Amending Certain Union Legislative Acts* {SEC(2021) 167 final} - {SWD(2021) 84 final} - {SWD(2021) 85 final},

Responsible Research and Innovation (RRI): Science Lost?

Responsible research and innovation is a relatively recent creation by the EU Commission. It "means that societal actors work together during the whole research and innovation process in order to better align both the process and its outcomes, with the values, needs and expectations of European society" (Directorate-General for Research and Innovation, 2014). Rooted in previous discussions about the ethical, legal and social implications (ELSI) of scientific activity, the idea aims to bridge the gap between the scientific community and society at large[9] and comes after previous programs and ideas that aim to establish a better connection with society. The evolution is described as follows: "In 2001, the 'Science and society' action plan was launched to set out a common strategy to make a better connection between science and European citizens. In 2007, under the seventh framework programme for research and technological development (FP7), 'Science and Society' became 'Science in society (SiS)' with the main objective to foster public engagement and a sustained two-way dialogue between science and civil society. This effort is pursued under part V 'Science with and for Society' of Horizon 2020" (Directorate-General for Research and Innovation, 2014).

Finally, it is since 2010 that the formula responsible research and innovation (RRI) takes shape.

The responsible research and innovation framework consists of six dimensions: multi-actor and Public Engagement (PE); Gender Equality; Science Education; Open Science; Ethics, as a way of ensuring high quality results; and, sixth dimension, the development of harmonious governance models that "integrate public engagement, gender equality, science education, open access/science and ethics".

Just two very brief remarks on RRI.

It is worth noting how the idea of public Engagement (PE) as "co-creating the future by bringing together [...] researchers and innovators, industry and SME, policymakers, non-governmental organizations (NGOs), civil society organizations and citizens" (Directorate-General for Research and Innovation, 2014) seems to relegate researchers (while the position of innovators might be different) to the position of co-authors without any greater consideration of their specific activity. In other words, if the dialogue between scientists and society and public engagement are rightly considered a value, the formal equalization of scientists (i.e., research specialists), innovators and citizens (who quite legitimately may have different backgrounds and specializations in their lives) seems something that, if not properly clarified, can create dangerous misunderstandings. At the origin is the idea that there is no substantial difference between scientific research (as an activity that

Brussels, 21.4.2021. Significantly the proposed regulation does not use the word "precaution" in any part of its 85 Articles.

[9] Previous programs and ideas aiming at establishing a better connection between science and European citizens (2001) and at fostering public engagement and a sustained two-way dialogue between science and civil society (2007).

expands knowledge about the world) and innovation (as the social application of acquired scientific knowledge).

The second remark is about what scientific fields are at the origin of such an attitude in the EU. The most relevant and problematic areas refer to human genetics, GMOs, synthetic biology, geoengineering and ICT: "These have catalysed an increasing willingness at a policy level to discuss, challenge and rethink linear models of science policy and the social contract for science (in which scientific freedom is exchanged for the promise or expectation of socially – beneficial impacts) and risk-based regulation as a predominant innovation governance paradigm" (Owen, Macnaghten, & Stilgoe, 2012).

UN Sustainable Development Goals (Sdgs): Science Regained?

Risk can be basically defined as follows: "...the product of the probability of an undesirable event and the effect of that event". The risks of technology are one of the traditional ethical concerns in the ethics of technology. Risks raise not only ethical issues but other philosophical issues, such as epistemological and decision-theoretical issues as well (Franssen et al., 2018). Risk is divided into three main areas: risk assessment, risk evaluation, and risk management, each of which having its own problematic aspects. In the time period considered in this paper (starting after World War II), the Risk-based approach was first adopted in the field of nuclear energy applications. It represents the "predominant paradigm of innovation governance" (see above) and is exactly what Responsible Research and Innovation (RRI) policy aims to overcome, at least in the EU.

Recent developments in the global arena (and even in the EU) has shown a change in the attitude towards science and its applications (innovation).

The most important document is the Resolution adopted by the UN General Assembly on 6 July 2017, defining the UN Sustainable Development Goals (SDGs). In this resolution there is no quotation of Precautionary principle/approach neither of Responsible research and innovation and the widely used concept is that of *risk*, in different combinations.

In some cases, it appears as risk-based regulation or "to promote resilience and disaster risk reduction". In other parts it is used in a more generic sense, saying that "sustainable development cannot be realized without peace and security; and peace and security will be at risk without sustainable development". In Goal 3, it is "risk protection" and the capacity of all countries, in particular developing countries, for early warning, risk reduction and management of national and global health risks. In Goal 11 it is quoted for holistic disaster risk management at all levels.

Science and technological innovation are considered as indispensable tools in order to realize sustainable goals in some specific areas, such as the need for effectively regulate harvesting and end overfishing, illegal, unreported and unregulated fishing and destructive fishing practices and implement science-based management plans (Goal 14.4) or to "enhance North-South, South-South and triangular regional

and international cooperation on and access to science, technology and innovation or to enhance the use of enabling technology, in particular information and communications technology (Goal 17).

Science and technology are involved in the promotion of a "United Nations interagency task team on science, technology and innovation for the Sustainable Development Goals, a collaborative multi-stakeholder forum on science, technology and innovation for the Sustainable Development Goals and an online platform" (Goal 70).

In Summer 2021 Working Group I delivered its contribution to the *Sixth Assessment Report of the Intergovernmental Panel on Climate Change*. The document explicitly uses the concept of Risk-based approach: "Physical climate storylines are complementary to probabilistic or unconditional **risk-**based approaches, and are particularly suitable to explore low-likelihood changes or events, which are often associated with the highest impacts. They also facilitate providing local context to large-scale trends and changes, by conditioning the projections on locally relevant circumstances". They define the approach in the following terms: "A commonly-used approach, often called the risk-based approach in the literature and referred to here as the 'probability-based approach', produces statements such as 'anthropogenic climate change made this event type twice as likely' or 'anthropogenic climate change made this event 15% more intense'" (IPCC, 2021).

Moving into a different field we find a similar approach. The EU Artificial Intelligence Act (Proposal, 2021)[10] is strongly based on "proportionate risk-based approach" (p.3) which is used as a fundamental key for addressing "various sources of risks through a clearly defined risk-based approach" which is the key guidance for the regulatory strategies to be implemented. Responsible innovation is mentioned only twice (pp. 11 and 34), while the Precautionary principle/approach is never mentioned.

How the Exploration Has Been Carried Out

The exploration has been conducted searching two databases. The first, *Pubmed*, is a freely accessible online biomedical database, developed by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine (NLM) in the US. The second, *Nexis Uni*, is an academic search engine, which aggregates legal and economic information, and global news. In this case, the search was limited to the Law Reviews and Journals section of the search engine, so as to restrict the results to scientific publications of a legal nature.

Both databases have been searched in July 2021 using the leading ideas mentioned in Par. 2. More specifically, the chosen keywords have been: "research

[10] Proposal for a regulation of the european parliament and of the council laying down harmonised rules on artificial intelligence (artificial intelligence act) and amending certain union legislative acts com/2021/206 final.

freedom", "freedom of research", and "freedom of scientific research"; "precautionary principle" and "precautionary approach"; "responsible research and innovation", "responsible research" and "responsible innovation"; "risk-based approach".

The data were then organised according to a timeline based on four frames:

Period 1 (1946–1991): starting with the end of the World War II;
Period 2 (1992–2009): starting with the Rio Declaration on Environment and Development;
Period 3 (2010–2019): starting with the introduction of the concept of Responsible research and innovation in the Science and Society Action Plan of the EC Directorate general for Research and Innovation and embracing the; embracing the period of conceptualisation of the Risk-based approach;
Period 4 (2020–2021): starting from the outbreak of the Covid-19 pandemic.

These are indicative time frames, which are made up of different numbers of years (46 years for Period 1, 18 years for Period 2, 10 years for Period 3; 2 years for Period 4) and identified on the basis of when the topic under investigation arose. The data that emerge are therefore not perfectly comparable. However, it seems to us that they are sufficient to bring out some useful trend lines for an initial exploration. In some cases, in the following paragraph, the data are presented by referring to the average number of references to a certain keyword in a year, calculated by dividing the total number of references in a certain Period by the number of years of which it is composed.

To provide a more comprehensive legal framework and in particular an insight into the European approach, *Eurlex* and *InfoCuria Case Law* were also consulted. *Eurlex* is the online portal of the EU law, providing official and comprehensive access to EU legal documents (mainly including treaty law, legal acts of the institutions, and EU case law); *InfoCuria Case Law*, the official case-law database of the European Court of Justice (as well as the General Court and the European Union Civil Service Tribunal). In this case, the results are not broken down by time periods, but serve to give a rough overview of the 'European' use of the keywords under focus.

The survey is not intended to be statistically significant, but only to describe, in broad terms, the most evident trends that have emerged over the years in the scientific and legal fields, and to compare them. The analysis only concerns the recurrence of terms, without examining the specific contexts in which they are used or the connotation they have assumed in practice from time to time. Furthermore, it is important to bear in mind that the two main databases investigated, although very extensive, do not cover the whole existing scientific and legal literature at a global level, with the consequence that the data presented concern limited territorial realities and, for example, do not take into account any publications in languages other than English.[11]

[11] This might be relevant in particular with regard to the literature about freedom of scientific research which is an issue typical of EU countries.

The figures below compare data from the scientific and legal literature. They show how, in the two reference contexts (the scientific and the legal one), the incidence of each term (which contributes to defining the balance between freedom and progress in research and safeguards built to protect participants and the community as a whole) has evolved over time.

Discussion of the Results of the First Exploration

The data collected in the legal database show that the concept of Freedom of research is not very recurrent (Figure 24.1), while the notions of Precautionary principle/approach and Risk-based approach are very widespread, with a tendency for the former to remain constant and a significant increase in the latter in more recent years (Figures 24.1 and 24.2). The references to the Risk-based approach, in particular, have gone from an average of 30 per year in Period 2 to an average of 331 per year in Period 3. The principle of Responsible research and innovation has become established starting from Period 2, moderately increasing its presence, without approaching the consistency of the other two notions (Figure 24.1). It however surpasses the presence of the references to Freedom of research, especially in the last two years (Figure 24.3).

The data collected in the biomedical database show first a very consolidated presence of the references to the concept of Freedom of research, which are clearly predominant compared to any other element considered in this analysis and in constant and progressive increase, in particular starting from Period 3 (Figure 24.4). The notions of Precautionary principle/approach, Risk-based approach and Responsible research and innovation emerge from the 1990s onwards and gradually increase their presence (Figure 24.5). While in Periods 3 and 4 the presence of the terms relating to risked-based approach and Precautionary principle/approach have

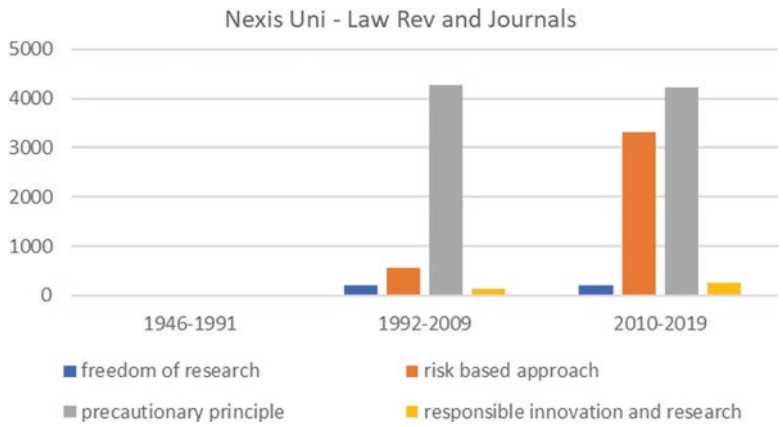

Fig. 24.1 *Nexis Uni* – Comparison of 4 items

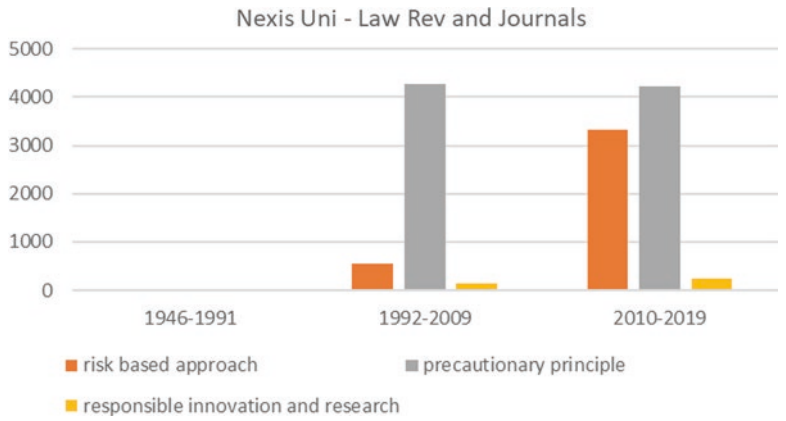

Fig. 24.2 *Nexis Uni* – Comparison of 3 items

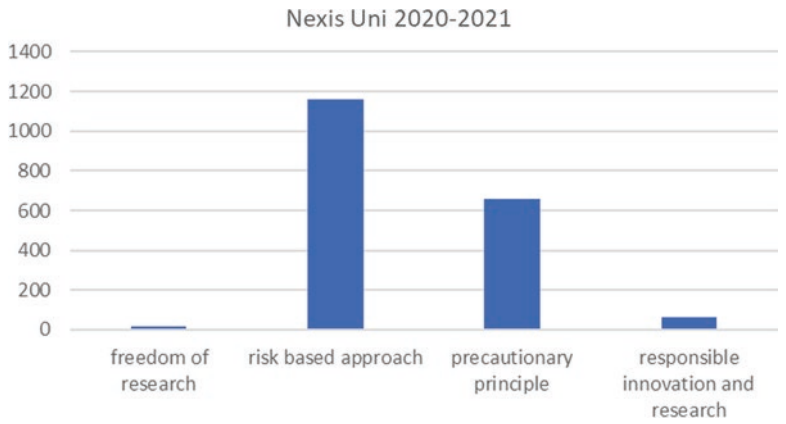

Fig. 24.3 *Nexis Uni* – Comparison of 4 items in years 2020/2021 (Period 4)

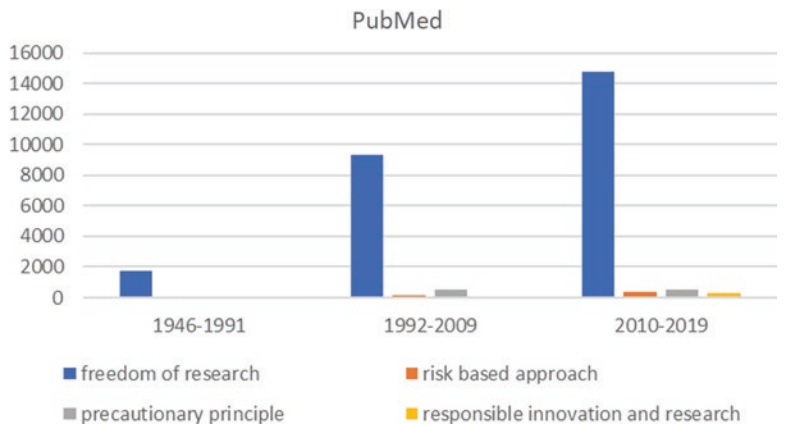

Fig. 24.4 *PubMed* – Comparison of 4 items

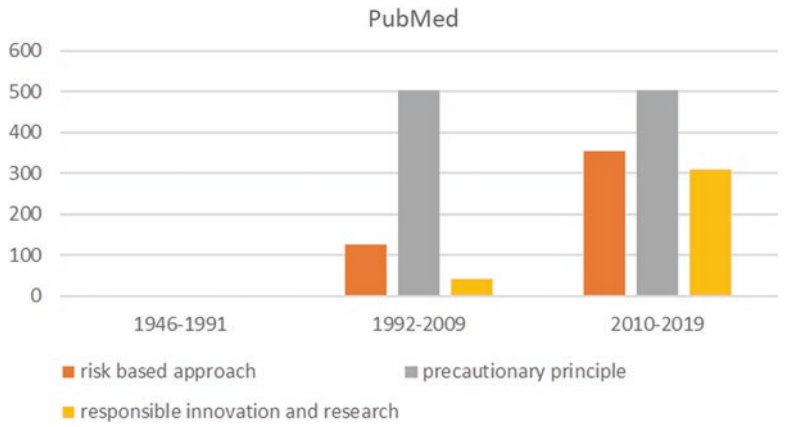

Fig. 24.5 *PubMed* – Comparison of 3 items

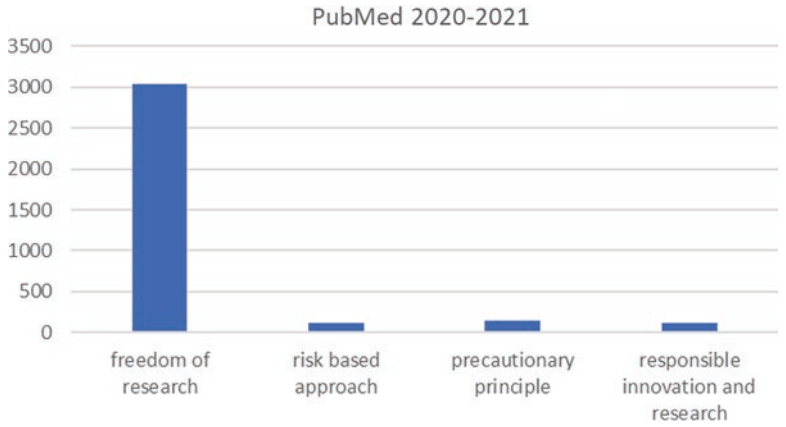

Fig. 24.6 *PubMed* – Comparison of 4 items in years 2020/2021 (Period 4)

tended to remain constant (albeit with a slight increase - Figures 24.5 and 24.6), that of Responsible research and innovation has seen a significant increase in Period 4, compared to Period 3 (from an average of 3 recalls per year to an average of 60 - Figure 24.6 and Figure 24.10), catching up with the other keywords.

As far as European Union law is concerned, a reading of the data taken from the *Eurlex* database (Figure 24.7) shows that the principle of Freedom of research is only occasionally referred to, while the consistency of references to the Precautionary principle/approach is clearly predominant, even compared to the other keywords searched. In the last two years, however, references to the principle of Risk-based approach and Responsible research and innovation have seen a small increase. Between Period 3 and Period 4, references to the Risk-based approach went from an average of 73 per year to 87, while those to RRI went from an average of 4.5 to an average of 9.5. Analysis of the data from the Court of Justice database (*InfoCuria*)

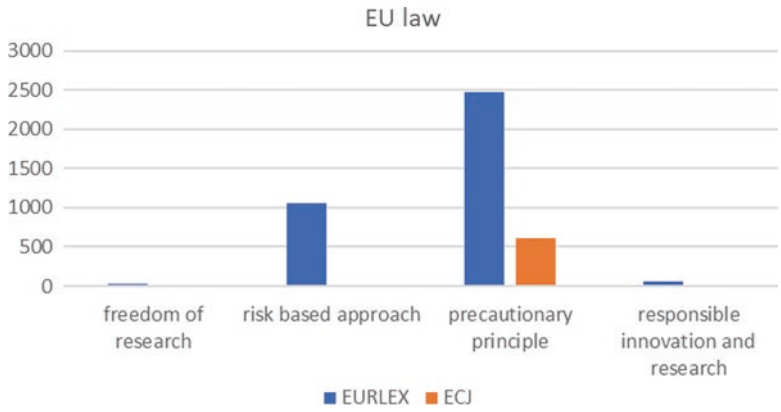

Fig. 24.7 *EURLEX* and *InfoCuria* - Comparison of 4 items

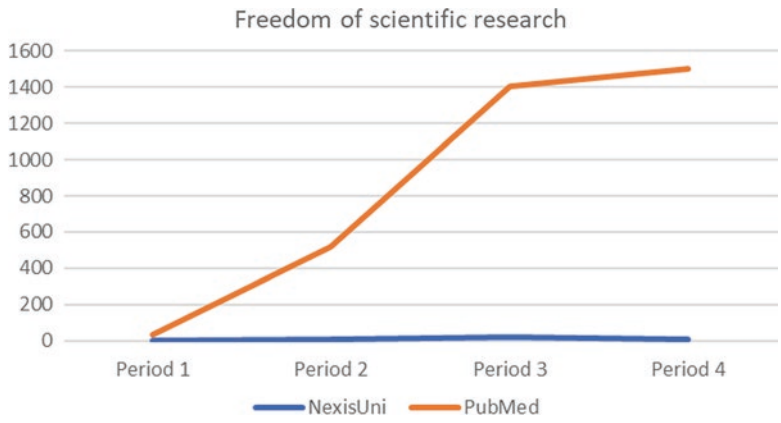

Fig. 24.8 Comparison *Nexis Uni-PubMed* on the freedom of scientific research

also shows that, in case law, the Precautionary principle is frequently applied, while the concepts of Risk-based approach and Responsible research and innovation are applied little or not at all. The particularly significant presence of the former term in the Court of Justice case-law is probably justified by its place within treaty law.

A comparison of the data collected in the two databases - NexisUni and *PubMed* - shows how references to Freedom of research prevail in the scientific literature, whereas these are not very frequent in the legal literature, despite the described constitutional framework (Figure 24.8).

References to a Risk-based approach and to Responsible research and innovation have increased over the years, with an increase in the former more evident in the legal literature and an increase in the latter more evident in the scientific literature (Figures 24.9 and 24.10).

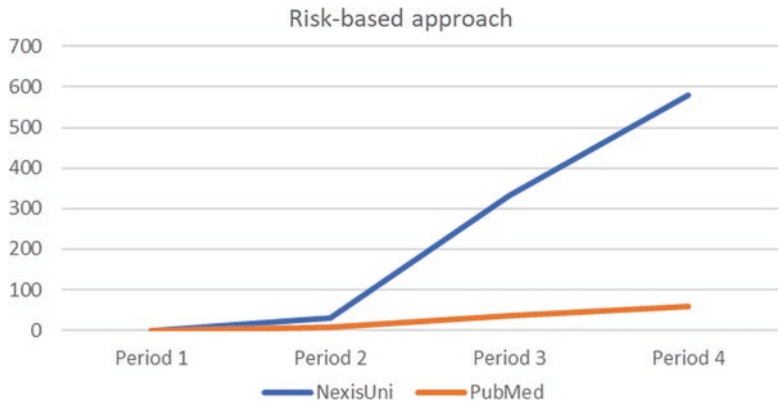

Fig. 24.9 Comparison *Nexis Uni-PubMed* on the risk-based approach

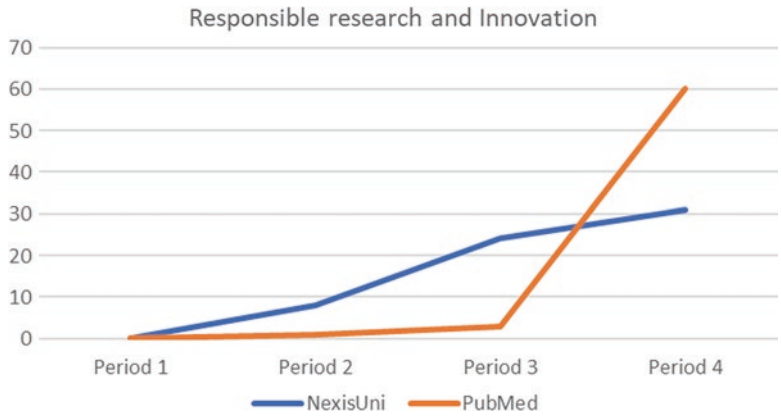

Fig. 24.10 Comparison *Nexis Uni-PubMed* on the responsible research and innovation

Finally, references to the Precautionary principle/approach are increasing in both databases, but, in the pandemic years, there seems to have been a slowdown in the upward trend in the legal literature, which turns into a reversal (Figure 24.11).

Lines for Further Research

As made clear in Par. 1, the present work does not aim at in depth analyzing the most important guiding ideas present in the field defined by the dilemma of how to treat science and technology in our societies: namely, Freedom of scientific inquiry, the Precautionary principle/approach, Responsible research and innovation, and the Risk-based approach.

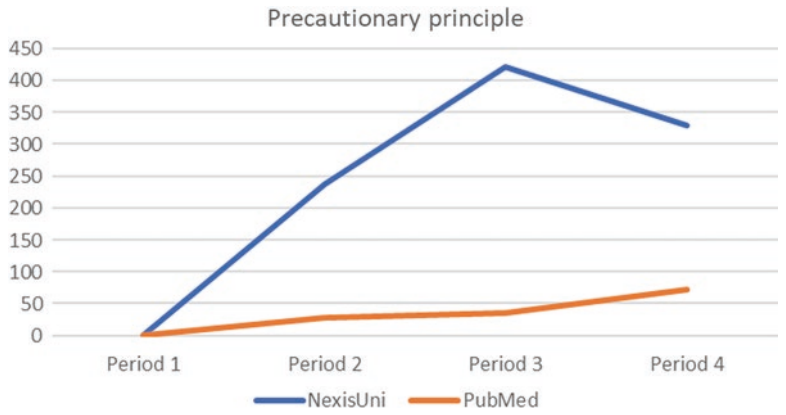

Fig. 24.11 Comparison *Nexis Uni-PubMed* on the responsible research and innovation

Our purpose here was to take a purely quantitative first step that gives a rough indication of the distribution over time of publications focused on those ideas in the scientific and non-scientific (i.e., legal) literature. This allows us to lay the foundations for a necessary second step (the analysis of the publications, their contents, theoretical tendencies, and more) having in mind some evidence that the mere quantitative approach offers and with the aim to verify some prima facie emerging patterns.

What follows is just a list (not necessarily presented in order of importance) of some possible lines of research.

(a) **The distribution of studies on Freedom of scientific research in scientific and legal databases**. Figure 24.4 shows the clear predominance of the concept of Freedom of research in *PubMed* compared to any other guiding idea considered in this analysis and its constant and progressive increase, in particular starting from Period 3. This is in radical contrast to Figure 24.1, which shows the low incidence of the term in the legal database (*Nexis Uni*) of the concept of Freedom of research. The suspect of a not great interest of the issue among jurists seems to be confirmed by Figure 24.8 and Figure 24.7, which shows a great recurrence of Precautionary principle in *EURLEX* and *InfoCuria* and the substantial absence of Freedom of research (which is also one of the fundamental freedoms enshrined in the EU Charter of Fundamental Rights – Art. 13).

The reasons for this apparent lack of interest on the part of jurists in a fundamental constitutional principle deserve further investigation. Can this be explained by the fact that this constitutional provision is initially present only in European (and not North American) constitutions and that the legal production is in European languages other than English? But even if this were the case (as is to some extent possible) how can one justify the great interest in Freedom of research in scientific publications, where North American journals are largely present?

(b) **Risk-based approach and Responsible research and innovation**. The Risk-based approach has a huge development in legal databases since the 1990s (second period) while there seems to be a substantial lack of interest in *Pubmed* (Figure 24.9). Interestingly, the Responsible research and innovation curve has a similar shape (even though with very different quantities) over the same time period in *Pubmed*, while there is a relative increase in interest in the legal databases (Figure 24.10).

If we consider that RRI moves inter alia precisely from the need "at the policy level to discuss, challenge and rethink linear models of science policy [...] and risk-based regulation as the predominant paradigm of innovation governance" (see above), it will be interesting to explore in depth (a) the reasons for this seemingly contradictory success of both contrasting criteria (albeit partially in different doctrinal areas) and (b) the reasons for the wide use of the concept of risk and the Risk-based approach in recent UN and EU documents (see above).

(c) **The relative dynamics of the Precautionary principle/approach v. Responsible research and innovation**. Another noteworthy aspect concerns the relationship between the Precautionary principle/approach and Responsible research and innovation. They share a similar cultural concern about the risks associated with uncritical trust in science and certain science and technology applications, although the former focuses on the uncertainty of science and the latter on the (indistinguishable) science-innovation continuum. Figure 24.1 shows a relative decrease in Precautionary principle/approach from the second to the third period in legal publications, counterbalanced in the same time period by a relative increase in Responsible research and innovation, so that the total of the two 'Precautionary principle/approach + Responsible research and innovation' in the two periods appears stable to slightly increasing. In contrast, in *PubMed* the growth of RRI is much more important (Figure 24.5).

Is the scientific publications sector more mobile and responsive than the legal sector? What are the reasons for these differences? Are they due to cultural differences or to the still nationalistic legal approach, whereby many jurists still publish in their own languages? Or are these differences due to the different role played by PP and RRI in the public debate on science and technology? What role does distribution play between European authors (PP and RRI are more popular in the EU than in the US and English-speaking countries) and authors from other countries?

(d) **The relative dynamics of Precautionary principle v. Precautionary approach**. As we noted above (in section "Rio Declaration and Precaution: Science and Uncertainty"), the line between *principle* and *approach* is quite unstable, and the way the PP is interpreted ranges from a strict dogmatic rigidity to something that under the label of "principle" in practice works as an "approach".

This is something that deserves to be explored in depth, not least in consideration of the legal relevance of the PP in EU law and caselaw.

(e) **The incidence of the pandemic on different guiding ideas:**

- Precautionary principle/approach: references to the Precautionary principle/approach in the pandemic years seem to have been a slowdown in the legal literature while in the scientific literature they have maintained an upward trend (Figure 24.11).
- Responsible research and innovation: references to Responsible research and innovation in the pandemic years seem to have undergone a strong increase, especially in the scientific literature (Figure 24.10).

These data, however, refer to a period of 19 months, coinciding with the outbreak of the pandemic, and therefore require further and more in-depth analysis. Will these results be confirmed over time and if so, why?

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Chapter 25
Conscientious Objection

Mark R. Wicclair

Abstract Historically, conscientious objection has been associated with military service. Currently, however, it does not occur exclusively in response to compulsory military service. With increasing frequency, health care professionals, including those who practice in institutional settings such as hospitals and long-term care facilities, conscientiously object to providing specific medical services. This chapter provides a framework for managing conscientious objection within institutional settings. Criteria are provided for determining when refusals to provide medical services are conscientious objections. Reasons are offered for accommodating conscientious objectors and for denying or limiting accommodation. A *reasonable accommodation* approach, which consists in five requirements, is explained and defended: (1) Conscience-based refusals will be accommodated only if a requested accommodation will not impede a patient's/surrogate's timely access to information, counseling, and referral. (2) Conscience-based refusals will be accommodated only if a requested accommodation will not impede a patient's timely access to health care services offered within the institution. (3) Conscience-based refusals will be accommodated only if the accommodation will not impose excessive burdens on other clinicians, supervisors, department heads, or the institution. (4) Whenever feasible, health professionals should provide advance notification to department heads or supervisors. (5) Conscience-based refusals will be accommodated only if it will not enable invidious discrimination.

Keywords Conscientious objection · Accommodation · Institutional management · Moral integrity · Professional obligations

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Introduction

Historically, conscientious objection has been associated with military service. Currently, however, it does not occur exclusively in response to compulsory military service. With increasing frequency, health care professionals, including those who practice in institutional settings such as hospitals and long-term care facilities, conscientiously object to providing specific medical services. Appropriately managing conscientious objection within institutional settings requires understanding: (1) when a refusal to provide a medical service is a conscientious objection; (2) reasons for accommodating conscientious objectors; (3) reasons for denying or limiting accommodation; and (4) the basics of institutional management.

When Is a Refusal to Provide a Medical Service a Conscientious Objection?

Refusals to provide medical services are *conscientious objections* only if they are based on practitioners' *moral* convictions. Moral convictions can be secular, based on religious beliefs, or a combination of both. Medical services that most frequently occasion conscientious objections include those associated with reproduction and end-of-life decision making. Conscientious objections related to the former category include refusals to offer, provide, or assist in performing abortions and refusals to offer or provide contraceptives—especially emergency contraception (EC). Conscientious objections related to end-of-life decision-making include refusals to forgo life-sustaining treatments—especially medically provided nutrition and hydration (MPNH); refusals to offer or provide palliative sedation to unconsciousness; and refusals to participate in donation after circulatory determination of death (DCDD).

Health care professionals can object to providing medical services for a variety of reasons that are not based on their moral convictions and, therefore, not conscientious objections. Refusals that are not conscientious objections include the following:

- An objection to providing a medical service because it is not clinically indicated. Suppose a pediatrician refuses to provide growth hormone when parents request it for their son who is well within the normal height range for his age. The parents request growth hormone to increase their son's chances of becoming a basketball star. Or suppose a surgeon refuses to perform surgery on a brain tumor because she concludes that it is "inoperable." Insofar as both refusals are supported by accepted clinical norms and standard of care, they are not conscientious objections.
- An objection to providing a medical service to avoid a substantial health risk to the practitioner. For example, if a physician or nurse refuses to treat patients with life-threatening infectious diseases such as Ebola, SARS, or COVID-19 because

they do not want to put themselves at risk of dying, the refusal is not a conscientious objection. Although refusing to provide or assist in providing abortions commonly is based on moral objections, there are other reasons. For example, in view of the violence that has been directed against abortion providers in the U.S., practitioners who are not morally opposed to abortion might refuse to provide or assist in providing abortions out of a concern for their safety. Insofar as a refusal is based on a concern for the practitioner's health or safety, it is not a conscientious objection.

- An objection to providing a medical service for financial reasons: For example, if a practitioner refuses to treat Medicaid patients due to low reimbursement rates, the refusal is not a conscientious objection.
- An objection to providing a medical service because it is illegal or contrary to the profession's code of ethics: If practitioners in Arkansas believe they have a moral obligation to provide gender-affirming therapy for adolescents but refuse to provide it because it is illegal, the refusal is not conscience-based.[1] Similarly, if a physician has no moral objection to medically assisted dying but refuses to provide it because it is illegal and/or violates the profession's code of ethics, the refusal is not conscience-based.
- An objection to providing a service because it is beyond the scope of the practitioner's clinical competence: For example, if a general practitioner refuses to provide palliative services to terminally ill patients in intractable pain because she lacks the necessary training and expertise, the refusal is not a conscientious objection.

Generally, health professionals have an occasion to assert *conscientious objections* and justify refusing to offer or provide a medical service by appealing to their *moral convictions* only when the medical service they refuse to offer or provide is legal, professionally accepted, clinically appropriate, and within the scope of the practitioner's competence. In institutional contexts, conscientious objections are limited to refusals to offer or provide medical services that are offered within the institution.

Health professionals can believe they have a moral and/or professional obligation to provide a medical service that is not permitted within an institution (e.g., tubal ligations or emergency abortions in Catholic hospitals that prohibit them). These situations involve a different type of conscientious objection, which is sometimes referred to as "conscientious commitment" (Dickens & Cook, 2011; Harris, 2012). Rather than objecting to providing a medical service, practitioners object to rules that prohibit them from providing a medical service. Whereas conscience-based *refusals* are based on "negative appeals to conscience," conscientious commitment is based on "positive appeals to conscience" (Wicclair, 2009, 2011). This chapter will only consider conscientious objections that arise when health

[1] When Arkansas lawmakers overrode the governor's veto on April 6, 2021, Arkansas became the first U.S. state to ban gender-affirming therapy for minors (Arkansas Act 626, "Arkansas Save Adolescents from Experimentation (SAFE) Act").

professionals refuse to provide a medical service and assert negative appeals to conscience.[2]

Reasons for Accommodating Conscientious Objectors

A key question that arises in relation to health professionals' conscience-based refusals is whether they should be accommodated—whether they should be permitted to refuse, without penalty, to provide a medical service that is legal, professionally accepted, clinically appropriate and within the scope of their clinical competence.

There are several reasons that favor accommodation. Foremost among them is that accommodation provides "moral space" in which health professionals can practice medicine without undermining their moral integrity (Wicclair, 2011). Moral integrity is threatened when the relevant moral beliefs are core moral convictions—that is, beliefs that are integral to a person's self-conception or identity (Wicclair, 2011, 2017).

Enabling health professionals to practice medicine without compromising their moral integrity is valuable for several reasons. First, from the perspective of health professionals with conscience-based objections, moral integrity can be an essential component of their conception of a good or meaningful life. In this respect, moral integrity has intrinsic worth or value to them and compromising it can result in substantial moral harm to them. Second, a loss of moral integrity can be devastating. It can result in strong feelings of guilt, remorse, and shame as well as a loss of self-respect—additional sources of moral harm. Third, although available evidence is equivocal, it has been claimed that a loss of moral integrity can result in a general decline in a person's commitment to morality and moral principles, which is particularly undesirable in health professionals. Charles Hepler advances a claim along these lines in relation to members of his profession (pharmacy): "We would be naive to expect a pharmacist to forsake his or her ethics in one area (e.g., abortion) while applying them for the patient's welfare in every other area" (Hepler, 2005, 434). Fourth, respect for persons, a widely recognized ethical principle, requires us to allow others to act based their personal values and beliefs and thereby maintain their moral integrity. Finally, it can be claimed that moral integrity generally has intrinsic worth or value. That is, it can be maintained that having firm and consistent moral convictions and a disposition to consistently act in accordance with them (to act conscientiously) are intrinsically valuable character traits and worthy of respect. It is arguable that all other things being equal, a world with such people is a better place than one in which people with those characteristics are absent. To be sure, insofar as moral integrity can involve a commitment to any ethical and/or religious

[2] Typically, legal and institutional conscience clauses that protect conscientious objection in health care are limited to negative appeals to conscience.

beliefs, it does not guarantee ethically acceptable behavior. For example, depending on the content of a person's moral convictions, maintaining moral integrity can result in invidious discrimination, genocide, cruelty, and so forth. Nevertheless, like courage and honesty, admiration and respect for moral integrity are at least partially independent of an assessment of ends and consequences. That is, although we might justifiably withhold our admiration and respect if we judge the ends and consequences to be excessively bad, our admiration and respect are not contingent on a favorable assessment of them. Accordingly, it is not implausible to claim that, like courage and honesty, which also can serve immoral ends and produce undesirable consequences, moral integrity is a moral virtue.

There are additional reasons to accommodate and provide health professionals with moral space in which to act in accordance with their moral convictions. First, insofar as the exercise of conscience—for example, a critical care nurse's refusal to participate in DCDD—is an autonomous action, constraints on the exercise of conscience also are constraints on autonomy. Accordingly, insofar as autonomy is valuable and worth protecting, so, too, is the exercise of conscience. Second, ethical epistemic modesty or humility supports accommodation (Sulmasy, 2008). Ethical epistemic modesty is the view that although ethical beliefs can be correct or incorrect and justified or unjustified, we might be mistaken when we think that a particular ethical belief is correct or justified. This recognition suggests modesty or humility, a rejection of dogmatism in relation to beliefs that we do not accept, and another reason to accommodate. Third, the "moral outliers" of today can be harbingers of moral progress. Examples include physicians who refused on ethical grounds to withhold life-saving medical interventions for newborn infants with Down syndrome before it was generally recognized to be an ethically unacceptable practice; and physicians who refused for ethical reasons to involuntarily sterilize women when it was a permitted practice. Fourth, some practices (e.g., abortion, palliative sedation to unconsciousness, and DCDD) continue to be controversial. Accommodation acknowledges the controversial nature of such practices and gives health professionals who have moral objections to them an opportunity to opt out. Fifth, accommodation expresses tolerance and promotes cultural diversity; and it fosters diversity within the health professions. If no effort were made to accommodate individuals from non-dominant cultures and religious traditions, they might be discouraged from entering health professions. In addition to its intrinsic value, diversity in the health professions can have instrumental value insofar as it can facilitate more effective patient-provider communication and better patient outcomes. Finally, a failure to accommodate conscience-based refusals may discourage people who value moral integrity from entering a health profession. An unintended consequence might be to pre-select for individuals who are ethically insensitive—clearly an undesirable outcome.

Reasons for Limiting or Denying Accommodation

Despite the many reasons for accommodating conscience-based refusals, there are also reasons to limit or deny accommodation. First, a health professional's conscience-based refusal can have an unacceptable impact on patients. Depending on the circumstances, refusing to offer or provide a legal, professionally accepted, and clinically appropriate medical service can undermine patient autonomy, health, and well-being. These are three core values of the health professions, which are advocated in major professional codes, such as the American Medical Association (AMA) *Code of Medical Ethics* (American Medical Association Council on Ethical and Judicial Affairs, 2017) and the American Nurses Association (ANA) *Code of Ethics for Nurses with Interpretive Statements* (American Nurses Association, 2015). Accordingly, these three values set general ethical constraints on accommodation.

Second, refusing to provide a medical service or information about it can impose burdens on colleagues, department heads, supervisors, and institutions, which can set ethical limits to accommodation. Depending on the specific circumstances, accommodation can impose substantial burdens on the health professionals who are called on to provide the information or service that an objector refuses to provide. For example, in hospitals that offer DCDD, accommodating an intensivist's or a critical care nurse's ethical objection to participating in the practice can require other clinicians to substitute for them. Other intensivists may be required to be on call more frequently, and the workloads of other intensivists and nurses may increase significantly. Such changes can be a substantial hardship. The burdensomeness can vary with the personal situation of the other intensivists and nurses. For example, it might be more of a burden to health professionals who have other substantial responsibilities (e.g., family, research, teaching, and/or community service) than to health professionals with fewer other responsibilities. Similarly, to enable a hospital or long-term care facility nurse to be exempted from caring for patients who are unable to take nutrition and hydration orally and who themselves or whose family members have decided to forgo MPNH, it might be necessary to switch assignments with other nurses, which, depending on their work loads and life circumstances, might be a substantial hardship.

Depending on the specific circumstances, accommodation also can impose substantial burdens on department heads, supervisors, and institutions. For example, to accommodate a critical care nurse who has a conscience-based objection to caring for patients admitted to the ICU for complications subsequent to abortion, the supervisor will have to make the necessary work reassignments, which may require significant modifications and rescheduling. It might even require hiring an additional (part-time) nurse, a potential burden to the institution. Accommodating physicians can be burdensome to department heads and other administrators. For example, to accommodate an intensivist with a conscience-based objection to offering palliative sedation to unconsciousness—an accepted procedure within the hospital—the department head might have to make significant modifications to the work

assignments and on-call schedules of other ICU physicians. Accommodation may even require hiring another intensivist, which can be burdensome to the institution. Moreover, as the frequency of requests for accommodation increases, the burdensomeness of making the necessary staffing and schedule changes can also increase.

Institutional Management of Conscientious Objection

Fair, consistent, and transparent management of conscience-based refusals requires an institutional policy. The primary goal of such policies should be to protect the moral integrity of clinicians without placing excessive burdens on patients, surrogates, other clinicians, supervisors, department heads, or the institution. Another important goal is to prevent invidious discrimination. Institutional policies can foster these goals by incorporating five requirements that define *reasonable accommodation*.

Reasonable Accommodation Requirements

- Conscience-based refusals will be accommodated only if a requested accommodation will not impede a patient's/surrogate's timely access to information, counseling, and referral.

This requirement is less demanding of objectors than a corresponding requirement in what Dan Brock refers to as the "conventional compromise," which requires practitioners who object to providing a medical intervention to inform patients about it "if it is medically relevant to their medical condition" (Brock, 2008). The first requirement states only that the patient/surrogate must receive the relevant information in a timely manner. It does not obligate the objecting practitioner to provide it. This can be a significant difference for health professionals with a moral objection to a medical intervention and who believe that informing patients/surrogates about it makes them morally complicit in wrongdoing and thereby undermines their moral integrity. For example, an emergency department (ED) physician who has a conscience-based objection to EC might believe that he would be morally complicit in the perceived wrongdoing of others e.g., (health professionals who provide EC and patients who take it) and, therefore, morally culpable if he were to inform rape victims about its availability. To be sure, this conception of moral complicity is subject to challenge. However, for health professionals who accept it, providing information about medical interventions that are contrary to their moral convictions can undermine their moral integrity.

The first requirement does not oblige practitioners who accept this conception of moral complicity to compromise their moral integrity unless there are no acceptable alternative means for patients/surrogates to receive pertinent information in a timely

manner. To satisfy the first requirement, a clinician who objects to disclosing information about a procedure may need only to direct patients/surrogates to other health professionals who will provide timely disclosure. If this, too, is perceived as unacceptable complicity, sometimes it might be feasible to implement procedures that do not require any participation by the objecting clinician. For example, if an ED physician in a large university medical center objects to offering EC to rape victims, it might be feasible to arrange for triage personnel to assign rape victims to non-objecting physicians. Hence, depending on the circumstances (see the third requirement), the conventional compromise requirement that clinicians inform patients/surrogates about medical interventions that are contrary to their moral convictions can unnecessarily compromise the moral integrity of health professionals.

It is recommended that conscientious objection policies discourage expressions of moral disapproval when physicians who cannot in good conscience inform patients/surrogates about a treatment option refer to practitioners who will inform them. For example, an ED physician who is morally opposed to EC should not say to a rape victim: "I believe that all measures to prevent pregnancy are morally wrong. However, if you nevertheless want to learn about such measures, there is another physician who can give you that information." A more appropriate statement would be: "There is information that you might find helpful that I am unable to provide. However, I can refer you to another physician who will give you that information."

- Conscience-based refusals will be accommodated only if a requested accommodation will not impede a patient's timely access to health care goods and services offered within the institution.

Like the first requirement, the second is also less demanding of objectors than the corresponding requirement of the conventional compromise, which obligates practitioners who refuse to provide a medical intervention to *refer* patients to another health professional who is willing and able to provide it. (Brock, 2008, 194) The second requirement states only that accommodation must not *impede a patient's timely access* to health care goods and services offered within the institution. It does not require referral or any other specific action by objecting practitioners. This can be a significant difference for health professionals with a moral objection to a medical intervention who believe that referral to a health professional who will provide it makes them morally complicit in wrongdoing and thereby undermines their moral integrity. For example, an intensivist who is morally opposed to palliative sedation to unconsciousness, a procedure that is offered within the hospital, might believe that it would compromise her moral integrity to refer a patient or surrogate to an intensivist who will provide it. The second requirement does not obligate the intensivist to provide a referral and undermine her moral integrity unless her failure to do so will impede a patient's timely access to the procedure. However, it might be possible to satisfy the second requirement without requiring the intensivist to provide referrals. For example, it might be feasible to arrange for other members of the health care team to review the charts of the objecting intensivist's patients to

identify those for whom palliative sedation to unconsciousness is an acceptable option.[3] It might be possible to assign the responsibility of offering the procedure to intensivists who have no moral objection to offering it. Or, if patients or surrogates request palliative sedation to unconsciousness, it may suffice for the intensivist to alert the department head, who can assign the responsibility of presenting that option to intensivists with no moral objections. When referral by an objecting clinician is not required for a patient to receive a medical intervention in a timely manner, depending on the circumstances (see the third requirement), it might be possible to accommodate and protect an objector's moral integrity without compromising patient health or well-being. Hence, the conventional compromise requirement that practitioners provide referrals can unnecessarily compromise their moral integrity.

Although the second requirement might not require objectors to provide referrals, it does prohibit them from *obstructing* access to legal, professionally accepted, and clinically appropriate medical interventions that are contrary to their moral convictions. Failing to inform can cross the line into obstruction when a health professional has the exclusive responsibility to inform patients/surrogates about a medical intervention that is offered within the institution, and they intentionally refrain from informing patients/surrogates about it when it is a clinically appropriate option because it is contrary to their moral convictions. Lying to patients/surrogates can be another means of obstruction within an institutional setting. For example, in response to a parent's question, a pediatric nurse who is morally opposed to forgoing MPNH might falsely state that forgoing it is illegal or contrary to hospital policy.

- Conscience-based refusals will be accommodated only if the accommodation will not impose excessive burdens on other clinicians, supervisors, department heads, or the institution.

This requirement sets context-dependent practical limits to accommodation. Unfortunately, there is no simple rule for determining when burdens are "excessive," in part because excessiveness is largely context dependent. Whether an accommodation will impose excessive burdens depends on a variety of contextual factors, including the number of staff members whose clinical competencies overlap with those of the objector; the willingness of other practitioners to provide the medical service at issue; the number of health professionals within a service, a unit, and the institution who request accommodation; the frequency of such requests; the existing responsibilities and work-loads of health professionals, administrators and staff; and the availability of funds to pay overtime or hire additional staff. Moreover, in assessing burdensomeness, it may be necessary to consider factors outside the institutional environment, such as a practitioner's overall life circumstances.

[3] A Report of the AMA Council on Ethical and Judicial Affairs (CEJA) provides criteria for determining when it is appropriate to offer palliative sedation to unconsciousness (CEJA Report 5-A-08, "Sedation to Unconsciousness in End-of-Life Care"). Available online at: https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/public/about-ama/councils/Council%20Reports/council-on-ethics-and-judicial-affairs/a08-ceja-palliative-sedation.pdf; accessed July 19, 2021.

A willingness to accept a burden, provided it is not a result of coercion or undue pressure and the agent is not overly servile or self-deprecating, may warrant inferring that the burden is not excessive. However, since there are situations in which it is justified to expect agents to bear burdens that they do not want to accept, an unwillingness to accept a burden does not warrant inferring that the burden is excessive. Hence, although the standard of excessiveness is partially subjective, it is not exclusively subjective.

To be sure, there undoubtedly are clear cases of burdens that are excessive and burdens that are not excessive. For example, if a nurse needs to be home to care for her young children during the night, requiring her to change from a day to a night shift would be an excessive burden. Similarly, it would be an excessive burden to require the only intensivist who is not morally opposed to DCDD to be on call throughout the year for DCDD cases. By contrast, if accommodating a nurse who is morally opposed to DCDD does not require other nurses in the unit to significantly increase their workloads or alter their schedules, it would not be an excessive burden on the nurses. Setting up the accommodation also is unlikely to be an excessive burden on the nursing supervisor or administrator. Despite such clear cases, there is no bright line that separates burdens that are excessive from those that are not excessive, and there is no consensus on a standard of excessiveness.[4] A fair process approach along the lines recommended below ("Procedures for Reviewing Requests for Accommodation") can help to develop standards for an institution and reduce actual and perceived arbitrariness in determining whether burdens are excessive.

- Whenever feasible, health professionals should provide advance notification to department heads or supervisors.

This requirement enables department heads and supervisors to accommodate conscience-based objections with a minimum of inconvenience and disruption. Moreover, since advance notification can give practitioners who are asked to substitute more time to make necessary professional and personal adjustments, such notification also can minimize burdens to them. Although advance notification cannot guarantee accommodation, it can increase the likelihood that needed staffing assignments and schedule changes can be made. For example, if a newly hired ob/gyn nurse informs a supervisor that she has a conscience-based objection to participating in second and third trimester abortions, an accommodation is more likely to be feasible than if she waits to inform the supervisor until she is asked to participate in a second trimester abortion. Finally, by facilitating continuity of services within the

[4] Title VII of the 1964 Civil Rights Act (42 USCS § 2000e et seq. (2005)) and regulations and guidelines issued by the United States Equal Employment Opportunity Commission (EEOC) govern the accommodations that employers in the U.S. are legally required to make. Employers are required to "reasonably accommodate" conscience-based objections of health professional employees unless it would result in an "undue hardship" on the employer. The EEOC provides interpretive guidelines and case examples that help to specify the concept of "undue hardship." They are posted on the EEOC Web site: http://www.eeoc.gov/; accessed July 19, 2021.

institution, advance notification also can minimize the burdens that patients will experience due to conscience-based refusals.

When health professionals do not object in principle to a medical intervention, such as abortion, DCDD, palliative sedation to unconsciousness, or forgoing MPNH, advance notification can be more challenging but still not infeasible. For example, suppose a neonatal intensive care unit (NICU) physician and an NICU nurse are not ethically opposed in principle to providing aggressive treatment to pre-term neonates. Indeed, they both routinely provide such care. However, they both have conscience-based objections to continuing aggressive life support for one NICU patient, a pre-term infant with an extremely poor prognosis. Although continued aggressive treatment is contrary to the physician's conception of "good medicine" and the nurse's conception of "good nursing practice," it does not violate established professional norms and is not outside the boundaries of "appropriate medical/nursing care." To facilitate advance notification of NICU administrators, the physician and the nurse should attempt to identify their respective general criteria for deciding when providing aggressive treatment to premature newborns is contrary to their conceptions of "good medicine" and "good nursing practice," respectively. Generally, to facilitate advance notification, health professionals should attempt to anticipate the types of situations in which they are likely to request exemptions.

- Conscience-based refusals will be accommodated only if it will not enable invidious discrimination.

It is one thing for health professionals to object to providing a specific medical service (e.g., abortion or EC); and quite another thing to object to providing a medical service to African American or Muslim patients and yet be willing to provide the same medical service to white or Christian patients. Ethical codes of major health professions prohibit invidious discrimination; and it is a settled view—one based on defensible and widely shared conceptions of justice, equality, dignity, and respect—that racial, ethnic, religious and gender-based prejudice or bias are ethically wrong. Even if they are conscience-based (i.e., rooted in fundamental moral beliefs), accommodation for objections based on such discriminatory beliefs is unwarranted.

It is, of course, possible to question whether a particular specification of the scope of invidious discrimination is justified. For example, although it is a settled view that race-based prejudice is ethically unacceptable, it might be questioned whether moral disapproval of LGBTQ patients reflects prejudice or unjustified bias. The AMA added sexual orientation to the specified types of prohibited discrimination in 1993 and gender identity in 2007.[5] This expansion indicates that the scope of

[5] The AMA Board of Trustees (BOT) approved adding discrimination based on sexual orientation in 1993 and the House of Delegates (HOD) approved it 5 years later. See ((Schneider & Levin, 1999), 1287–8) The BOT approved the addition of gender identity in 2007 (BOT Report 11, E-9.03, "Recommendations to Modify AMA Policy to Ensure Inclusion for Transgender Physicians, Medical Students, and Patients"). The Council on Ethical and Judicial Affairs (CEJA) approved it in the same year (CEJA Report 2-I-07).

recognized invidious discrimination within a profession can change over time. Such changes correspond to changes in accepted views within and outside the profession about the scope of invidious discrimination and, arguably, appropriately limit conscience-based refusals. It is beyond the scope of this chapter to specify the scope of "invidious discrimination." Suffice it to say that however it is specified, invidious discrimination should not be accommodated.

Procedures for Reviewing Requests for Accommodation

In some situations, there may be no need for a formal procedure to review and approve or deny requests for accommodation. For example, when an intensivist objects to continuing life support for a patient, common practice is for the physician to arrange a transfer of care to an intensivist who is willing to continue life support for the patient. And if another physician is willing and able to accept the patient and continue life support, prior review and approval generally is not required. A similar practice is common when physicians object to discontinuing life support.

However, when health professionals are unable to find willing substitutes or when accommodation requires more extensive reallocations of responsibilities within a service, unit, or institution, a formal review of requests for accommodation may be required. Criteria for triggering a formal review process may differ from institution to institution, but each institution's accommodation policy should specify when formal approval is required.

The assignment of responsibility for an initial review of accommodation requests may vary depending on the size and culture of the institution and frequency of requests. Options include department heads and supervisors, a designated administrator or ombudsperson, or the institutional ethics committee. However, considerations of efficiency may favor limiting the role of the ethics committee to providing assistance with hard cases, hearing appeals, conducting periodic reviews of past decisions, and fine tuning the policy. Whatever mechanism is chosen for initial reviews; it should be specified in the institution's conscientious objection policy.

If requests for accommodation are denied, health professionals should have an opportunity to appeal the decision. An opportunity for appeal can help to reduce the perception of arbitrariness as well as actual arbitrariness. It also can contribute to achieving the aim of properly determining when it is and is not justified to deny requests to accommodate. The institutional ethics committee is an appropriate body to hear appeals. Review by a committee with a diverse membership is especially apt insofar as four of the five requirements include context-dependent terms such as "timely" and "excessive." Whatever mechanism is chosen to review appeals, it should be specified in the institution's conscientious objection policy.

The five reasonable accommodation requirements provide criteria for evaluating requests for accommodation and determining whether to approve or deny them or offer partial accommodation. However, several bioethicists maintain that objectors' reasons must also be scrutinized (Card, 2007, 2014, 2017a, b; Kantymir & McLeod,

2014; LaFollette & LaFollette, 2007; Meyers & Woods, 1996). Robert Card is a leading advocate of assessing objectors' reasons. He proposes a "reasonableness" standard and advocates the following "reason-giving requirement:" An accommodation should be granted "only if the practitioner makes the objection and its reasoned basis public, and the justification offered for the exemption is subjected to assessment" (Card, 2017a, 82). Two of his criteria for assessing "grounding reasons" seem plausible: They must be genuinely held core moral beliefs (beliefs associated with a person's moral integrity); and they must be consistent with relevant empirical information.

An example of an objection that fails to satisfy the second criterion is a pharmacist whose conscience-based objection to dispense EC is based on mistaken beliefs about its mechanism of action. A study of South Dakota pharmacists reported that 36.6% of the respondents did not correctly identify the mechanism of action of EC, and 19% incorrectly identified it as most similar to that of the abortifacient mifepristone (RU-486) (Van Riper & Hellerstedt, 2005). Another study reported that 35.8% of New Mexico pharmacists surveyed mistakenly believed that "[o]ral emergency contraception is also known as RU-486" (Borrego et al., 2006, 37). Such mistaken beliefs about EC are not limited to pharmacists. For example, similar findings are reported for family medicine physicians and nurses (Wallace et al., 2004). If such demonstrably mistaken beliefs about the mechanism of action of EC are essential to a health professional's conscience-based objection to dispense it, accommodation is unwarranted.

Kantymir and McLeod propose a constraint against "baseless" empirical beliefs (Kantymir & McLeod, 2014). They maintain that "empirical beliefs that ground a healthcare professional's objection need to be defensible" (Kantymir & McLeod, 2014, 19).[6] Their language suggests, perhaps unintentionally, that health professionals have the burden of demonstrating that their empirical beliefs are defensible and not baseless. However, to better protect the moral integrity of health professionals, those who conduct reviews of objectors' reasons should have the burden of ascertaining that an empirical belief is demonstrably false.

A third of Card's criteria for assessing objectors' reasons, "a justified conscientious objection must not be based on a discriminatory belief" (p. 91), also seems plausible; and it corresponds to the fifth reasonable accommodation requirement. However, he proposes additional necessary conditions. Grounding reasons must be: (1) reasonable (2) subject to evaluation in terms of their justifiability; and (3) based

[6] The example they cite is a physician who supports a refusal to give children the MMR (Measles, Mumps, and Rubella) vaccine by claiming there is a link between the vaccine and autism. There is a significant difference between this example and the example of mistaken beliefs about the mechanism of EC. In the MMR case, if the belief about the connection between the vaccine and autism were true, a physician would have a reason to object to giving it on *clinical* grounds. By contrast, if the belief that EC is an abortifacient were true, that belief would not give health professionals a reason to object to it on clinical grounds. Instead, health professionals who are morally opposed to abortifacients would then have an *ethical* reason to refuse to prescribe, dispense, and administer EC.

on reasonable conceptions of the good. Card offers the following justification for this comprehensive assessment of reasons:

"Since conscientious objection essentially involves moral beliefs, and the validity of ethical beliefs (and acts based upon them) depends upon critically assessing their justification, then a proper view on conscientious objection must examine the justificatory reasons of objecting providers" (Card, 2017b, 222).

It is undoubtedly desirable for *anyone*, including health professional conscientious objectors, to have basic critical thinking skills that enable them to reflect on their core moral convictions, critically assess them, and provide a public justification. However, as desirable as it may be, it is unclear whether this ability is an appropriate criterion for accommodation. People can have sincere and deeply held self-defining core moral convictions and yet lack the critical thinking skills that would enable them to provide a satisfactory justification of their grounding reasons; or they might opt to shield core convictions, especially if they are faith-based, from public scrutiny. It is unclear why an inability (or unwillingness) to provide a convincing public justification should disqualify conscientious objectors from being considered for accommodation.

In defense of a justification requirement, Card considers a case in which an employee stayed home from work. In this case, Card claims, it is appropriate for the employer to ask for a reason, and it matters whether it was illness or a desire to "catch up on watching favorite television shows" (Card, 2017a, 93). To be sure, from the perspective of determining whether the absence is excusable, the reason does matter. In this case, there are unambiguous and uncontestable criteria for what counts as an unsatisfactory justification. However, unless unambiguous and defensible criteria are specified for assessing conscientious objectors' grounding reasons, requiring a justification that will satisfy the person or persons who conduct the review (e.g., department heads, supervisors, or members of ethics committees) risks introducing unjustified bias and subjectivity. There is a similar problem in relation to the concepts of "reasonable" and "reasonable conceptions of the good," neither of which is specified by Card.[7] The point of accommodation is to give health professionals moral space in which they can act according to their convictions, and to shield them from being subject to others' moral approval or disapproval.

Some bioethicists maintain that an appropriate model for reviewing requests for accommodation by health professionals is the process for determining whether individuals qualify for conscientious objector status in the military. (Card, 2016; LaFollette & LaFollette, 2007; Meyers & Woods, 1996). However, it is doubtful that

[7] Card asserts that the "reasonable conceptions of the good" requirement is based on Rawls' ideal of "public reason." However, as Card rightly acknowledges, this ideal applies to deliberations about *basic social structures*: "*when organising the basic institutional structure of society*, we can rightly ask that individuals only act upon *reasonable* conceptions of the good" (Card, 2017b, 223) ("reasonable" is the only word emphasized in the original). Objecting physicians are not addressing basic institutional arrangements. They are only requesting an exemption from offering or providing a medical service. Therefore, it is questionable that the Rawlsian public reason ideal applies to them.

the primary objective of the military review process is to determine whether an applicant's reasons for requesting objector status are reasonable or justified. Rather, the primary objective is to determine whether they are the "right" reasons according to U.S. law. As the Supreme Court identified a key right reason in a landmark 1965 decision, applicants for conscientious objector status must oppose *all* wars.[8] Requiring a substantive "right reason" from health professionals who request accommodation is inconsistent with the goal of providing them moral space to act according to their moral convictions and maintain their moral integrity.

More importantly, due to its rigorousness and adversarial nature, the military review process does not provide a suitable model for reviewing requests for accommodation by health professionals. Compelling reasons for requiring a rigorous review in the case of applicants for conscientious objector status in the military do not apply to health professionals. Conscientious objectors in the military receive exemptions from serving in combat that can significantly reduce the risk of death, serious injury, and emotional and psychological trauma. Arguably, fairness requires a rigorous test when determining which individuals to exempt from such substantial potential burdens and harms. By contrast, the conscience-based accommodations that health care professionals receive generally do not exempt them from comparable burdens and harms. Moreover, the third reasonable accommodation requirement significantly reduces the risk of unfairly shifting burdens from health professionals who request exemptions to those who do not. In addition, in view of the substantial risks and burdens that combat soldiers can face, conscripts—compared to health professionals—have a significantly stronger incentive to feign conscientious objection.

There is a less adversarial and more appropriate conception of the function of reviewing objectors' reasons. According to this conception, the primary function is to engage health professionals in a process of reflecting on the nature and depth of their objection. An objective is to facilitate moral clarity on the part of health professionals who request accommodation rather than to enable department heads or members of ethics committees to assess the "reasonableness" of objectors' reasons.

Meyers and Woods report having discovered some local physicians "declared conscientious objection out of economic or aesthetic concerns, rather than genuinely moral or religious reasons" (Meyers & Woods, 2007, 20). If these physicians had discussed their objections with department heads, they might have come to understand that that there are significant differences among economic, aesthetic,

[8] *United States v Seeger* (380 U.S. 163 (1965)). The Selective Service Act in effect at the time required opposition to all war based on "religious training and belief" which was defined in the Act as "an individual's belief in a relation to a Supreme Being involving duties superior to those arising from any human relation, but [not including] essentially political, sociological, or philosophical views or a merely personal moral code." In *Seeger*, the Supreme Court held that the test of whether a belief is "in a relation to a Supreme Being" is "whether a given belief that is sincere and meaningful occupies a place in the life of its possessor parallel to that filled by the orthodox belief in God of one who clearly qualifies for the exemption. Where such beliefs have parallel positions in the lives of their respective holders we cannot say that one is 'in a relation to a Supreme Being' and the other is not."

and moral reasons. With the guidance of department heads, they also might have come to understand that accommodation of conscientious objection is intended exclusively for moral objections.

Health professionals also can have moral objections to actions when their objections are not based on core moral beliefs. Although performing such actions might give rise to feelings of unease or discomfort, they may not rise to the level of threatening an agent's moral integrity. For example, an intensivist might object to maintaining a severely demented elderly patient on life support because she believes it is an unjust use of resources. When discussing the grounds of her objection with her department head, the intensivist might realize that she routinely accepts comparable injustices and maintaining the patient on life support does not threaten her moral integrity. She might also conclude that avoiding the discomfort she feels would not justify placing additional burdens on her colleagues. When the moral integrity of clinicians is not at stake, clinicians might consider what Dominic Wilkinson refers to as "conscientious non-objection," which is to make "a considered decision…to provide a legal and professionally accepted medical course of action requested by or on behalf of a patient despite a personal belief that this action would be morally wrong" (Wilkinson, 2017, 134).

To be sure, there may be cases in which the person or persons conducting a review and a health professional disagree about the nature and depth of the latter's conscientious objection. In cases in which health professionals steadfastly insist that their moral integrity is at stake, the value of protecting the moral integrity of health professionals favors a policy of deferring to their own assessment of the nature and depth of their objection. This deference to health professionals' own judgments applies only to an assessment of their reasons. It is the responsibility of department heads, supervisors, and/or ethics committees to determine whether the five reasonable accommodation requirements are satisfied and accommodation is warranted.

Objections to Reasonable Accommodation

Reasonable accommodation might be rejected on the grounds that it can require health professionals to compromise their moral integrity. Undeniably, since four of the five requirements are context dependent, satisfying them can require health professionals to compromise their moral integrity.

In response, this objection fails to recognize that individuals acquire special obligations, such as obligations to respect patient autonomy and to promote patient health and well-being, when they enter a health profession. Hence, depending on the circumstances, fulfilling one's professional obligations may require compromising one's moral integrity. However, individuals who plan to enter a health profession can minimize the risk of being in situations that threaten their moral integrity by judiciously selecting practice disciplines and specialties or sub-specialties. For example, pediatric residents who plan to pursue a fellowship and who have

conscience-based objections to offering parents a full range of legal and professionally accepted end-of-life options should consider fellowships in areas other than critical care. Health professionals can further minimize the risk of finding themselves in situations that compromise their moral integrity by a careful choice of practice environments and locations. For example, a physician or nurse with a conscience-based objection to caring for patients who refuse MPNH should not practice in a hospice setting. Similarly, health professionals with a conscience-based objection to a medical service may find a more accommodation-friendly environment in a large urban medical center than in a small rural community hospital.

A second objection rejects reasonable accommodation on the grounds that conscientious objection is incompatible with the professional obligations of physicians (incompatibilism) (McLeod, 2020; Rhodes, 2006; Savulescu & Schuklenk, 2017; Smalling & Schuklenk, 2017a, b; Stahl & Emanuel, 2017).[9] A common argument for incompatibilism draws upon a contrast between conscientious objection to performing compulsory military service and conscientious objection to providing specific medical services (Stahl & Emanuel, 2017; Smalling & Schuklenk, 2017a, b). Unlike compulsory military service, it is claimed, becoming a physician is a *voluntary choice*. Military conscripts have not chosen to become soldiers; and if they are assigned combat roles, they have not voluntarily accepted those roles or the corresponding role obligations and responsibilities. Exempting conscientious objectors from combat prevents them from being compelled to act against their conscience. By contrast, it is argued, when individuals enter the medical profession, they do so voluntarily, and in doing so, they explicitly or implicitly agree to accept the obligations of the profession. Individuals who are conscientiously opposed to providing a legal and professionally accepted medical service have no legitimate claim for accommodation because they can avoid acting against their conscience by choosing a profession, medical specialty, or practice location and environment that will not require them to act contrary to their conscience.

This line of argument fails to justify incompatibilism. At most, it supports the claim that insofar as individuals voluntarily decide to enter the medical profession, they are bound by the corresponding professional obligations. To support incompatibilism, it needs to be shown further that refusing to provide a legal, professionally accepted, clinically appropriate medical service within the scope of a physician's clinical competence because it violates their moral convictions is contrary to their professional obligations. A common argument for incompatibilism invokes a principle that I shall designate the Patient's Interest First Principle (PIFP)—the principle that physicians have an obligation to put patients' interests or well-being above their own self-interest.

It is a generally recognized principle that physicians have an obligation to put patients' interests or well-being above their own self-interest. In view of the wide recognition of the PIFP, it is not implausible to claim that individuals explicitly or implicitly agree to accept this principle when they voluntarily enter the medical

[9] This argument can be generalized for other health professions.

profession (Stahl & Emanuel, 2017; Smalling & Schuklenk, 2017a, b). However, the PIFP is general and needs to be specified. It clearly prohibits physicians from considering their financial interests when making recommendations to patients. But beyond that, what are the scope and implications of the PIFP? Is there no significant ethical difference between a physician's financial interests and his or her interest in maintaining moral integrity? Are there no limits to the sacrifices of their own well-being that physicians are obligated to make for the sake of their patients' health or well-being? Surely, there must be limits or physicians would not be able to take vacations, refuse to make house calls, limit their practice hours, refuse to expose themselves to excessive financial losses or risks of harm, and so forth.

What are the implications of the PIFP for conscientious objection? Typically, incompatibilists simply assume, without support, that conscientious objection is incompatible with the PIFP. Ronit Stahl and Ezekiel Emanuel are representative of this approach (Stahl & Emanuel, 2017). The authors cite the following statement in the American Medical Association (AMA) *Code of Medical Ethics* (1.1.1): "physicians' ethical responsibility [is] to place patients' welfare above the physician's own self-interest" (Stahl & Emanuel, 2017, 1381). However, if the AMA *Code of Medical Ethics* is the basis for interpreting the PIFP, one would have to conclude that conscientious objection is not inconsistent with that principle. The same chapter of the *Code of Medical Ethics* addresses conscientious objection and recognizes its value:

"Preserving opportunity for physicians to act (or to refrain from acting) in accordance with the dictates of conscience in their professional practice is important for preserving the integrity of the medical profession as well as the integrity of the individual physician, on which patients and the public rely. Thus physicians should have considerable latitude to practice in accord with well-considered, deeply held beliefs that are central to their self-identities" (1.1.7) (American Medical Association Council on Ethical and Judicial Affairs, 2017).

The *Code* also explicitly denies that conscientious objection is incompatible with the obligations of physicians. It states that, with three specified limitations, "physicians may be able to act (or refrain from acting) in accordance with the dictates of their conscience *without violating their professional obligations*" (1.1.7; emphasis added).[10]

Stahl and Emanuel are aware of this qualified acceptance of conscientious objection in the *Code of Medical Ethics*. However, they maintain that the AMA's position on conscientious objection is "internally inconsistent" (Stahl & Emanuel, 2017, 1381). This response fails to consider whether physicians who satisfy specified constraints on conscientious objection—including, but not necessarily limited to those

[10]The three specified limitations are: "Physicians are expected to provide care in emergencies, honor patients' informed decisions to refuse life-sustaining treatment, and respect basic civil liberties and not discriminate against individuals in deciding whether to enter into a professional relationship with a new patient" (1.1.7).

cited in the *Code*—can satisfy a plausible interpretation of the PIFP.[11] Elsewhere, I consider several accounts of the professional obligations of physicians and argue that none supports incompatibilism (Wicclair, 2008, 2011). I will not repeat those arguments here. Suffice it to say that providing a plausible and convincing defense of incompatibilism is a more formidable challenge than its proponents acknowledge.

Conclusion

Institutional management of conscientious objection should be based on the recognition that there are reasons for and against accommodating health professionals' conscientious objections. First and foremost, among the reasons favoring accommodation is to provide moral space in which health professionals can maintain their moral integrity. The primary reason to limit or deny accommodation is the potential negative impact on patients, colleagues, administrators, and institutions. Accordingly, the primary aim of institutional management is to accommodate health professionals' claims of conscience without significantly compromising other important values and interests.

Fair, consistent, and transparent management of conscience-based refusals requires an institutional policy. Institutional policies can promote the goal of accommodating health professionals' conscientious objections without significantly compromising other important values and interests by incorporating five reasonable accommodation requirements: (1) Conscience-based refusals will be accommodated only if a requested accommodation will not impede a patient's/surrogate's timely access to information, counseling, and referral. (2) Conscience-based refusals will be accommodated only if a requested accommodation will not impede a patient's timely access to health care services offered within the institution. (3) Conscience-based refusals will be accommodated only if the accommodation will not impose excessive burdens on other clinicians, supervisors, department heads, or the institution. (4) Whenever feasible, health professionals should provide advance notification to department heads or supervisors. (5) Conscience-based refusals will be accommodated only if it will not enable invidious discrimination.

In some situations—for example if a physician who objects to providing care for a particular patient is able to facilitate an intra-institutional transfer to another physician—there may be no need for a formal procedure to review and approve or deny requests for accommodation. However, there will be situations, for example, when accommodation requires extensive reallocations of responsibilities within a service,

[11] The *Code* includes the following additional guideline: "Several factors impinge on the decision to act according to conscience. Physicians have stronger obligations to patients with whom they have a patient-physician relationship, especially one of long standing; when there is imminent risk of foreseeable harm to the patient or delay in access to treatment would significantly adversely affect the patient's physical or emotional well-being; and when the patient is not reasonably able to access needed treatment from another qualified physician" (1.1.7).

unit, or institution, when it is appropriate to require a formal review of requests for accommodation. Different institutions may adopt different criteria for triggering a formal review process, but each institution's accommodation policy should specify when formal approval is required.

The assignment of responsibility for an initial review of requests for accommodation may vary depending on the size and culture of the institution and frequency of requests for accommodation. Options include department heads and supervisors, a designated administrator or ombudsperson, or the institutional ethics committee. However, considerations of efficiency may suggest limiting the role of the ethics committee to providing assistance with hard cases, hearing appeals, conducting periodic reviews of past decisions, and fine tuning the policy. Whichever mechanism is chosen for initial review, it should be specified in the institution's accommodation policy.

If requests for accommodation are denied, health professionals should have an opportunity to appeal the decision. An opportunity for appeal can help to reduce the perception of arbitrariness as well as actual arbitrariness. It also can contribute to achieving the aim of properly determining when it is and is not justified to deny requests to accommodate. The institutional ethics committee is an appropriate body to hear appeals. An explanation of the appeals process should be included in the institution's accommodation policy.

When reviewing a health professional's reasons for requesting accommodation, the review process should avoid an adversarial approach, such as that adopted by military review boards for assessing applications for conscientious objector status. According to the recommended non-adversarial approach, the primary function of reviews of objectors' reasons is to engage them in a process of reflecting on the nature and depth of their objections. An objective is to facilitate moral clarity on the part of health professionals who request accommodation rather than to enable *others* (e.g., department heads, supervisors, or ethics committees) to determine whether conscientious objections are sufficiently "reasonable." Compared to an adversarial approach modeled on the military review process, this approach has the advantage of being more protective of health professionals' moral integrity. If there is a disagreement between the person(s) conducting the review and the health professional concerning the nature and depth of objections, respect for moral integrity favors accepting the latter's assessment. This deference to health professionals' own judgments applies only to an assessment of the nature and depth of their objections. It is the responsibility of department heads, supervisors, and/or ethics committees to determine whether the five reasonable accommodation requirements are satisfied and accommodation is warranted.

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Chapter 26
Institutional Liability in Research

J. C. Scharf-Deering and Tracy Wilson-Holden

Abstract In this chapter, we explore a pragmatic approach to balancing the risks and rewards related to engagement in research through a regulatory lens. The purpose of this chapter is to provide insight for investigators, researchers, ethics committee members and research administrators into the complex roles and responsibilities of academic research administration in protecting institutions, individuals, and ideas. We discuss consequences to institutions and individuals when there is a failure to engage in ethical and compliant research. The chapter includes a process tool that institutions can use to redress issues. Finally, we anticipate how routine review, education, and evaluation can help institutions anticipate new and emerging areas of research and related liability.

Keywords Research risks · Training · Communication · Root cause · Mitigation · Culture change · Assessment tool

Background, Definitions and Review of Literature

Institutional liability in research seems like a phrase that has a clear meaning. However, it may not be so clear once we begin to break down the topic into the three key parts: liability, institution, and research. Liability has a clear legal definition implying accountability or responsibility according to law or contract. Institutional liability can be viewed from several perspectives including legal, reputational, academic, and civic, among others.

"Institution" as a term can also mean different types of entities operating according to various laws, policies, norms or practices. Additionally, what do we mean when we say "research?" Do we use a definition from regulatory policy that covers and governs federally-funded research in the United States of America - "systematic

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investigation designed to contribute to generalizable knowledge?" (cf. United States Department of Health and Human Services, 2021a, b, c, d, e, f). Or rather do we mean "research" to encompass more broadly scholarship, inquiry, and other forms of investigation that result in an outcome or other work product or project? As examples, is a student thesis or a metal sculpture a creation that touches on our topic?

For the purposes of this chapter, we will concentrate on those institutional liabilities associated with the research endeavor. Our main –and largely shared experience – is through research development, participation, and regulatory review at a Tier 1 private college in the United States of America. In addition to faculty, staff, post-doctoral fellows, and undergraduate students, our program works with several professional schools and graduate students. Our program and campus include advanced degree programs in business, engineering, nonprofit management, medicine, nursing, dentistry and law school. Each of these disciplines has its own code of conduct and moral and ethical guidelines.

We write from a lens of research compliance – which serves to help manage risk and responsibility across the research spectrum through training, education, review, monitoring, and support. The structure of our office includes not only research compliance, but sponsored projects. In the model in which we work, the core team reports to the vice president for research and technology management. Our team also includes staff dedicated to the licensing and protection of intellectual property through the office of technology transfer.

The central compliance office includes university compliance, export controls, and research liaisons from the general counsel. Other university-wide components that comprise our definition of institution include offices and teams designed to protect people, property, and material resources. The animal resource center and environmental health and safety, including laboratory safety and training, have more direct links to research protections. However, information security and human resources are equally valuable in making sure data stay secure and individuals have the proper education and credentials to conduct research. The institution itself also participates in a variety of voluntary and compulsory external audits and accreditations. Each of these components are pieces of the puzzle we use to manage and provide robust stewardship of the research process.

As we set out to research this topic, we found that there is very little in the way of widely published and available research on the topic of institutional liability in relation to research institutions. The closest we encountered was literature focused narrowly on liability in clinical research (Singh, 2009); Zlotnik et al., 2005) or other specialized topics, such as liability for review and ethics committees (Hoffman & Berg, 2005; McHale, 2005; Onixt & Sterling, 2009). The concept of enterprise risk management from business models had a moment in academia, however, there was apparently a narrower focus on financial audits and controls (Bromiley et al., 2015). We may see a shift in research administration offices as many respond to new and forthcoming challenges of sharing information across administrative functions to respond to engagement in international activities, including research contracts, and welcoming foreign students and scholars to campus in the face of changing regulatory requirements.

What are the Moral or Ethical Issues?

We consider research as a type of social contract [cf. Gibbons, 1999]. From research funding to reporting of funding sources and potential conflicts of interest in presentations and publications, the university and the individuals conducting research and scholarship share these formal and informal obligations with each other and the larger community. Alongside our faculty, staff, and students, we help to take ideas from proposal to publication and serve as stewards of research and scholarship, sponsored or otherwise.

Poorly designed, conducted, or reported research can be considered wasteful – or unethical - even if there are no real harms to persons (Resnik, 2020). Projects that misuse funds and resources, including time and effort, can erode public trust in institutions of higher learning and in the mission of education institutions (Oransky et al., 2021). Lack of transparency and accountability can lead to a lack of trust in the process of scholarship, scientific research and the basic and translational results.

Investigators and institutions have an ethical obligation to facilitate the transfer of knowledge. Research or scholarship that is directly supported by federal dollars comes with all the rights, privileges and responsibilities related to government oversight and accountability (Guerra-Pujol, 2017). The contract requires that institutions have an expansive and robust system of internal controls. At a Tier 1 institution, there may be hundreds of policies and many committees made up of peers and administrators to help investigators navigate the regulatory landscape. This includes regular updates to policy and implementation of processes.

The regulations are the roadmaps we use. The regulatory framework helps us to translate the larger, ethical concerns and moral quandaries into a more systematic process for review and consideration. The forms, questions, and systems with which researchers engage help to establish and document that risks have been considered and addressed by the university and the researcher.

The history and origins of these governing policies in the United States is beyond the scope of this chapter; however, it is important to state that these are rooted in promoting moral and ethical research and scholarship [cf. United States Department of Health and Human Services, 2021a, b, c, d, e, f]. The human subjects regulations were designed to do just that: protect human subjects, including vulnerable populations. The most recent iteration of the governing policies on conflicts of interest requires the lofty and significant ambition for institutions seeking federal funds to promote objectivity in research [cf. United States Department of Health and Human Services, 2021a, b, c, d, e, f]. Research regulations governing animals are myriad and address everything from humane treatment to enrichment [cf. (United States Department of Health and Human Services, 2021a, b, c, d, e, f]. Other chapters in these volumes delve more deeply into these topics and the bioethical dilemmas.

Key in this process, as we will discuss further, is the role of education and professional development of investigators, committee members, and administrators. The ethical mission to promote and develop scholars with a strong ethical grounding is not only required by funding, but an imperative for agents in research

administration. This mission expands beyond the institution and into the broader community. Recent literature suggests that clear, concise, and jargon-free reporting of research can improve not only visibility within a discipline, but also across disciplines (Chawla, 2020).

Liability Concerns – What Are the Risks for Institutions, Individuals, and Ideas?

There is no scarcity of ways in which an academic institution can find itself embroiled in controversy or litigation (Cohen, 1999). The administration of the research enterprise includes the oversight, record keeping, and staffing of many mandatory regulatory committees such as the Institutional Review Board (IRB), the Conflicts of Interest Committee (COI), the Institutional Biosafety Committee (IBC) and the Institutional Animal Care and Use Committee (IACUC). In addition, there are many other issues of research that an institution must address through a clearly defined process for ensuring that regulations are met. These include research misconduct, export controls, intellectual property and laboratory safety inspections and training.

Further, in the current environment of rapidly advancing scientific discovery, there are areas where regulation has not caught up with the risks institutions face, but an institution must nevertheless be prepared to mitigate its liability (Mills & Mills, 2017). Examples include undue foreign influences in research (Fischer, 2021; United States Department of Health and Human Services, 2021a, b, c, d, e, f], as well as the security of electronic data and information (Flagg & Arnold, 2021).

Deficiencies in oversight can result in a variety of real consequences for institutions. Chief among these consequences are direct effects on funding for research from external sources and agencies. The need to return funds to an agency is a common reality that institutions can face. Additional concerns include the potential for increased oversight and audits of grants, decreased awards in the future, and even the temporary halting of all research being conducted by the institution (Cohen, 1999; Hilts, 1999; Marshall, 1999; Matthews, 2000; Wadman, 2001). Negative publicity focused on research conducted at an institution can result in falling national rankings for specific programs, or the university as a whole, diminished alumni engagement, criminal liability for individuals (United States Department of Health and Human Services, 2021a, b, c, d, e, f). The Office of Research Integrity provides numerous examples and case study summaries that demonstrate the potential for overall reputational damage to the institution (cf. United States Department of Health and Human Services, 2021d, e, f).

Entire areas of promising research can be abandoned or subject to a moratorium (Rinde, 2019), and the career path of individuals can be irreparably damaged if needed equipment, supplies and mentorship are no longer available at the institution. (Couzin, 2006).

Discovering the Problem

A report of the occurrence of research non-compliance can be identified from multiple avenues. Ideally, those involved know the correct office or individual to notify when a concern arises. In fact, institutions are generally required to publicize contact information for those in charge of evaluating research concerns. Most institutions also have an integrity hotline that is managed and staffed by an external organization. Individuals within or outside of the institution can use this hotline to report issues of concern about individual or institutional behaviors. These issues include allegations of unethical or illegal behaviors, including shortcomings of regulatory compliance, scientific misconduct, information security breaches, and misuse of research funds. Allegations are then triaged and brought to the component of an institution responsible for review.

This is not, of course, the only way concerns can be identified. Routine review and monitoring of research projects, including funding allocation and spending, as well as review of approved protocols, can also identify areas of concern. Internal or external financial audits can result in the need to work with researchers. Requests for review and additional information can also be initiated by external entities, including government agencies, research sponsors, and media requests.

Evaluating Why Things Happened

When a negative event has occurred, it is important to evaluate the root causes. The liability to an institution is real regardless of the cause, however, mitigation of future risks will vary significantly. Ultimately, we cannot guarantee that negative research experiences will never occur, but it is incumbent on an institution to fully evaluate the situation and plan effectively for better processes in the future (Fig. 26.1).

The initial goals when an institutional risk in research occurs should be focused most carefully on that particular situation. Halting the current risk and determining if there are other continuing risks that need to be addressed will be the essential initial focus. Once the immediate harm is mitigated, it is important for the institution to look into the circumstances that allowed the lapse to occur. This should involve a thorough review that documents step-by-step what happened, noting what institutional processes and procedures exist that should have controlled the situation, identifying where lapses exist, and ultimately determining where responsibility should be placed.

The need to follow both institutional policy and federal regulations, where applicable, will guide how exactly the assessment is completed. Most institutions have clearly defined processes for investigating wrongdoing. The most effective protection for an institution is to precisely follow the investigatory path that is outlined in internal documentation. Critical elements to the process should include a thorough, well-documented, in-depth evaluation of credible concerns and strict adherence to

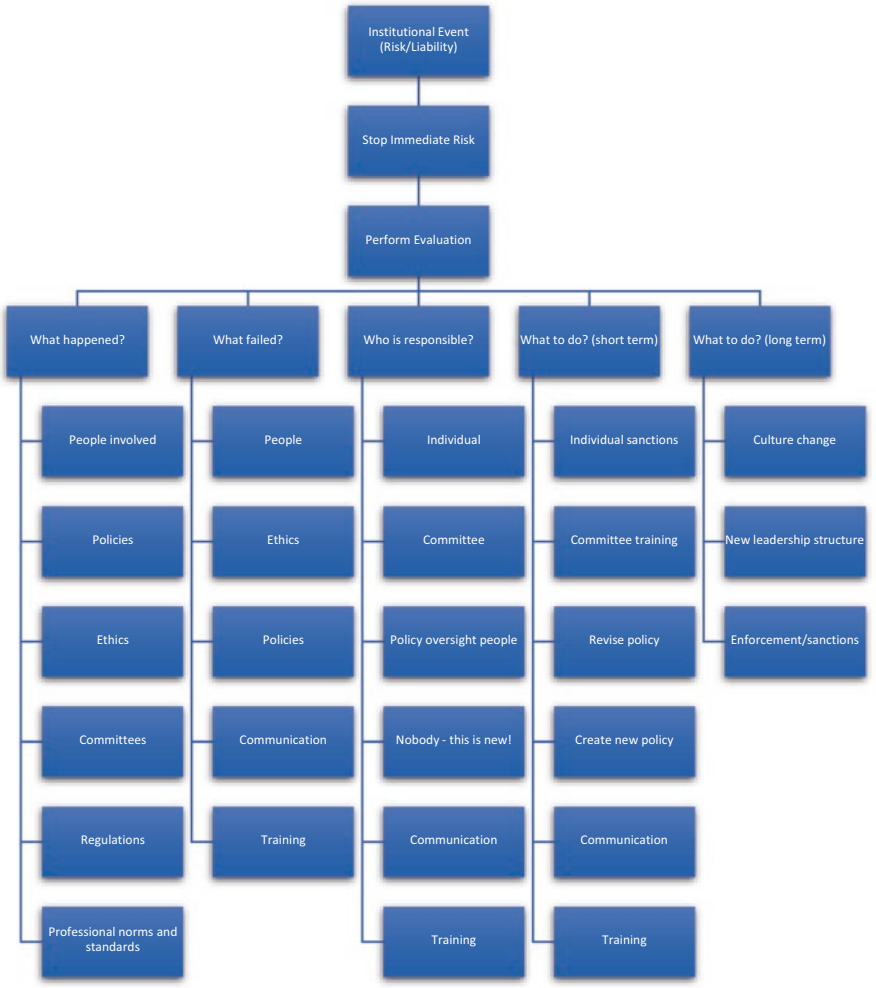

Fig. 26.1 Institutional liability evaluation graphic

any confidentiality statutes. Issues that are not properly addressed or investigated will almost certainly not resolve themselves, and there is an increased chance that a similar event will occur again in the future.

Once the institutional process and investigation have been completed, the institution will need to consider two areas of correction. The first is to put in place the needed changes that will address the specific problem that occurred. Then leadership will need to look at the issues identified more globally and determine what must be done to address the root causes that allowed the problem to occur in the first place. We will dig into these assessments in the following sections.

Mitigation of Situation-Specific Issues

If a review has merit and an investigation moves forward, a key element will be determining responsibility. Both the individual and the institution are under review regarding root causes and where processes failed and/or could be improved. Was the behavior intentional, unintentional, or is it unclear (Haven et al., 2021)? When an individual is found at fault, the root cause of the lapse should become clear through the investigation. Those involved in substantiated allegations of non-compliance should face some degree of sanction. Sanctions against individuals can be severe and commensurate with the degree of harm. Research may be immediately halted or suspended, contracts may be terminated, and debarment from funding or conducting specific types of research can occur. Separation from the institution is a possibility. In extreme scenarios, there may be individual or institutional fines, repayment of funds, and/or jail time.

At the very least, a review will recommend additional education or retraining to recommit to the regulatory and research rules. There may also be added oversight or additional reporting of results. Renewal of a protocols may be required more frequently, such as a 6-month renewal cycle as opposed to annual.

Many times, the education and training components are managed within the institution. These are opportunities for individuals to take corrective measures and participate in additional training sessions to reacquaint themselves with policy and best practices. Investigators may also be referred to additional training related to coaching, management, review of human resources policies or procedures, depending on the nature of the case and resolutions suggested by the review process. Often, such requirements are in addition to the routine mandatory training for specific areas of research.

Investigators may also be required to participate in additional remediation. One program that is widely known and well-respected is the P.I. Program, which operates out of Washington University in St. Louis (P.I. Program, 2021). The program provides professional training in research and research integrity. Elements of the program include leadership, mentoring, and coaching with the goal of helping researchers to be more effective communicators and decision makers. As previously mentioned, miscommunication and mismanagement can be contributing causes for concerns or misconduct in research.

Institution-Wide Improvements

Now we shift our focus from the specific incident and individuals involved to a global, institution-wide evaluation of the research concern. For example, we might consider whether an event is the result of a lapse in the research process, a research integrity issue, or some other type of problem that requires a comprehensive

solution. This will determine the pathway for review at the institutional level and what committee or committees will need to review, evaluate, or participate in the process.

All reviews include interviews and analysis of data, as well as a written report with recommendations. Those conducting investigations should be sure to delve deeply into whether the organization's units have effectively communicated their policies, practices and expectations effectively to researchers. It is also important to be sure that committees, schools, departments and individual faculty members gave clear and proper guidance and instruction. In addition, the quality of training and mentoring should be evaluated.

Once areas for improvement have been identified, it is essential that the institution deploy resources so that the necessary steps can be taken to mitigate future risks. Possible considerations are the need to create a new department or division, an increase in support or administrative compliance staff, policy revisions, and enhanced training (Pizzolato & Dierickx, 2021), mentoring, and leadership programs for faculty.

The authors recognize that this approach may seem aspirational and unrealistic. However, we believe that without sustained and supported organizational change in response to ethical violations, institutions are destined to have continued liability.

Mitigating Risk with Emerging Issues

Providing a safety net of general ethical guidance that addresses emerging ideas, research, and technology is a final concept to consider. Institutions need to be prepared to nimbly handle novel issues that can create significant institutional liability. Specific policies and regulations that would provide guidance on concerns around new technologies and procedures may not yet exist, however, institutions must create a culture and structure that allows for appropriate reflection and assessment of risks before any action is taken that could endanger research subjects or the institution. This is particularly difficult in research organizations where the faculty are motivated, innovative, creative, and competitive.

Overarching guiding principles that insist on ethical behavior by all members of the community can be helpful. A culture of integrity must be visible and prevalent, and it must permeate every level of leadership and every laboratory, department, school and center. Formal education and community-wide distribution of important policy and procedural standards, as well as resources and contact information, is also key. Structured, low-stakes opportunities for faculty, staff, students and postdoctoral scholars to consider and discuss in small groups how they might handle an ethically-charged situation can also be an incredibly valuable way to enhance the culture at an institution. Finally, there can be no greater influence on culture than that of individual mentors who are properly informed, ethically guided, and effective at communicating.

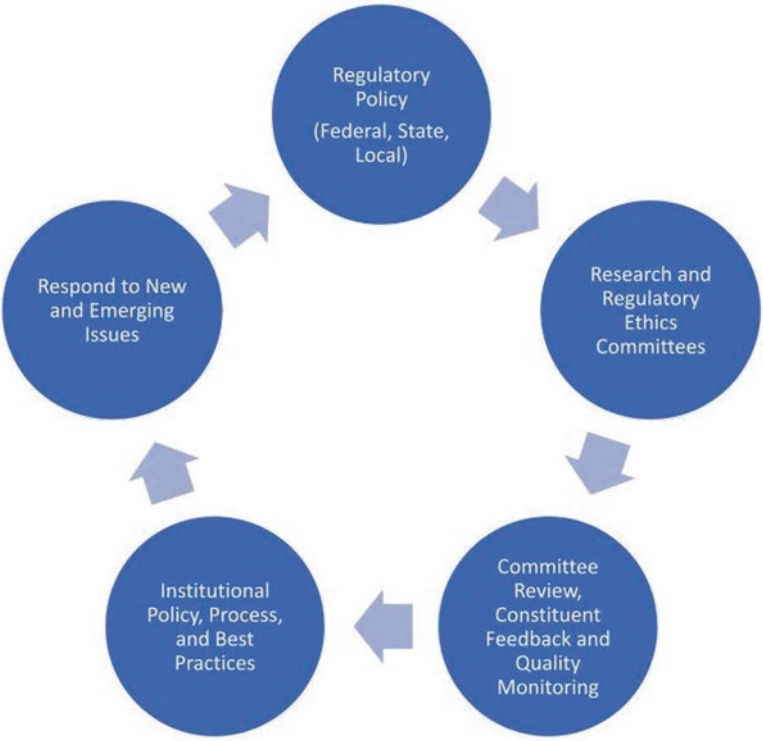

Fig. 26.2 Administrative structure – continuous process improvement

Collectively, a North Star ethics statement, a practiced culture of integrity, formal training, and the ready availability of resources, contact information and good mentoring combine to create an ideal environment where issues can be discussed, debated, and considered so that good, ethical decisions are most likely. Where such a culture exists, institutional liability in the research setting will be minimized (Fig. 26.2).

Institutional Liability Assessment Tool

The purpose of these volumes is to provide researchers and committees with guidance that can be helpful for them to make decisions and deliberate in practical scenarios. To that end, we have created an assessment tool to facilitate considerations when an unfortunate event occurs at an institution. Rather than a "checklist" of things to do, this is intended to enhance conversations and spark discussions that start with ensuring the immediate risk is halted and culminate with contemplating what larger, system-level improvements should be made.

The Institutional Liability Assessment Tool includes three stages. First is a thorough evaluation, followed by situation-specific mitigation, and finally, institution-wide improvements. A version of the tool appears at the end of this chapter heading. Institutions are free to use this tool as a guide, but the tool is not meant to be comprehensive and it cannot capture the nuances of individual institutions. Informed leaders will need to consider how the questions presented in the Institutional Liability Assessment Tool will apply at their institution.

Of additional benefit is the opportunity to test how the tool can be used by applying it to hypothetical situations. The examples below can be used in a group setting, or by an individual, to practice how they might handle each situation if it occurred at their institution.

Example 1: A researcher has published a paper that draws conclusions counter to the University's mission.

Example 2: Research is published that allegedly includes falsified figures.

Example 3: Research is conducted without IRB approval, and subjects are harmed as a result.

Example 4: New technology created and owned by the university is usurped by an outside entity.

Example 5: Regulators announce publicly that they have found fraudulent billing activity in the institution's research enterprise.

Example 6: It is alleged that animals used in research were mistreated.

Example 7: There is potential evidence that a faculty member has bullied and sexually harassed members of their research group across several years.

Example 8: It is discovered that a researcher has a significant outside interest that was not previously disclosed to the institution.

Example 9: Research is published that does not disclose accurately author affiliations and conflicts of interest.

Institutional Liability Assessment Tool

UPON DISCOVERY OF EVENT

- Is there credible evidence of an event?
- What activities need to be halted immediately?
- What individuals/offices need to be informed about the event?
- What committees need to be informed about the event?
- Are there external entities that need to be consulted or informed?
- Is there a need to gather documentation so that it is preserved?

EVALUATION.

Gather information:

- Who was involved and who should be interviewed about the event?

- What committees had oversight?
- What institutional policies govern the incident?
- What national/external/funding policies and regulations govern the incident?
- What professional/societal standards are involved?
- What documentation needs to be gathered about the incident/event?

Determine where the breakdown(s) occurred:

- Were required approvals obtained to complete the activity?
- Was the approval process thorough and valid?
- Were there ethical violations?
- Should personnel have received required training related to the incident?
- Were personnel aware of the rules/risks/policies/procedures?

Determine who is responsible:

- Was there an individual, intentional lapse of judgement?
- Did personnel complete required training?
- Were individuals aware of their responsibilities?
- What role did supervision, or lack thereof, play in the incident?
- Was committee documentation and communication effective?
- Were individuals given incorrect information? If so, by whom?
- Are policies governing the incident clear and directive?

SITUATION-SPECIFIC MITIGATION

- Should any individual be sanctioned?
- Should committees receive training related to this event?
- Should policies be revised due to this event?
- Should specific communication about this event be distributed?
- Should any individual or group undergo required training/re-training?
- Will there be institutional sanctions (i.e., paying back grant funds)?
- Will the institution be at risk for reputational damage?
- Is there a requirement for notification to the community?

INSTITUTION-WIDE IMPROVEMENT

- Was the event reported in a timely and confidential manner?
- Has this happened in other areas? Is this an isolated event?
- Is there a need to better communicate standards? If so, by whom?
- Is there a need for enhanced education of personnel?
- Should a new or revised policy be implemented?
- Should a new leadership structure or development of a new office or department be established?

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Chapter 27
Research Assessments Should Recognize Responsible Research Practices. Narrative Review of a Lively Debate and Promising Developments

Noémie Aubert Bonn and Lex Bouter

Abstract Research assessments have been under growing scrutiny in the past few years. The way in which researchers are assessed has a tangible impact on decisions and practices in research. Yet, there is an emerging understanding that research assessments as they currently stand might hamper the quality and the integrity of research. In this chapter, we provide a narrative review of the shortcomings of current research assessments and showcase innovative actions that aim to address these. To discuss these shortcomings and actions, we target five different dimensions of research assessment. First, we discuss the content of research assessment, thereby introducing the common indicators used to assess researchers and the way these indicators are being used. Second, we address the procedure of research assessments, describing the resources needed for assessing researchers in an ever-growing research system. Third, we describe the crucial role of assessors in improving research assessments. Fourth, we present the broader environments in which researchers work, explaining that omnipresent competition and employment insecurity also need to be toned down substantially to foster high quality and high integrity research. Finally, we describe the challenge of coordinating individual actions to ensure that the problems of research assessments are addressed tangibly and sustainably.

Keywords Research assessment · Research culture · Research environment · Research integrity · Research careers

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Abbreviations

ACUMEN	Academic Careers Understood through MEasurement and Norms
CRediT	Contributor Role Taxonomy
DARE	Diversity Approach to Research Evaluation
DORA	San Francisco Declaration on Research Assessments
EOSC	European Open Science Cloud
EQUATOR	Enhancing the Quality and Transparency Of health Research
EUA	European University Association
FAIR	Findable, Accessible, Interoperable, and Reusable
FOLEC	Latin American Forum for Research Assessment
HRB	Health Research Board Ireland
IDRC	International Development Research Centre
ISE	Initiative for Science in Europe
IUPIU	Indiana University – Purdue University Indianapolis
KNAW	Royal Netherlands Academy of Arts and Sciences
NFU	Netherlands Federation of University Medical Centres
NOW	Dutch Research Council & Institutes
ORCID	Open Researcher and Contributor ID
OS-CAM	Open Science Career Assessment Matrix
RQ+	Research Quality Plus
SOPs4RI	Standard Operating Procedures for Research Integrity
UCU	University College Union
VSNU	Association of Universities in the Netherlands

Brief Introduction to Research Assessments

Throughout their careers, researchers will face dilemmas and need to make decisions regarding the ethics and the integrity of their work. Earlier chapters in this volume illustrate the substantial challenges and dilemmas involved and the impact that researchers' decisions can have on research, knowledge, and practices. But decisions are not limited to research practices, they also need to be made about researchers themselves. Deciding which researchers should receive grants, which are allowed to start a career in academia, which are promoted, and which obtain tenure are complex issues that shape the way in which research systems operates.

In this chapter, we provide an overview of the complexities of research assessments. More specifically, we provide a critical overview of the problems that current research assessments generate and showcase innovative actions that are introduced with a view to improve the process[1]. We start by briefly introducing research

[1] Note that this chapter was submitted in the summer of 2021. Given the speed at which initiatives in research assessment are moving, we recognise that this chapter fails to include important recent developments, including the Agreement on Reforming Research Assessment and the Coalition for

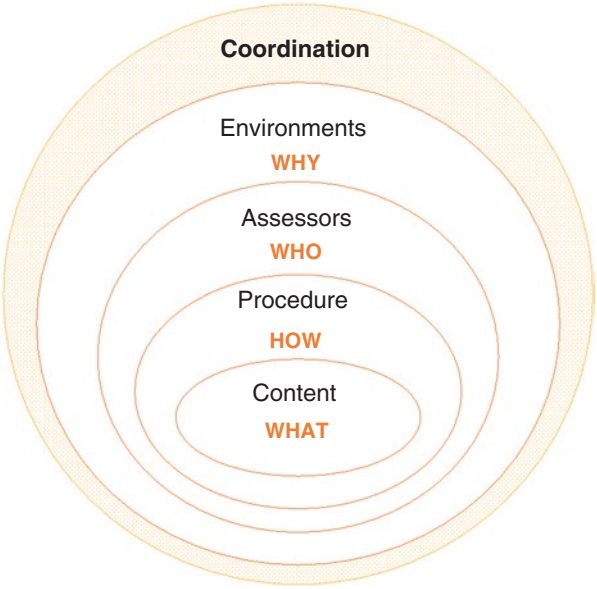

Fig. 27.1 The five dimensions of researcher assessments addressed in this chapter

assessments[2] and the debate on whether they are fit for purpose. We then discuss problems of research assessments on five different dimensions: the content; the procedure; the assessors; the environments; and the coordination between these dimensions (Fig. 27.1).

Research assessments entail important decisions about what matters (i.e., what should be valued in academic careers and research outputs), about who decides what matters, and about how what matters can be measured. In addition to the inherent complexity, the decisions needed for research assessments depend on several stakeholders with their own distinct interests. Given the profound complexity, the high stakes, and the many actors involved in such decisions, it is no surprise that research assessments raise substantial controversies. Before introducing the problems and latest innovations in research assessments, we thought that it may help to provide a quick historical snapshot of the evolution of the discourse. This historical snapshot is high-level initially, but we will detail and document each point in greater depth throughout this chapter.

Advancing Research Assessment linked to it, the Future Research Assessment Programme in the UK, numerous advances in piloting narrative CVs, and other core initiatives which gained momentum after the chapter was drafted.

[2] Throughout this chapter, we use the term 'Research assessment' interchangeably to refer to the assessment of researchers, research teams, research institutes or research proposals. Given that the term 'research assessment' is most commonly used in current discussions to describe the process through which research resources — be it funding, hiring, recognition, tenure, or promotions — are distributed, we used this term in its broad, interchangeable sense throughout this chapter.

Scientists have scrutinised the attribution of success in academic research for well over half a century (Hagstrom, 1975; Merton, 1957; Zuckerman & Merton, 1971), yet we can pin the beginning of the debate on research assessments on the 1980's, when the growing investments in research led to a substantial growth of the academic workforce (Alberts et al., 2015). This growth introduced a stronger need for fair distribution of research resources, for example in funding allocation, hiring, tenure, and promotion. Publication metrics which had made their appearance some years earlier – namely publication counts, the H index, citations counts, and journal impact factors – started being used in research assessments as an opportunity for broad scale, rapid, and comparative research assessment that provides a greater sense of objectivity than traditional peer-review qualitative assessment (Gingras, 2016). Quite rapidly however, it became clear that the newly adopted metrics influenced the publication practices of researchers also in less desirable ways. Early metrics focused on quantity, for instance by using the number of scientific papers researchers published as an indicator of success. This focus on quantity invited high volumes of lower quality scholarly outputs (Butler, 2003). To address this problem, journal impact factors and citation counts started being used in assessments, asking researchers to place impact before volume. This change had the desired effect and redirected the scholarly output towards prestigious high impact journals (Larivière & Sugimoto, 2018a). With occasional exceptions, assessors and researchers overall appeared to be satisfied with the new methods until the early 2000's. The beginning of the twenty-first century brought with it a vivid interest in meta-research, research integrity, and bibliometrics. Researchers started understanding that research was vulnerable to misconduct and inaccuracies (Ioannidis, 2005; Martinson et al., 2005), and that research assessments could influence research in harmful ways (Abbasi, 2004). Not only did impact-metrics influence the types of research being done, but they also made research move away from important integrity and quality aspects such as reproducibility and open science (Moher et al., 2018). At the same time, researchers were growing more aware of the high pressure and highly competitive environment they worked in and the impact this had on their work (Anderson et al., 2007; De Vries et al., 2006). Consequently, researchers and research communities joined forces to address these challenges and in started demanding change in the way in researchers are assessed.

The San Francisco Declaration on Research Assessments (DORA; American Society for Cell Biology, 2013), The Metric Tide (Wilsdon et al., 2015), and the Leiden Manifesto (Hicks et al., 2015) were among the first key documents to specifically address and raise awareness on the faults of the current assessment. Mostly focused on metrics, these pioneer works were then followed by position statements from numerous groups and organizations who broadened the issue towards research climates, research careers, and research integrity. In Table 27.1, we showcase a selection of position statements and documents from general and broad-reaching groups. The 11 documents displayed in Table 27.1 are only a tiny selection of the booming number of positions papers, initiatives, perspectives, and recommendations now available from different research institutions, research funders, learned associations, and policy groups. Consequently, it would be fair to say that the debate on research assessments has reached strong momentum, and that substantive changes likely are underway.

Table 27.1 Selection of position statements specifically addressing research assessments

Year	Issuing organization	Title
2013	American Society for Cell Biology	San Francisco Declaration on Research Assessments (American Society for Cell Biology, 2013)
2013	eLife	Reforming Research Assessments (Schekman & Patterson, 2013)
2013	Science in transition	Why science does not work as it should and what to do about it (Dijstelbloem et al., 2013)
2015	Higher Education Funding Council for England	The Metric Tide (Wilsdon et al., 2015)
2015	Centre for Science and Technology Studies	The Leiden Manifesto (Hicks et al., 2015)
2018	Global Young Academy	Publishing models, assessments, and open science (Global Young Academy, 2018)
2018	Moher et al.[a]	Assessing scientists for hiring, promotion, and tenure (Moher et al., 2018)
2019	European Universities Association	Reflections on University Research Assessments – Key concepts, issues and actors (Saenen & Borell-Damián, 2019)
2020	Science Europe	Position Statement and recommendations on Research Assessment Processes (Science Europe, 2020)
2020	World conferences on Research integrity	The Hong Kong Principles for assessing researchers: Fostering research integrity (Moher et al., 2020)
2020	Research on Research Institute	The changing role of funders in responsible research assessment: progress, obstacles and the way ahead (Curry et al., 2020)
2020	Latin American Forum for Research Assessment (FOLEC)	Towards a transformation of scientific Research assessment in Latin America and the Caribbean series (Latin American forum for Research assessment (FOLEC), 2020a, 2020b, 2020c)
2021	European Open Science Cloud (EOSC) Co-Creation projects	Draft vision for FAIReR assessments (European Open Science Cloud, 2021)

[a]Moher et al. (2018) references several additional papers that address research assessments

Problems and Innovative Actions

Changing research assessments is a complex endeavour that requires multiple stakeholders, coordination, and finetuning. In the following sections we introduce a selection of key problems with current research assessments and describe a number of promising actions currently taken to address these problems and improve research assessments.

Problems with research assessments can happen on several interconnected dimensions, some of which are incredibly difficult to tackle. As a starting point, it is essential to address problems with the indicators and the approaches contained in the assessments themselves. But although the *content* of assessments is a necessary starting point for tackling assessments, it is not the only dimension that needs to be

addressed to fully make research assessments fit for purpose. The *procedure* followed and the *assessors* responsible for assessing researchers are also important in enabling changes. Even if the indicators, the procedure, and the assessors are optimal, the research culture plays an additional role in ensuring that changes to research assessments indeed improve the practices and decisions of researchers. Consequently, the *environment* in which researchers work, albeit complex and difficult to address directly, also needs a place in initiatives that aim to change assessments and help foster better research. Finally, a good *coordination* of efforts is needed to ensure that the changes are profound, coherent, and sustainable.

In the following section, we describe key problems and innovative action on the *content*, *procedure*, *assessors*, *environments*, and *coordination* of research assessments. Table 27.2 summarizes the main points addressed.

Table 27.2 Frequent challenges in research assessments and examples of initiatives to improve research assessments

	Problems	Examples of initiatives
Content	**Exaggerated emphasis on outputs**	**Diversify spectrum of indicators** Open science badges; Publons, ORCID, open peer review; CRediT; Reporting guidelines (EQUATOR Network) **Use assessment models that consider broader activities** ACUMEN; OS-CAM
	Quantity over quality	**Limit the number of outputs considered** Swap full publication lists for a limited number of key accomplishments (e.g., Cancer research UK)
	Inappropriate use of metrics	**Raise awareness and mobilize for action** DORA; Leiden Manifesto; The Metric Tide; Hong Kong Principles **Combine metrics with human input** Diverse examples are available in the repository '*Reimaginging academic assessment: Stories of innovation and change'* developed by DORA in collaboration with EUA and SPARC Europe **Enable research to find better ways to assess researchers** Open Science Policy Platform (e.g., Working Group on Rewards; Expert Group on Indicators; Mutual Learning Exercise on Open Science – Altmetrics and rewards) **Use more comprehensive metrics** Altmetrics, PlumX
	Narrow views of impact	**Consider a broader spectrum of impact (e.g., societal impact)** More comprehensive metrics (see above); RQ+ **Allow more open and personal descriptions of impact** Narrative CVs and portfolios (e.g., UK Royal Society Resumé for researchers, Health Research Board Ireland; Dutch Research Council; Swiss National Science Foundation)

(continued)

Table 27.2 (continued)

	Problems	Examples of initiatives
	Obstacles to diversity	**Broaden diversity and inclusion policies** Athena Swan; Policies in hiring and promotion; IUPUI recognition of equality, diversity, and inclusion activities in tenure and promotion **Ensure greater granularity of research contributions and team dynamics** CRediT; DARE **Allow more diversity of academic profiles** Open University UK diversification of career paths; Ghent University new career track; Dutch Recognition and Reward Programme **Enable team recognition** Dutch Spinoza and Stevin prizes
Procedure	**Assessment time and resource involvement**	**Reduce the resource involvement needed to review applications** Post peer-review lottery (i.e., allocating grants randomly after initial quality check) **Reduce the frequency of assessments** Longer-term funding; Fewer in-career assessments e.g., Ghent University
Assessors	**High potential for biases**	**Enlarge diversity of assessors' profiles** Science Europe recommendations on research assessments; Obtain 360° input from colleagues **Avoid biasing elements** Avoid adding the applicant's photo to the applications; Move the biography to the end of applications **Train assessors to minimize biases** Tampere University; HRB Ireland; 'Room for everyone's talent'
	Unclear terminology and undefined abstract concepts	**Clearly define the terms used in assessments (e.g., excellence, impact)** Dutch Recognition and Reward Programme, Norway Universities
Environments	**Career instability and Hyper-competition**	**Raise awareness** ISE Position on precarity of academic careers; Camille Noûs; UK UCU strikes **Help researchers have a more secure salary** Swedish Regeringskansliet initiative
	Environments not conducive to integrity	**Help institutions create healthier research environments** SOPs4RI European Commission project
Coordination	**Lack of coordination and harmonization between stakeholders**	**Call for more responsible assessment practices** European Commission's 'Towards 2030' vision statement; European Commission Open Science Policy Platform **Make funding contingent on responsible assessments** Wellcome UK **Combine efforts** Dutch Recognition and Reward Programme; FOLEC; Universities Norway; Responsible Research Network Finland

Note: The initiatives presented in this table are detailed and documented throughout the text. Abbreviations are explained in the Abbreviation section

Content

Reflection on research assessments should necessarily start with the elements of researcher's professional behavior that are assessed and their impact on the quality and relevance of research. Understanding the problems with the core elements that are used within research assessments is an important starting point to better understand what needs to change.

The problems related to the content of research assessments are too numerous to be able to cover in a book chapter. For simplicity, we selected five key issues that we believe play an important part in the current discourse on research assessments: i) the exaggerated focus on research outputs; ii) the valuation of quantity over quality; iii) the inadequacy of currently used metrics; iv) the narrow definitions of impact; and v) the obstacles current research assessments impose on diversity.

An Exaggerated Focus on Research Outputs

The Problem When looking at research assessments in practice, it is clear that these depend almost exclusively on research *outputs*, most notably on scholarly papers published in international peer-reviewed journals.[3] This focus on outputs has nothing surprising. Considering that a large proportion of research is funded by public investments, it is natural to expect that researchers generate products (in this case research reports) that will ultimately enable tangible benefits for society. Yet, the way in which research outputs are currently measured is problematic in a number of ways.

For one, the exaggerated emphasis on *research outputs* means that current assessments are oblivious to most of researchers' commitments. Publishing papers, as important as it is, is far from the only activity researchers spend their time and efforts on (Ziker, 2014). Teaching and providing services — the two other pillars of academic careers — and other essential tasks such as mentoring, reviewing or team contributions almost always take second place or are even ignored in research assessments (Schimanski & Alperin, 2018). And within the pillar of 'research', many activities and processes that would provide invaluable information on how the research is conducted are largely ignored from current output-oriented assessments, creating a culture "that cares exclusively about what is achieved and not about how it is achieved" (Farrar, 2019). For example, the detailed methods, the approaches, the specific contributions, or the translation of research in practice are rarely considered in research assessments (Aubert Bonn & Pinxten, 2021b). This lack of

[3] Although research papers are now the most common output currency for career advancement in academia, other indicators such as patents, books, or conference proceedings are also being used in different disciplines. Nevertheless, scholarly papers are dominating the assessment even in disciplines in which they were not common decades ago and in which they have a limited relevance for the transmission of knowledge.

consideration for research processes risks losing sight of important procedural concepts thought to be highly important in advancing science, such as quality, integrity, and transparency (Aubert Bonn & Pinxten, 2021a).

Innovative Action In the past few years, there has been an increasing awareness that linking research assessments almost exclusively to research outputs may be problematic (Farrar, 2019). Principle 5 of the Hong Kong Principles, and recommendations 3 and 5 of the DORA directly address this issue, stating that a broader range of research activities should be considered in research assessments. One concrete initiative which may be a first step in solving this problem is the provision of greater visibility to a range of activities that are part of researchers' daily tasks. The Open Science badges — registration, open data, open materials — are a good example of a simple change that allows readers or eventually assessors to quickly capture open science practices behind published works (Kidwell et al., 2016). The presence of reporting guidelines, such as those available on the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) Network (EQUATOR network, n.d.) can also summarize details and procedures and provide information on the transparency and reproducibility of the work. The increasing availability of open and transparent peer-review and initiatives that provide visibility of peer-review commitments such as Publons (Publons, n.d.) or ORCID (Open Researcher and Contributor ID) (ORCID, n.d.) are other examples that can help enrich the indicators used to assess researchers. The Contributor Role Taxonomy (CRediT) which provides more information on the roles, and responsibilities that researchers take is another example we will discuss further in Sect. 27.2.1.5 (Alperin et al., 2019; CASRAI).

Broader indicators are increasingly visible in more formal assessments procedures. For instance, the Academic Careers Understood through MEasurement and Norms (ACUMEN) portfolio provides a template that considers indicators from a very diverse array of activities (European Commission, 2019). While the ACUMEN remains largely quantitative, its broad coverage of research activities is a good reminder that assessments can be much more comprehensive. The European Commission's Open Science Career Assessment Matrix (OS-CAM) is a similar model of assessment that includes a broad array of research activities such as teaching, supervision and mentoring, professional experience and even has an explicit section on research processes (European Commission, 2017). We will discuss other ways of broadening assessments such as narrative CVs and portfolios in Sect. 27.2.1.4.

Quantity Over Quality

The Problem Another important problem of researcher assessments is their tendency to value quantity over quality. Many researchers feel encouraged to publish as many papers as possible and are sometimes offered tangible incentives such as financial rewards to publish more (Hedding, 2019; Muthama & McKenna, 2020). Assessing researchers on the number of published papers does indeed lead to more publications, but it tends to do so at the detriment of research quality (Butler, 2003;

Moed, 2008). It can also encourage questionable research practices such as 'salami slicing' — "the spreading of study results over more papers than necessary" (Embassy of Good Science, 2021) — and can tempt researchers to favour journals where acceptance rates are high rather than journals suited for their work or journals with thorough peer-review procedures. Unsurprisingly, the longing for quantity also works in favour of predatory publishers and paper mills whose business model is targeting authors desperate to publish regardless of quality (Hedding, 2019; Vogel, 2017).

To address this problem, research and funding institutions are increasingly modifying their assessment procedures to focus on impact rather than on quantity. Nevertheless, the impressive numbers of peer-reviewed publications or books that are very often stated in researchers' biographies reminds us that productivity is still considered an important indicator of accomplishment within the research community and the research culture. Quantity indicators also remain key to institution-level assessments; a point we will discuss further in the Coordination section.

Innovative Action The obvious solution to reduce the focus on quantity should be to look more at quality. But even though ways to assess quality are starting to pierce, the endeavour is a bit more complex that it may seem. For example, Eyre Walker and colleagues showed that, when scientists assess a published paper without knowing the journals in which the paper was published, they are generally inconsistent and unable to judge its intrinsic merit or to estimate the impact factor of the journal in which the paper was published (Eyre-Walker & Stoletzki, 2013). However, assessing quality of publications is not the only way assessments can deviate from quantity indicators. In the past few years, several research and funding institutions diverted assessments away from quantity by asking researchers to select only a subset of their work — generally three to five key accomplishments or contributions (e.g., publications, events, changes in practice, committee participation, etc.) — and to describe why these accomplishments matter (see for example (Cancer Research UK, 2018)). Focusing on a limited number of outputs enables a more in depth assessment which is likely to refocus the assessors' attention away from quantity towards content, meaning, and quality.

Inappropriate Use of Metrics

The Problem As we mentioned above, most research assessments swapped volume-metrics for impact-metrics to incite researchers to publish in more prestigious journals. Among those, the journal impact factor, citations count, and the H-index raise important challenges.

Of all impact-informed metrics available, the journal impact factor is probably the most widely used in current research assessments. In a review of their use in North American academic review, promotion, and tenure document, McKiernan and colleagues found that 40% of research intensive institutions explicitly mention

journal impact factors (McKiernan et al., 2019). The journal impact factor of a given year is the ratio between the number of citations received in that year for publications in that journal that were published in the two preceding years and the total number of "citable items" published in that journal during the two preceding years. (Larivière & Sugimoto, 2018b; Wikipedia, 2021). The journal impact factor was designed to help librarians select the journals they should subscribe to, but it was never intended to influence researcher evaluations. On the contrary, Eugene Garfield — widely known as the father of journal impact factors — explicitly warned against using journal impact factors for assessing individual scholarly articles (Garfield, 1998). Nevertheless, the seductive power of a single metric that would allow to quantify the 'value' of journal articles quickly won over research assessments. Unfortunately impact factors introduced substantial problems of their own. First, the mere fact that journal impact factors became recognized as a measure of success reduced their objectivity as a measure of success; a phenomenon known as Campbell's law (Hatch & Schmidt, 2020). In fact, journal impact factors incite strategic responses from researchers, many of which are now considered to be questionable research practices. These include among others selective reporting, 'spin', p-hacking, HARK-ing (hypothesizing after results are known) and non-publication of negative results (de Rijcke et al., 2015; Gingras, 2016; Larivière & Sugimoto, 2018a; Wouters, 2014). Journal impact factors further suffer from fundamental weaknesses that allow them to be gamed relatively easily (Ioannidis & Thombs, 2019).[4] In addition, impact factors are a journal-level metric and are therefore not a valid measure for the impact of individual papers or of the authors of that paper. Indeed, the distribution of citations in a journal tends to be so skewed that impact factors provide little information on the number of citations individual papers in that journal can expect (Brito & Rodriguez-Navarro, 2019; Larivière et al., 2016). Finally, by the way journal impact factors are calculated, they ignore slow citation (i.e., citations two or more years after publication), thereby potentially bias against innovative research (Schmidt, 2020). Despite these fundamental flaws, journal impact factors are still widely used in researcher assessments and are frequently described as an indicator of the quality of individual research papers (Aubert Bonn & Pinxten, 2021b).

Without even entering the colossal debate on the relationship between citation metrics and research quality, it may be relevant to consider the actual number of citations which are also frequently used in researcher assessments despite the fact that these require more time to accumulate. Citations are problematic in different yet connected ways. To begin, numbers of citations provide no information on the reasons a paper is cited. Citations used to provide background information, to build

[4] From these problems, we can mention the unequal citation practices for different topics or article types as well as the imbalance between the numerator — which contains all citations to a journal for the given years — and the denominator — which only contains the number of 'citable items', and thereby excludes editorials, commentaries, news and views, and other items that are increasingly taking predominance in high impact factor journals (Ioannidis & Thombs, 2019; Larivière & Sugimoto, 2018a).

an argument, to support a theory, to raise a problem, or to criticize a paper all count in the same way (Larivière & Sugimoto, 2018b). Citations can also be manipulated, for example through peer-reviewer or editor requests, or by forming citation cartels (Baas & Fennel, 2019; Fong & Wilhite, 2017). They are also prone to biases unrelated to the intrinsic merit of a paper (Urlings et al., 2021). And finally, direct citations are often only partially and sometimes not at all supported by the cited article, suggesting that researchers often cite papers without reading or even downloading them (Drake et al., 2013).

The H-index — or Hirsch Index for its inventor Jorge E. Hirsch — is another indicator that is frequently used in research assessments. The calculation is quite simple: a researcher has an h-index of x when she or he published at least x papers which were cited at least x times each. In other words, the h-index combines impact and productivity to provide information at an individual level. Nonetheless, the H-index is also strongly criticized. First, the misleading simplicity of a single number to judge researchers is already problematic, especially when comparing researchers from different fields of expertise. Furthermore, although the H-index combines paper and citation counts, it will never be higher than the total number of papers a researcher has published, regardless of the number of citations these papers have (e.g., a researcher with 10 papers cited 10 times each will have a higher H-index than a researcher with 9 papers cited 100 times each) (Larivière & Sugimoto, 2018b). Similarly, as an ever-growing metric, the H-index provides senior researchers with a clear advantage that makes them largely invincible when compared to junior researchers, even after they stop being active in research. Jorge E. Hirsch himself stated that the H-index could "fail spectacularly and have severe unintended negative consequences" (Hirsch, 2020, p. 4), and several metrics experts have deemed it inappropriate in measuring researcher's overall impact (Waltman & van Eck, 2012). Despite all this, the H-index continues to be used often in research assessments.

Although many other metrics exist, the journal impact factor, citation count, and H-index are the three most frequently used in researcher assessment. On top of their individual flaws, an overarching criticism of these metrics is that they fail to capture the core qualities they aim to measure. More specifically, while several institutions use these metrics as a proxy to assess the quality and impact of the work (McKiernan et al., 2019), they provide very little information that could be validly interpreted as *quality* or *impact* (Aubert Bonn & Pinxten, 2021b). Instead, these metrics provide information on the visibility, the attention, and the citation patterns within academia (Larivière & Sugimoto, 2018b; Sugimoto & Larivière, 2018). Garfield himself qualified citations as an indicator of "the utility and interest the rest of the scientific community finds in [the work]" (Garfield, 1979, p. 372), not as a measure of quality. Knowing that impact-informed metrics are even believed to "*discourage rigorous procedures, strict replication/confirmation studies and publication of negative, non-statistically significant results*", it is important to rethink how we use — or at least interpret — impact metrics (Lindner et al., 2018).

Once again however, reinterpreting the role of impact metrics on research assessments requires changes at the core of research communities. Researchers who have

spent decades building a career on inadequate indicators may find it daunting to give up their high rankings to adopt a new system in which they may rank less excellent or even poorly. Increased awareness, discussion, and mobilisation are still needed.

Innovative Action The Declaration on Research assessments (DORA, 2021) strongly advocates against using the impact factor in individual research evaluations,[5] supports the consideration of value and impact of all research outputs, and argues that evaluations of scientific productivity must be transparent and explicit. Along the same line, the Leiden Manifesto and The Metrics Tide pledge for the development and adoption of better, fairer, more transparent and more responsible metrics (Hicks et al., 2015; Wilsdon et al., 2015). These three initiatives, recently joined by the Hong Kong Principles for assessing researchers (Moher et al., 2020), play a crucial role in raising awareness about the shortcomings of widely used research metrics. Awareness is only the first step towards actual change but these initiatives have brought together a community that supports the change. DORA already has nearly 20,000 signatories — over 2000 of which are organizations. And changes are indeed starting to happen at the research institutions, funders, and policy level. For instance, several research institutions now make sure that metrics are not used in isolation, but only as a complement to reflective qualitative peer-review (examples of institutions that have concretized these changes are available in the repository '*Reimaginging academic assessment: stories of innovation and change*' developed by DORA in collaboration with EUA and SPARC Europe (DORA, 2021)).

As part of the Horizon 2020 program, the European Commission also created an Open Science Policy Platform in which several expert groups were created to discuss better research assessments and indicators. These include the Working Group on Rewards, the Expert Group on Indicators, and the Mutual Learning Exercise on Open Science – Altmetrics and Rewards (Open Science Policy Platform, 2017).

New metrics are also becoming available to help balance research assessments. Simple paper downloads, for example, may capture readers who do not cite works, such as non-academic users of the work (Winker, 2017). More complex composite metrics have also been built. Altmetrics is a prime example of the diversification of the elements that can be captured on a single piece of work. Altmetrics include a wide array of inputs, such as open peer reviews reports, social media capture, citations on Wikipedia and in public policy documents, mentions on research blogs, mass media coverage, and many more aspects which help provide a broader overview of how the work is being used. The PlumX metrics, although governed by different calculations, works in similar ways. These innovative metrics are gaining increasing visibility on publisher's websites, but their use in formal researcher assessment is still very limited.

[5] In fact, DORA's first principle states directly that assessors should "not use journal-based metrics, such as Journal Impact Factors, as a surrogate measure of the quality of individual research articles, to assess an individual scientist's contributions, or in hiring, promotion, or funding decisions" (American Society for Cell Biology, 2013).

Narrow Views of Impact

The Problem In addition to the overreliance on outputs and the problem of inadequate metrics we delineated above, indicators currently used in research assessments can be criticized because they provide a very narrow view of research impact. Two main dimensions deserve to be discussed here.

The first dimension concerns the impact research has on practice, policies, or society. As we previously mentioned, researchers are often expected to dedicate a portion of their time to the key pillar of 'Services', but typically their involvement in 'Services' is almost entirely absent from researcher assessments (Schimanski & Alperin, 2018). In addition, in the rare instances where 'Services' are considered in review, promotion, and tenure assessments, their consideration almost exclusively targets services provided within the institution or the research community — such as participation on university boards or editorial boards — rather than services provided to the public or to society (Alperin et al., 2019). Citations-based metrics only consider recognition and visibility within the scientific (and citing) community and provide only a restricted view of academic impact (Lebel & Mclean, 2018). Impact on practice, policy and society are not captured and are even obscured by these narrow metrics. For example, the need to publish in high impact factor journals often translates in a need to publish in English-language international journals; a decision that can reduce the societal impact of locally relevant research projects (Gingras & Mosbah-Natanson, 2010). Academic environments themselves, through their funding objectives, missions, and expectations, value discovery but largely disregard how we can best implement discoveries in practice (El-Sadr et al., 2014).

A second dimension that is important to reconsider is the impact that research has on knowledge advancement. In fact, current assessments tend to conflate impact with ground-breaking findings (Aubert Bonn & Pinxten, 2021b). While this idea has long been embedded in the notion of scientific discovery, it also undermines the importance of non-ground-breaking work in advancing knowledge. Borrowing the words of Ottoline Leyser, chief executive officer of UK Research and Innovation:

> It is worth remembering that the term "ground-breaking" comes from construction. There is often a ground-breaking ceremony, but then the building must be erected. This comes only after much preparation, from determining the ideal location to securing all the planning permissions. Likewise, for every ground-breaking discovery, a huge amount of work has paved the way, and follow-up work to solidify the evidence and demonstrate reproducibility and generality is essential. High-quality work of this sort is rarely recognized as excellent by the scientific enterprise but is excellent nonetheless, and without it, there would be no progress. (Leyser, 2020: 886)

The overemphasis on ground-breaking discovery has shaped a research system in which replication studies and negative results are largely invisible despite their crucial value in solidifying knowledge (Bouter & Riet, 2021; Ioannidis, 2018; Munafò et al., 2017).

Innovative Action To better capture the impact that research has on practice, policies, society, or research itself, research assessors need to broaden the scope of

indicators they use. We already mentioned that alternative metrics can help capture interest that would otherwise be missed. Another notable effort that may help capture societal impact in research is the Research Quality Plus (RQ+) evaluation approach used at the International Development Research Centre (IDRC) in Canada (Ofir et al., 2016). Although emphasising expected impact in a funding application is sometimes criticized for being artificial and highly theoretical (Brooks, 2013; Kirschner, 2013), the RQ+ provides a structured method through which societal impact can be estimated before the research takes place. Since the RQ+ is used for evaluating research proposals, it is not directly applicable to assessing researchers' past accomplishments. Nonetheless, it might be a good model to inspire areas of impact that could be considered in future research assessments.

To capture the impact that the research has in building knowledge, several research institutions and funders started adopting narrative CVs in which researchers are encouraged to describe, in their own words, the impact of their work. A good example of these narrative CVs is the Résumé for researchers provided by the Royal Society in the UK (Royal Society, n.d.). In the Résumé for researchers, applicants are provided with unstructured space to discuss their contributions to the generation of knowledge, the development of individuals, the wider research community, and the broader society. These open descriptions enable assessors to consider a broader, more diverse, and more personal perspective of impact that may have been invisible otherwise. While these narrative CVs are not easy to write and more demanding to assess than quantitative metrics, they are increasingly adopted in research institutions. Several other funders, such as the Health Research Board Ireland, the Dutch Research Council, and the Swiss National Science Foundation are also experimenting with open and narrative CVs (Hatch & Curry, 2020).

Obstacle to Diversity

The Problem In addition to the issues presented above, current research assessments also often fail to promote diversity and inclusion in research. Gender inequalities, for example, are seen in both citation metrics and publication outputs (Beaudry & Lariviere., 2016; Larivière et al., 2013), even more so in the disrupted working conditions of the COVID-19 pandemic (Minello, 2020; Viglione, 2020). Women are also more likely to be strongly involved in teaching, in the hands-on facets of research, or in other contributions that are essential to science but are less likely to result in first- or last-author publications (Astegiano et al., 2019; Macaluso et al., 2016). Similar issues also afflict ethnic groups and geographic regions, not only in funding opportunities and access (Check Hayden, 2015), but also in the fair attribution and recognition of their work (Powell, 2018; Rochmyaningsih, 2018). The same hurdles are faced by researchers with disability, even when policies are in place to tackle the injustice (Brock, 2021). Consequently, research assessment's excessive reliance on publication metrics may further tax diversity and inclusion issues in academia. But diversity and inclusion is not only about disadvantaged

groups. Diversity of skills, contribution, and career profiles is also an essential aspect that is largely ignored in current assessments and inclusion policies. Indeed, research assessments tend to assess researchers individually and to expect them to fit a one-size-fits-all model of success in research (Aubert Bonn & Pinxten, 2021b). This individual and uniform model of assessment contradicts the highly collaborative, differentiated, and complementary roles that are intrinsic to research (Bothwell, 2019). Overlooking the still growing differentiation of research tasks disregards the unique contributions from non-leading members of research teams as well as the essential role of research support staff (Payne, 2021). Individual assessments and uniform expectations also increase competition between researchers; a feature which is known to be highly problematic and is often mentioned as a cause for research misconduct and questionable research practices (Anderson et al., 2007; Aubert Bonn & Pinxten, 2019).

Innovative Action The lack of diversity in research is a priority on the agenda of several large funders and research organisations. The Athena Swan Charter, for example, plays an important role in inciting research institutions to achieve gender inclusivity ("Athena Swan Charter, n.d."). Several institutions already have internal policies, quotas, and initiatives to promote greater diversity in hiring and promotion, yet some of these policies have raised hefty debates in the past ("College oordeelt over voorkeursbeleid TU Eindhoven", 2020; Dance, 2019). Going one step further, the Indiana University – Purdue University Indianapolis (IUPIU) decided not only to encourage activities that promote equality, diversity, and inclusion, but also to recognize their inherent value by considering them in researchers' tenure and promotion application ("IUPUI approves new path to promotion and tenure for enhancing equity, inclusion and diversity", 2021). Despite these important initiatives, the impact that the indicators used in assessing researchers have on diversity and inclusion is rarely addressed, and there is growing realization that diversity and inclusion should be more prominent in research assessments (Labib & Evans, 2021).

The role an individual has in the research team has also received increasing attention in the past few years. Assessors realise that knowing the ways in which researchers collaborate can provide invaluable information. As a result, interesting initiatives that enable greater visibility on the team aspect of research are starting to pierce. The Contributor Role Taxonomy (CRediT), for example, provides an added level of granularity to authorship and helps to understand the dynamics, roles, and responsibilities in team research (Alperin et al., 2019; CASRAI, n.d.). Although contributor roles have not yet fully secured their place in research assessments, more and more journals provide contributorship sections to the papers they publish. Whether the future of academia is one in which contributor roles take over authorship, however, remains to be seen (McNutt et al., 2018; Smith, 1997). Another interesting initiative in the recognition of teamwork is the Diversity Approach to Research Evaluation (DARE; Bone et al., 2020). The DARE approach provides tools to measure and understand how collaborators connect and deal with diversity. While the approach is more informative than evaluative, knowing more about the

dynamics in research teams is a starting point to gather information on the characteristics of strong research teams.

There is also a growing belief that the lack of diversity in the profiles of individuals that succeed in academia may weaken effective team work (Aubert Bonn & Pinxten, 2021c). Diversifying the profiles of academic employment, therefore, may help build research climates in which success comes from joint efforts rather than from competition between individuals. One early example of such initiative is the Open University in the UK, where more flexibility is given to researchers to enable to focus on different pillars of their work (Parr, 2015). As a result, researchers could pursue a career in which knowledge exchange is valued before their teaching and research achievements. The recently implemented career track at Ghent University, Belgium and the Dutch Recognition and Reward Programme are two other well-known initiatives to address the need for diversifying researchers' profiles (Ghent University Department of Personnel & Organization, 2018; VSNU et al., 2019). The position paper 'Room for everyone's talent' from the Dutch Recognition and Reward Programme nicely illustrates how such a diversification may take shape. Specifically, researchers have the opportunity to select a unique combination of key areas they wish to specialise in and be assessed on. These key areas include research, education, impact, leadership, and patient care. While all researchers are expected to demonstrate sufficient competencies in the research and education areas, they can choose the extent to which they favour these and any other areas and can change areas of specialties at different stages of their career.

Finally, the initiative contains a clear acknowledgement of the need to reward team efforts, The Dutch's highest research awards, the Spinoza and the Stevin prizes, are now also open to team applications, making another step forward in the recognition of research as team work (Hoger Onderwijs Persbureau, 2019).

Procedure

The Problem Changing researcher assessments is a complex endeavour that extends far beyond the elements and indicators assessed. It is also important to discuss the time and resource commitments that research assessments simply.

Researchers need to invest substantial time in building a prestigious CV and in applying for research funding. While the peer-reviewed process through which research is funded is most likely essential for good quality research, the low success rate of current funding schemes (typically 5–10% of the applications are granted) suggests that a lot of efforts are ultimately wasted. Past research has shown that many researchers consider the preparation of funding proposals to be the most "*unnecessarily time-consuming and ultimately most wasteful aspect of research-related workload*" (Schneider et al., 2014, p. 41) and that researchers wished they could spend less of their time on it (Aubert Bonn & Pinxten, 2020a). In fact, Herbert and colleagues estimated that the amount of time spent preparing grants for

the Australian National Health and Medical Research Council in 2012 (Herbert et al., 2013) reached 550 working years of researchers' time — the equivalent of 66 million Australian dollars (around 42.5 million Euros at the time of writing). Considering the low success rate of these applications, competitive funding channels come with phenomenal research time investments. Building a tenure dossier and applying for different research positions is also no small task, and since grants and non-tenured research positions are typically short-term, the time investment involved is substantial.

In turn, the colossal demands for research money and opportunities also lead to increasing numbers of applications which raise faster than the investments in research funding (Rockey, 2012). This growing demand creates a pressure on funders who face an excess of applications to review, and who will, in turn, require peer reviewers and selection committee members — most of the time researchers themselves — to invest their already scarce research time in the review process (Aubert Bonn & Pinxten, 2020b; Gingras, 2016).

Innovative Action With the large amount of demands for funding and career opportunities, it is difficult to reduce the volume of research assessments. Nevertheless, there are ways in which the time and resource investment can be reduced to alleviate the burden of both researchers and assessors. One such initiative is the post-peer-review lottery of funding applications which proposes that, after a first thorough quality check to select proposals that are sound and methodologically adequate, assessors should select the winning applications randomly rather than through lengthy deliberation. This radical idea would not only increase efficiency of research funding assessments (Gross & Bergstrom, 2019), but it would also guard against the 'natural selection of bad science' by allowing unusual and unfashionable topics with high risk of negative findings to be funded (Smaldino et al., 2019). The lottery approach may even help reduce career insecurity in academia, a point we will discuss further in Sect. 27.2.5 (ISE task force on researchers' careers, 2020). Another way to reduce the burden of research assessment is to reduce the frequency at which researchers are evaluated. Longer terms funding and research contracts could help in this matter, while further alleviating worries around the lack of security of research careers. Similarly, reduced evaluative frequency for employed researchers may help reduce the evaluative burden. Ghent University is currently experimented this change in its new career track, moving from a review interval of 3 year to one of 5 years starting in 2020 (Ghent University Department of Personnel & Organization, 2018).

Assessors

The Problem The assessors themselves are not so frequently on the agenda for change to research assessments, despite their direct relevance to assessment processes. Particularly, when reflective and qualitative peer-review takes precedence, a

great deal of subjectivity is introduced in the assessment process. Subjectivity is not a bad thing but it leaves substantial room for personal biases and involuntary discrimination in research assessments. For instance, assessors will naturally be tempted to cherry pick the information that confirms their already formed opinion (confirmation bias), to base their assessment on easily accessible anecdotal information (accessibility bias) or to let contextual aspects such as the reputation of universities listed on the CV of applications shape their views of individual candidates (halo effect (see for e.g., Clauset et al., 2015; Kwon, 2021)), to name only a few (Hatch & Schmidt, 2020). In addition, many assessment procedures ask assessors to value highly abstract concepts – for example 'excellence', 'high impact' – differences in interpretation, misunderstandings, and unfortunately biases can then easily happen (Hatch, 2019).

Innovative Action Diversity is an important keyword if we want to reduce the influence of biases. Indeed, guidelines explicitly recommend that research and funding organisations should strive to ensure that reviewer pools and hiring committees contain diverse profiles (Science Europe, 2020). In addition, diversity should target not only gender and ethnicity, but also the profiles of assessors and their seniority. For example, there is increasing realisation that the input for researcher assessments, for example the reference letters used, should come from superiors as well as from those supervised or managed by the researcher being evaluated (i.e., 360° feedback; Vitae, n.d.). Other ways to reduce biases on research assessments have been proposed, for example avoiding photos of the candidate on the application or moving educational history with potentially biasing university names to the end of the evaluation, but the efficacy of such approaches remains largely undocumented (Hatch & Curry, 2019). Finally, training assessors to ensure that they have a clear understanding of the assessment process and providing unambiguous definition of the key concepts that are assessed (e.g., impact, excellence, quality, etc.) can help reduce biases (Hatch, 2019; Science Europe, 2020). A few universities and organisations are starting to implement these recommendations. For example, Tampere University now informs and trains evaluators across campus about responsible evaluation practices (DORA, 2021). Similarly, the Health Research Board (HRB) Ireland also started raising awareness, training staff, and providing guidance for reviewers as a way to minimize gender inequalities and reduce unconscious biases (Health Research Board, 2019), much like the Dutch Recognition and Reward Program in which training and instructions are provided to assessment committees (VSNU et al., 2019). Others also started defining the terms they use to assess researchers. For instance, Norway Universities added clear definitions of the key concepts needed in assessments (DORA, 2021), while the 'Room for everyone's talent' position paper explicitly defines the concept of impact. Such initiatives are still scarcely exploited and not yet evaluated, but there is growing awareness of the need to inform, train, and support those who assess researchers.

Research Environments

The Problem We know that the environments in which researchers operate are problematic since they impose high pressures on researchers to perform and publish (Metcalfe et al., 2020; Nuffield Council of Bioethics, 2014; The Wellcome Trust and Shift Learning, 2020). Changing research assessments can likely help to reduce the 'publish or perish' culture. Yet, other elements in the environment of researchers are also important to consider to avoid wasting the huge efforts invested in changing research assessments.

First, the lack of stability in research careers is an essential aspect to consider. At the moment, there is a huge discrepancy between junior (temporary) and senior (permanent) positions in academia, and only between 3% and 20% (depending on the countries' estimates and faculties) of young researchers will be able to pursue the career in academia to which they aspire (Alberts et al., 2014; Anonymous, 2010; Debacker & Vandevelde, 2016; Larson et al., 2014; "Many junior scientists", 2017; Martinson, 2011; van der Weijden et al., 2016). In turn, this lack of stability creates an unhealthy working environment in which stress, mental health issues, and burn out thrive (Levecque et al., 2017; "The mental health of PhD", 2019; Padilla & Thompson, 2016). Furthermore, the scarcity of senior positions creates a perverse hyper-competition between junior scientists who wish to survive in academia. Hyper-competition not only worsens the situation, but it is also known to be an important driver of questionable research practices (Anderson et al., 2007; Aubert Bonn & Pinxten, 2019).

Beyond these interpersonal issues, the support, resources, and infrastructures that researchers receive is also essential to ensure that changes in research assessments are implemented effectively. Currently, junior researchers and PhD students often feel unsupported (Heffernan & Heffeman, 2019; Van de Velde et al., 2019) and the transition towards new expectations can generate frustration if the resources to fulfil these new expectations are lacking. For example, expecting researchers to preregister their research protocols or to make their data open and FAIR (i.e., Findable, Accessible, Interoperable, and Reusable (Wilkinson et al., 2016)) is a great step towards better research, but it comes with important needs for adequate infrastructures, training, and most importantly researchers' time. Similarly, demanding open access publication is increasingly requested by funders and institutions, but it needs to come with a budget for covering article processing charges, without which inequalities may ensue (Aubert Bonn & Pinxten, 2021a).

Innovative Action There are several initiatives that aim to improve research environments, and in many ways, the innovative actions mentioned throughout this chapter would help create a healthier, more collaborative research climate. Yet, we would like to provide more details on a three types of initiatives that target research environments directly. First, there are initiatives that play a crucial role in raising awareness and opening the discussion on the problem. Examples include the Initiative for Science in Europe (ISE) position paper on precarity in academic

careers and its associated webinar series (ISE task force on researchers' careers, 2020), the French movement of 'Camille Noûs' from Cogitamus Laboratories (Cogitamus Laboratory, 2020), and the University College Union strikes that took place at 74 Universities across the UK in early 2020 to denounce — among other things — the casualization and the lack of employment security of research careers (University and College Union, 2020). Second, more forceful initiatives also start to appear. For instance, at the end of 2020, Sweden produced a national bill to change to the way in which it funds research so that a greater share of researchers' salary would come from governmental non-competitive funding (Regeringskansliet, 2020). This bill came in response to a thorough investigation in which it was discovered that the constant search for competitive funding ultimately undermined research quality (Hwang, 2018; Regeringskansliet, 2019). In helping researchers to have a more stable salary, Sweden aims to reduce the hyper-competition and to lower the employment insecurity of researchers. The third initiative that is highly relevant when discussing research environments is the Standard Operating Procedures for Research Integrity (SOPs4RI) European Commission project that is ongoing until 2022 (Mejlgaard et al., 2020). The SOPs4RI project is creating a toolbox of best practices and guidelines to help research and funding institutions build research integrity promotion plans. In doing so, the SOPs4RI emphasizes that research integrity is not only a responsibility of researchers, but also of research and funding institutions whose operating procedures should foster healthy research environments. Simultaneously, the project is also empirically creating its own guidelines on topics that are overlooked in existing research guidance documents. One of the guidelines being produced directly targets ways in which institutions can build better and more collaborative research environments that foster research integrity.

Coordination

The Problem The final point that we find important to discuss is the need for thorough, intense, and continued coordination between different actors of the research system. In fact, to fully address the problems we described in this chapter, an open dialogue and thorough coordination between researchers, funders, research institutions, and policy makers as well as other actors such as publishers and metrics providers is needed.

Without coordination between stakeholders, changing research assessments is difficult and unlikely to happen on a large scale. For instance, in many countries, governments use performance-based attribution to fund research institutions, meaning that the share of funding received by research institutions largely depends on quantity indicators of outputs (Jonkers & Zacharewicz, 2016). Although using bibliometric indicators to distribute funding at an institutional level does not mean that universities should assess researchers using the same criteria (Debackere & Glänzel,

2004), the fear of underperforming often leads universities to use these indicators internally at a researcher-level (Aubert Bonn & Pinxten, 2021c; Engels & Guns, 2018). Similarly, the way in which universities are recognized is profoundly influenced by university rankings. University rankings strongly depend on impact factors and other publication metrics, and there is increasing awareness that they have profound flaws and should be interpreted carefully (Gadd, 2020). Yet, rankings are still a dominant way of attracting funding, researchers, and students, and most universities take strategic, organizational, or managerial action to improve their rankings (Hazelkorn, 2007). Lack of coordination with metrics-providers also play a role in the problem. In fact, most major metrics belong to profitable companies whose external agendas differ from those of the research communities (Larivière & Sugimoto, 2018c). Thorough communication with publishers is needed if we hope to shape metrics that align with the objectives of the research communities.

Changing researcher assessments is also something that is difficult to implement in single institutions. In the absence of a common approach of research assessments, there is a worry that researchers building a profile to succeed in one proactive institution may later be penalised if they want to migrate to another research setting in which their profile might be undervalued. In other words, the perceived 'first-mover's disadvantage' favours a stagnant status quo and builds a feeling of hopelessness that the highly needed changes will occur (Aubert Bonn & Pinxten, 2021c).

Innovative Action Ensuring the coordination of all stakeholders around the same objectives — and finding the means to achieve these objectives — is an extremely challenging task. Among others, the European University Association (EUA) briefing and The Metric Tide provide insights on this crucial need for coordinating actions at the level of research assessments, not hiding the complexity of the tasks it implies (Saenen & Borell-Damián, 2019; Wilsdon et al., 2015). Despite the challenge, best practice examples mentioned throughout this chapter have shown that coordinated changes are possible in practice.

Actors with broad influence and substantial budgets are essential here. For example, the European Commission's 'Towards 2030' vision statement addresses the issue of ranking, calling research institutions to move beyond current ranking systems for assessing university performance because they are limited and "overly simplistic". (Gadd, 2020). Broad reaching groups such as the European Commission Open Science Policy Platform we mentioned earlier and DORA also plays a role in coordinating changes by uniting different research institutes and member states to agree on a strategic plan of action. In South America, the Latin American Forum for Research Assessment (FOLEC) provides a platform for discussion between stakeholders on issues of research assessments (Latin American Forum for Research Assessment (FOLEC), 2020a, 2020b, 2020c). University alliances can also help coordinate changes. For example, in 2019 the consortium Universities Norway put together a working groups aiming to build a national framework for research career assessments. The group issued a report in 2021 in which they propose a toolbox for recognition and rewards of academic careers (Universities Norway, 2021). The Academy of Finland went through a similar process to create national

recommendations for responsible research evaluation (Working group for responsible evaluation of a researcher, 2020), and more and more university associations and academies are following this lead.

In a slightly more drastic approach, since 2021 the major UK research funder Wellcome decided that it would only provide funding to researchers working in organizations that can demonstrate that their researcher assessments are fair and responsible (Gadd, 2020). This strategic decision incites efforts from both the institution, which would be at a disadvantage if it did not work to ensure its eligibility to Wellcome funding, and the researchers who will push their institutions to ensure they remain eligible for this important source of funding.

Finally, the program 'Room for everyone's talent' we described above is an inspiring example to prove that profound coordination is possible. In 'Room for everyone's talent', five public knowledge institutions and research funders joined forces to ensure that Dutch research institutions would abide by the new assessment models. In addition, in the position paper announcing the new model, the five parties acknowledge their responsibility to take steps towards even tighter coordination. The position paper describes their commitment to connect with international organisations such as the European University Association, Science Europe, and Horizon Europe to encourage changes and harmonisation at a European level.

Way Forward

Changing researcher assessments is difficult and requires huge investments and efforts from a diverse array of stakeholders. We have argued that current research assessments have profound inadequacies, but that promising pioneering actions are starting to address these inadequacies and to align research assessments with responsible research practices.

To continue moving forward, we need to think of research assessments in their entire complexity, addressing not only their content, but also the processes, assessors, environment, and coordination needed for change. For each dimension, we must understand the problem, raise awareness, take action, and coordinate efforts to enable change.

Even though research institutions, research funders, and policy makers have a clear responsibility in enabling the change towards more responsible assessments, we, as researchers, also have an important role to play. For one, we should remember the biases and problems of research assessments when acting as peer-reviewers or assessors and ensure that we avoid shortcuts and biases as much as we can. But we should also play a role in shaping the tenacious research culture, helping to raise awareness and mobilise action around us. In the end, when we look at what was accomplished by DORA — which started from a small group of researchers and editors within the research community — researchers can help to drive the change.

But changing research assessments is not the end in itself. To avoid falling in the same pitfalls we are fighting with today, it is essential to understand whether the

changes to research assessments help contribute high quality and high integrity research (Moher et al., 2018). In this regard, research on research assessments is essentially important to allow us to understand, inform, and realign research assessments towards a better future. In short, we need evidence-based research assessment policies.

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Chapter 28
Coercion in Mental Health Treatment

Antoni Gomila

Abstract While a standard procedure in mental health internment facilities, physical restraint, as an extreme form of coercion in mental health, has been claimed to be abolished. Three sorts of arguments have been provided: an argument from dignity, and argument from informed consent, and a consequentialism argument. In this chapter we discuss these arguments and conclude that these arguments are not decisive to completely ban such forms of coercion. Restraint, in particular, may be justified in exceptional circumstances, where an imminent risk for the personal integrity of anybody involved, including the person with the mental health problem. However, this sort of case is infrequent, while restraint is often the first option. This conclusion also suggests that much can be done to prevent reaching such extreme circumstances where coercion may be the only option. The discussion also clarifies how coercion should be carried out, when justified, making it supervised and as short as possible.

Keywords Coercion · Mental health · Mechanical restraint

Introduction[1]

Mechanical restraint is a procedure for immobilization of the person, seclusion consists in closing the person alone in a special room, and chemical restraint refers to the use of sedation to reduce the state of alteration in which a person may be. They

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are routine procedures in mental health facilities that involve internment, as they also take place in similar facilities for intellectual disabilities and dementias (Al-Maraira & Hayajneh, 2019; Husum et al., 2010; APRAIS, 2005). All of them are forms of coercion. Several voices have protested in recent years against these practices. Various entities and associations, basically people with severe mental disorders, and concentious professionals involved in this area, have demanded the termination of coercive intervention guidelines, and in particular against mechanical restraint (Newton-Howes, 2010; Cartagena Manifesto 2016; Foundational Manifesto of the National Platform without restraints 2017; Fernández et al., 2018; Sugiura et al., 2020). Some residential facilities for the elderly already decided to become coercion-free (Evans et al., 2002). This chapter aims to add to this debate, which generally takes the form of a challenge to the mental health establishment, to the extent that established psychiatric practices are questioned and a change of attitudes is called for (Molodynski et al., 2016). Here we will examine this issue from a bioethical perspective, through consideration of the relevant arguments pro mechanical restraint.

Deep down, mental disorders continue to pose uncomfortable questions for us, not only because of the black history of psychiatry, ready to adopt practices of restraint and control in the past (Foucault, 1961; Porter, 2004; Busch & Shore, 2000) which may at first sight bias against its current orthodox procedures, but in general, because of the difficulty of finding ways to accomodate mental disorders into our lives. Humans are fond of viewing rationality, reflection and deliberation as distinctive properties of human agency (Broncano, 2017). However, people with such disorders often seem determined to go against their own well-being and their interests, and sometimes they can become a threat to others, at the same time that they experience suffering and pain, and face great difficulties for adjusting to their situations – making them seemingly a-rational at a minimum, if not clearly irrational. They are vulnerable and therefore must be protected, but their wellbeing may not be recognized by themselves, thus giving rise to a conflict between their wellbeing and their will. Our question, therefore, can be seen as a question about how to solve this dilemma, and about the limits: how far can one go with a person with a mental disorder in a situation of extreme alteration? The answer to this question involves considering the details of when, if ever, it may be legitimate to immobilize her, and for how long.

It can be argued, up front, that mechanical restraint is a practice that has been and is likely to continue to be abused (Evans & FitzGerald, 2002). This is probably true, insofar as there is no active prevention policy, to avoid reaching situations of lack of control and extreme alteration, and if the policy existed, it is not specified in an effective plan for progressive reduction to the minimum of such restrictive practices. According to a recent study (Bono & Beviá, 2017), mechanical restraint in mental health internment units is a common practice. Mental health professionals

chapter, the context of the debate was Spanish, and so were the references. For this one, in addition to fully revising it, I have tried to put the question in a general framework, so as to avoid reference to any country in particular.

resort to it as common practice, without clearly being instructed about prevention strategies which could allow reducing the use of this practice. As a matter of fact, the evidence favours a preventive intervention model, with the enhancement of community intervention, home and family support and individualized follow-up, as the best strategy to avoid relapses and involuntary internments, and that improves adherence to treatment and the person's involvement in their own process; but even this approach may involve some form of coercion (Molodynski et al., 2010). Despite the fact that studies show the effectiveness and efficiency (in terms of costs) of this community model, this approach is not yet taken for granted, to the extent that most of the expenditure on mental health is dedicated to pharmacy and hospital resources.

However, the fact that mechanical restraints are used too frequently is not a sufficient argument to affirm that they should never be used. The question is whether there can be situations that legitimize the use of restraint, once other, less coercive forms of intervention failed. In the case of nursing homes for the elderly, where this type of restraint was also frequent, a growing awareness that they are problematic and that there are available alternatives has generated a trend of coercion-free establishments. And the same occurs in the intellectual disability sector, where awareness developed about the problems of this type of intervention (Bowring et al., 2017). In the field of mental health, the manifestos to which we have referred clearly position themselves against its use, and in favor of its abolition.

The arguments used by this debate in all three domains – the elderly, intellectual disabilities and mental health – are similar, and can be grouped into three types, or main arguments. In the first place, it would be wrong to resort to mechanical restraint because it represents a humiliation that affects human dignity, and therefore human rights. It is also alleged that the basic principle that governs the health system of informed consent should also be applied in the field of mental health, denouncing the existence of coercive practices that impose "treatments" outside the will of the interned people. For this approach, coercion would only be legitimate if the person who suffers it were to authorize it. A third type of argument against coercion is utilitarian: the consequences of carrying out a procedure of this type end up being worse than the damage that it is intended to prevent. Let's examine these arguments in more detail to assess whether they go through.

The Argument from Dignity

The first type of argument is deontological, and in my opinion, it is the most powerful: mechanical restraint is claimed to be incompatible with respect of human rights, as they are recognized by the legal system. It is claimed that respect of human dignity does not allow treating anyone in this way: it is a degrading treatment, which affects the dignity and moral integrity of the person. The Spanish Constitution, for one, acknowledges as fundamental rights, among others, dignity (article 10), physical and moral integrity (article 15) and physical freedom (article 17). Coercion is thought to transgress these fundamental rights, in a way analogous to how we would

consider it degrading and/or humiliating to have people in jail tied up with chains, for example.

Certainly it is of particular concern, as we noted at the beginning, the treatment that people with severe mental disorders admitted to mental health facilities may receive. The recommendation REC 10 (2004) of the Council of Europe focused precisely on the protection of human rights and the dignity of people with mental disorders, proposing a series of measures to prevent degrading or inhuman treatment, especially in detention situations and involuntary internment. This final caveat, in any case, leads us to recognize from the outset a harsh but unavoidable reality: that sometimes it may be necessary to resort to the extreme measure of an involuntary internment on behalf of the care of the person – a measure that generally requires a judge to authorize it. Part of the mental health condition usually involves lack of awareness of the problem and the abuse of substances. As a consequence, the person may be in a state of alteration, in which she is not able to behave with due respect to others, or in which she may put her own life at risk. Involuntary internment is, in fact, a type of detention, a restriction of fundamental rights justifiable only for reasons of the wellbeing of the person in question, and of guaranteeing the rights and freedoms of other people. In this sense, it must be subject to the same type of control and supervision as other cases of detention to guarantee the respect of rights. Involuntary medical internment does not need to involve, though, physical immobilization or other forms of coercion.

In addition, these situations of coercion may further increase a state of already great alteration in those who suffer them, in the same way that they can occur in the case of a police arrest or a prison internment, which add to the state of alteration that justifies the decision of involuntary internment. So it is necessary to have protocols to deal with the situations of resistance and rebellion that may arise, to prevent them if possible. I do not know the statistics, but from my experience I can say that scapes are not infrequent in the facilities for people with mental health problems. Unfortunately, these scapes usually lead to an escalation of the deterioration that motivated the internment.

The question at this point is whether it is possible, to avoid the scalation, to resort to mechanical restraint in a situation of involuntary hospitalization in a non-humiliating or degrading way. From the outset, note that the patient's consent is not in question here. The treatment of participants in certain television reality shows may well be degrading, no matter how voluntary participation is. In other words: for this argument, what is relevant is the treatment received, regardless of whether the interested party agrees to receive it. So the question becomes whether physical coercion can be exercised in a non-degrading or humiliating way. Given the well-known antecedents regarding the use of mechanical restraints as a punitive practice in the old madhouses, it is understandable that coercion raises doubts, and that psychiatric institutions are not very transparent in this respect, despite the need to be particularly scrupulous in their implementation in any case, to defend its correctness.

These antecedents suggest two types of conditions in which mechanical restraint is clearly degrading and unacceptable: first, those that have to do with the reasons

that may lead to adopting this measure; second, those related to the way it is carried out. Indeed, it is unacceptable and unjustifiable a containment adopted for spurious reasons: as a form of domination, punishment, discipline, to make it clear to the patient "who's the boss". In other words, it is unacceptable to resort to physical coercion in the interest of the one that exercise the coercion. Conversely, a minimal requirement to consider physical coercion as correct is that the motivating reason is the interest and greater wellbeing of the one who suffers it, or the need to block a risk to damage a third person (another inmate, or a worker, say). Thus, as regards the reasons to resort to physical coercion several suggest themselves: a suicide attempt or another form of autolysis, say, and an imminent risk of aggression to a third party.

Now, it is also necessary that mechanical containment is the best way to produce such a benefit, that is, that there is no alternative, less intrusive measure that can give rise to that benefit. That coercion is indeed the lesser evil. It is at this point that the question of prevention and alternative courses of action takes on special relevance. For example, the usual justification for mechanical restraints in older people at night refers to the risk of falls from bed, but this risk can be minimized by placing the mattress on the floor (or on articulated beds, as low as possible), and/or helping the person to overcome midnight agitation through hypnotics. Coercion loses its legitimacy once an alternative is available that does not require its degree of intrusion.

Therefore, having a viable alternative that avoids affecting a fundamental right of the person eliminates the prima facie justification of coercion. On the other hand, consideration of the benefits and the harms of the decisions places us in the consequentialist approach, which we will examine below. For the moment, it suggests that the respect of the dignity of the person is not an all or nothing question, but has to do with the available alternatives and the way the action is carried out.

Regarding the way in which it is carried out, it is easy to identify some clearly unacceptable ways of carrying out mechanical restraint, as they clearly affect the dignity of the person. For example, carrying out coercion in a public space, without preserving the privacy of the patient, whether or not an exemplary objective is sought, is unacceptable. Second, when it becomes a form of torture, if the procedure ends up giving rise to damage, a wound, a dislocation, an ulcer. If it consists of a dehumanized treatment, such as leaving someone without food or drink, or without being able to go to the bathroom, while he is tied up. And above all, if a limit is not established on the duration of containment, and the patient is left completely alone for a long time. The measure, to be justifiable, should be proportional in any case, according to a principle of sufficient minimal restriction.

To sum up, the argument from dignity rightly questions psychiatric practices of abuse, such as physical coercion to force submission from the internment, as an extreme means of behavioral control when no life is in risk, and as a practice that endures much longer than the critical episode that triggers it. It does not rule out, though, the possibility of a coercion that is done as a last resort, in the interest of the person, or to avoid an imminent risk for somebody else, as long as the way it is carried out does not obliviate the wellbeing of the person restraint.

The Argument from Informed Consent

The second type of argument appeals to consent to medical treatments as a precondition for a treatment to be carried out. In this case, the argument does not appeal to fundamental rights, but to the right of citizens vis-à-vis the health administration, such as the right to privacy and confidentiality, non-discrimination, access to healthcare information and clinical documentation, and more relevant to the issue at hand, to prior informed consent. Thus, it is argued that mental health services should apply the same procedures as any other healthcare setting when offering their services, so that the patient is always to have the last word on what treatment she receives. If immobilization is justified as a medical intervention, then the patient should have the right to consent to it, just as patients have the right to consent to any other medical treatment.

Indeed, raising the question of informed consent in this context may come a misplaced or naif. For one thing, as it has been repeatedly pointed out (Francombe-Pridham et al., 2016; Inchauspe & Valverde, 2017), institutional mental health services tend to act coercively, if not in a compulsive way, as if assuming that the patient lacks the lights to understand, much less decide, what is best for her. Therapeutic measures are usually imposed by psychiatrists, instead of offering alternatives and allowing the patient to choose, often as a requirement in order to receive some kind of monetary help. It is as if the system presupposes the inability of the patient to make the best decisions in her best interest, precisely because of her mental disorder. This paternalism often becomes a form of blackmail when obtaining a social health benefit (a pension, access to housing…) is conditioned on the acceptance of a pharmacological treatment. Again, the fact that forms of coercion are questionable is not enough to establish the point that physical coercion would be correct were the patient to consent to it. To put the question in other words, what is at stake is whether the last word on which treatment is provided corresponds to the patient in all cases, or rather just in some of them, and to some extent.

As a matter of fact, legislation generally limits the scope of the patient's autonomy, and contemplates generic exceptions to prior informed consent (in the case of Spain, articles 8 and 9 of Law 41/2002): when there is a risk to public health and when it is a vital emergency and the patient is not in a position to decide. In this way, the legal regulation grants the healthcare system the ability to make decisions without taking into account the will of the patient at all times, as a requirement. This generic safeguard offers the basis for at least understanding the situation we have described in mental health facilities.

However, for this type of case, in which the patient may not be in a position to decide, it should also be taken into account that the law may delegate the consent to another person. In Spain, the Law 26/2015, that modified the system for the protection of childhood and adolescence, introduced a provision of informed consent by representation. In the case of non-adults, and those whose legal capacity to make decisions has been supplemented by a curator – a not uncommon situation in mental health (Dawson & Szmukler, 2006), where the responsibility of authorizing a

medical treatment rests with another person, the legal guardian. This legal prevention is seldom taken into account by mental health centers, which only request such authorization in cases of surgical interventions and risky diagnostic tests. Consent is not required for pharmacological prescriptions, in spite of the fact that the person under the guardianship rejects the medication. On the other hand, nothing similar happens with physical restraint, which is sometimes not even communicated, and which does not usually appear in the health record either. Here again the coercive dimension of psychiatry is made apparent. In reality, this practice rather makes it clear that physical restraint cannot be considered under any circumstances as a therapeutic measure, but rather as an extreme resource to neutralize the risks that a state of great agitation or behavior alteration entails for the person and/or a third party (La Fond & Srebnik, 2002).

However, taken by itself, this argument is insufficient to justify the abolition of physical restraint. It only allows one to conclude that the decision to immobilize someone should have the approval of her legal representative or guardian, or even the judge, in those cases in which the patient's ability to make decisions may be seriously affected. Besides, as the situation may be one of great urgency, there might be no time to request such prior informed consent, as the immobilization is a response to a situation of imminent risk. The legislation typically anticipates that in those situations the intervention can be carried out, again on reasons of gains and loses – which we will deal with in the next section, on the consequentialist argument. Within the consequentialist argument, though, the informed consent angle suggests the interest of adopting a prevention strategy by raising the issue of how to face a situation in which the pation may become aggressive or be a threat to herself, so that a common plan could be agreed beforehand.

One option to avoid a non-authorized coercive intervention could be to request a prior authorization as part of the admission to the facility. In other words, on registration the patient could be asked to accept restraint as a possible intervention, in case of necessity, in the style of the prior authorizations that some nursing homes for the elderly used to request at the time of admission. It does not seem highly recommended, but rather a *carte blanche* that in any case would require clarifying as explicitly as possible the extreme conditions in which containment could be used. It is also true that family members often accept this measure because they have been the victims of previous incidents and know first-hand the extreme situations that can lead to assault, and therefore a curator might accept the eventuality. Again, it can be viewed as a form of coercion, of blackmail: "unless you are ready for physical restraint, you will not receive medical assistance".

Be that as it may, the argument of the lack of informed consent, given the legal regulation in Spain for involuntary internment (which by the way, the Constitutional Court has declared not in accordance with the law to the extent that by affecting a fundamental right, it should be regulated by an organic and not ordinary law as it currently is), does not in itself constitute an argument against mechanical restraint. Rather, it constitutes a vindication of the patients' right to health, and a criticism of a coercive psychiatry, which decides independently of the patient and the family.

Nevertheless, as we have suggested, it could well be that, if requested, authorization for restraint from curators might go smoothly in most, if not all, cases.

The Argument from Consequences

The third type of argument, the utilitarian one, ponders mechanical restraint from the point of view of its consequences. If the positive consequences outweighed the negative ones, the immobilization procedure would be justified. To begin with, then, what positive consequences can such a procedure have? Positive for the patient, from the outset, there does not seem to be any. It is certainly about preventing the person from causing harm, to himself or to another person, during her agitated state, but immobilization by itself is a form of harm (Bird & Luiselli, 2000). In addition, an intervention of this type also involves health risks. In some cases, the death of the patient has occurred, or cases of troboembolism, (Evans et al., 2003); and also has consequences that can be traumatic. In the same way that the electroshocks of the 1970s, which were provided live and without anesthesia, undergoing mechanical restraint can cause a great suffering to the patient, with long-term effects. In addition to the trauma caused by the situation experienced, it can make any form of therapeutic alliance with the members of the health system impossible, when such alliance is even more essential in mental disorders than in other medical specialties.

The reader can easily submit herself to a mechanical restraint situation to understand the harshness of the five-point immobilization experience when it lasts beyond 10 min. If only because you can't scratch your nose, no matter how itchy. Or look at the cellular phone. And let's not say the feeling that comes from seeing that no one responds to a demand for help. It is a useful exercise to get an idea of the situation. There is also evidence of long-term effects of having been restraint (Chieze et al., 2019; Jaeger et al., 2013).

On the other hand, of course, there is the need to face a situation of personal alteration, which could lead to a damage that could sometimes be even greater, if it affected the patient's own life, or posed a serious threat to a third party. As it has already been pointed out in the discussion of the dignity argument, the question of how restraint is carried out comes to the fore, insofar as the actual procedure could be modified so as to minimize some of its negative consequences. If restraint is indeed decided when there is no other viable alternative, and it is carried out with such precautions, the argument of consequences also does not allow the conclusion that resorting to mechanical containment is never justified either. The benefits might then overcome the harm – but only in very extreme circumstances and for a very short time. From a consequentialist point of view, the justification of this procedure depends on whether there are viable alternatives, and on the specification of those exceptional conditions, where no other procedure is available. In any case, a consequentialist argument has to be based on the evidence of the beneficial effects, and

despite how often restraint is used, the evidence is not clear that this practice is beneficial (Prinsen & van Delden, 2009).

A Proposal on the Requirements

In view of the discussion of the reasons for and against mechanical restraint, therefore, the clearest provisional conclusion is the following: that it might be justifiable in exceptional cases, but only if there is not an possible alternative available, and it is carried out taking particular care so as to make it the shortest.

Now the question that suggests itself is whether there always are a viable alternative for the circumstances of great alteration and life risk (Paton et al., 2016). Unfortunately, there is not much in that respect: verbal deactivation techniques and seclusion, that is, confinement in padded or sensory rooms, where the patient is isolated, but not tied up. Verbal deactivation techniques are intended to calm the patient, reduce her state of agitation, of alteration, by keeping the conversation going, as a way to provide support. It involves speaking calmly, listening thoroughly to what the person tells us, trying to agree with something at least, offering understanding as a way to help. It is a common technique in dealing with people with severe mental disorders, whose emotional susceptibility makes them overreact to some daily events and through calm conversation we can achieve a decrease in their activation level. But unfortunately on these critical occasions of special agitation, which can be induced by substance abuse, verbal containment may be insufficient. Of course, it could be prolonged in time, in the style of the Open Dialogue proposal (Seikkula & Arnkill, 2016; Lakeman, 2014), hoping that the activation of the person is progressively reduced, but this passive attitude does not allow a way to react to an attempt of autolysis or of aggression.

As for seclusion, it is certainly an alternative to immobilization, but it does presuppose some form of initial restraint to be able to transfer the person inside the room. On the other hand, this formula imposes isolation, while immobilization does allow accompaniment, which should help to reduce the harshness of the experience. In many occasions, the immobilized patient reduces her agitation once the restraint has taken place and becomes open to verbal interaction. The evidence available is not yet clear on which procedure is preferable (Gleerup et al., 2019).

Of course, it could be argued that chemical restraint, or sedation, is also an alternative. In the case of intellectual disability, for example, it seems that antipsychotics are often used to this goal, even in cases without associated psychotic disorders. According to a recent study, 37.7% of adults with disabilities who present problematic behaviors take this type of medication (Bowring et al., 2017). In the case of serious mental disorders, the usual practice until 30 years ago were doses that kept the person with the disorder in a state of permanent apathy, so that they lack the will to oppose the wardens. Seen from this perspective, then, this type of practice does not meet the requirement of human respect in the first place. Having someone permanently half asleep as a means of avoiding problematic behaviors can be seen as

another form of coercion. In this case, it would not be a question of therapeutic prescription, but of blocking the will of a person by chemical means.

A different option consists of a punctual sedation, in a crisis situation. The latter is usually used in combination, rather than as an alternative, to mechanical restraint, to avoid having to exert extreme physical force, or the intervention of a whole bunch of people, in the placement of the fasteners. But sedation cannot be indefinitely prolonged, and dosification is relevant.

Therefore, as long as an alternative procedure is proposed, mechanical restraint can be justified. It should be a last resort procedure, for extreme cases, and for very short periods of time. In accordance with this approach, the conditions under which this measure can be used should be made explicit. It would be necessary to establish a shared responsibility of the team in this regard, and not leave it in the hands of the psychiatrist, since generally she is the one who deals the least with the person admitted, and may not know the possible reactions. It should not be carried out as an "easy" solution to a problem of keeping the internal order of the facility. I should not be a disciplinary measure, nor a way to alleviate the lack of resources or personnel, or as a way to be able to enjoy a rest without interruptions, for example, or for comfort.

There are requirements to comply with in the way to carry it out. The way to carry out the measure should be for the minimum time necessary, with continuous monitoring, as recommended in the report of the European Committee to Combat Torture (Bergk et al., 2011), with frequent visits and preferably presence, and with continuous monitoring of vital signs. In addition, in a place protected from the gazes of the curious, to preserve privacy and confidentiality. And replace it with some complementary pharmacological treatment to eliminate the restraints as soon as possible.

Lastly, a record of these exceptional situations should be kept, allowing their monitoring and external supervision, guaranteeing confidentiality. Transparency on the use of these exceptional measures, and external supervision on the timing and justification of their use, and on the effective implementation protocol, should be incorporated into the inspection of services, precisely as a guarantee of scrupulousness in the use of this measure.

Of course, it would be much better if those extreme situations could be avoided from the beginning. The goal should be to prevent the occurrence of these extreme situations. For instance, by psychoeducation of the patients to induce adherence (Lay et al., 2012). The best way to achieve the disappearance of immobilization practices is that they are no longer necessary, and that might happen by improving previous interventions. A reflexive analysis is required when physical restraint is decided, in order to shed light on what could have been done previously in order to prevent the critical situation, as a learning process. The community psychiatry intervention model offers the most effective and efficient guidelines, based on the available evidence, to maintain people's mental health in the longer term, and avoid relapses and readmissions. The objective must, without a doubt, be to eradicate mechanical restraints, but in the meantime, they should be kept at a minimum and carried out with particular care.

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