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Clinical and research ethics as moral strangers

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Abstract

This article takes issue with those who defend a brand of clinical research ethics that tends to substitute the ethics of clinical care of patients being recruited as trial subjects. The distinction between therapeutic and non-therapeutic studies is being disregarded by arguing that research is concerned with the pursuit of knowledge rather than with the medical benefits for patients. Non-competent patients may therefore be recruited for studies that will offer them no medical benefits in spite of involving them in the inherent risks of any biomedical trial. Supported by the World Medical Association, clinicians tend to shun the use of placebos in randomized trials, because of the therapeutic void created in the control group. Nevertheless, investigators continue to consider that scientific purity demands the use of placebos as the most appropriate comparator, even if risks to patient-subjects are increased. Equipoise and clinical equipoise have been suggested as adequate criteria to evaluate the need for a clinical trial, when genuine uncertainty about the equivalence of medical measures requires clarification. If equipoise is understood as a balanced situation where alternatives are equivalent and exchangeable in the view of experienced and current medical thought, no comparison seems warranted until a substantiated doubt about their true equivalence appears. Whereas respecting equipoise is an important measure to curb redundant research, new trials become mandatory if equivalence is reliably questioned. In the best interests of patients being recruited for clinical trials, they should continue to be the full beneficiaries of clinical ethics, in addition to receiving the protection of research ethics. Placebos and sub-medication for control groups are to be used sparingly, and best existing therapy should be employed as control when new and promising agents are developed.

Key words: clinical research, ethics, placebo in clinical trials.

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INTRODUCTION

Science moves faster than ethics, and consequently the agility of biomedical research far outstrips the pace of research ethics, even though both fields are increasingly active and productive. There are several reasons why a reflection on this mismatch is necessary and urgent. First, the soaring costs of research are straining the economy of universities, research institutes and government grants, requiring priorities to be set, value considerations to be analyzed, and some investigations to be curbed. Secondly, science is producing powerful technical instruments, the widespread influences of which are difficult to foresee: we do not know the ultimate consequences of genomic exploration and genetic manipulation, nor can we anticipate the effects nanotechnology might unleash. Both biology and medicine are evolving at a pace that may transform mankind's reality and its values, making ethical reflection all the more mandatory. And thirdly, citizens and communities are faced with alternative technical options where value estimates are of essence: should a community invest in a high-tech hospital or rather concentrate on primary-care facilities and develop an efficient referral system? Should an 82-year-old grandmother be subjected to cardiac surgery or will she be better off with medication? Will the people be better served with a proactive renal transplant strategy or should an increase in dialysis machines be contemplated? It is essential and urgent to find ways of reuniting and harmonizing clinical ethics and its emphasis on patients' well-being, with the biomedical sciences in search of knowledge.

James Lind was the first to use control groups in his study on scurvy (1747), and in subsequent decades many spectacular advances were brought about by observation and experimentation on animals, cautiously extrapolated to human beings, usually in desperate clinical situations. These pioneering work, as well as some famous

self-experiments, gave way during the 20th century to control group studies with human subjects. Research ethics started with isolated comments on the need and adequate form of including patients in research protocols (Amiel et al. 2001; Schwitalla 1929), the first formal normative being issued in Germany (1931) (Sass 1983), to be followed by the Code of Nüremberg (1947), the successive Declarations of Helsinki (1964–2000), the Belmont Report (1978)[1], Guidelines by the CIOMS (Council for International Organizations of Medical Sciences 2002), and Documents by the Nuffield Foundation, to name only the most well-known.

CHANGING SCENE OF BIOMEDICAL RESEARCH

Biomedical science has privileged methodological purity of research over clinical ethics concerned with patient-care: "patient volunteers are at risk of having their well-being compromised in the course of scientific investigation" (Miller and Brody 2003). The present review will look at the erosion suffered by such basic values as autonomy and beneficence, as well as the impact that the use of placebos and the denial of equipoise has on patient care, making it clear that research ethics and clinical ethics have become opponents to the detriment of the medical interests of patients. This trend has gained increasing momentum since the advent and enthusiastic reception of evidence-based medicine (EBM), although some criticism to EBM has been raised (Gupta 2004). At the same time, ethical considerations and norms concerning research have lost their stringency and become progressively less binding, to the point that the Declaration of Helsinki has been considered a marginal opinion that "provides minority statements devoid of justification or elaboration" (Lie et al. 2004). Reputed scientists have been quoted as stating that "the United States and most other countries have been ignoring the Declaration of Helsinki for years" (Macklin 2004). After the latest Declaration of Helsinki was launched in Edinburgh (2000), its weakness became apparent when it had to accommodate qualifying addenda to the paragraphs on placebos and on post investigational benefits.

In recent decades research has migrated to the commercial realm, one of its main purposes being to secure patents and develop marketable products. Pharmaceutical companies have doubled their R&D expenditures between 1997 and 2001, moving sizable portions of their research to less developed countries (Nuffield Council on Bioethics 2002). For-profit science stimulates much redundant research e.g. "me too drugs" (Angell 2004), and explains why research strategies have allowed the 90/10 gap, according to which most resources are channeled into investigations of interest solely to wealthy minorities. Much of biomedical science is driven by material interests, and less by therapeutic concerns, as illustrated by the redundant proliferation of certain well-selling medical drugs, and the detection of ethically dubious practices (Elliott and Abadie 2008). Criticism of this kind does not apply to research genuinely driven by a quest for knowledge or to such studies as are searching for a much needed solution to pressing social problems. It is also true, nevertheless, that studies sponsored by pharmaceutical companies increasingly divert resources and efforts to for profit investigations, concealed by vaguely claiming an overriding concern for the common weal. Unsubstantiated statements have been brought forth to suggest that every citizen is under obligation to serve as research subject, or that social benefit makes it acceptable to recruit children and the mentally incompetent in non-therapeutic research (Rhodes 2005).

The undisputable aim of medical research is to secure empirical evidence about the efficacy of medical diagnostic, preventive and therapeutic methods. EBM would seem to be the most legitimate of biomedical research endeavors. Nevertheless, this approach is plagued by methodological and ethical problems, having been freely used by health care providers, at times in disagreement with medical practitioners, to question treatments that may be empirically useful but lack sufficient evidence-based research, or where group evidence does not seem to apply to individual patients (Tavakoli et al. 2000). Many physicians give EBM only partial credence in their clinical decisions, not because they miss scientific rigor, but because research settings differ so much from their actual practice (Young and Ward 2001). Critics have noted that EBM tends to be applied in clinical situations that affect the wealthy, neglecting the health problems of the disadvantaged, where social and cultural factors are prevalent and trials are less likely to come up with patentable and financially attractive interventions (Rogers 2004). Research based on randomized clinical trials is the gold standard for many, but not all, trials, harboring its own ethical problems so that, in spite of flourishing research, medicine continues to be a practice based on knowledge, experience and intuition. Epistemologists have remarked that solid scientific methods such as internal validation, as proposed by EBM are obtained at the cost of fragile extrapolation of external validation. Studies in epidemiology are conspicuously prone to this validation discrepancy (Victoria et al. 2004).

Prominent scholars have defended stringent scientific standards in clinical trials, arguing that the distinction between research and therapy and the ethical implications thereof needed to be separately preserved (Miller et al. 1998) thus moving from a solid protection of research subjects, to a strong support of projects often oriented towards pragmatic goals only indirectly related to relevant biomedical inquiries, such as securing patents, developing marketable products, obtaining grants, and pursuing academic careers. The impact on

[1] A preliminary Belmont Report was issued in 1978, the full official version in 1979.

clinical medicine has been to recruit subjects who used to be excluded from research programmed because they lacked mental competence, either because they were too ill to be burdened with additional risks, or were living in a dependent condition and believing, rightly or not, that refusing cooperation might in some way have negative consequences for them.

THE DERAILMENT OF AUTONOMY

Prior to Helsinki, research subjects were expected to give "voluntary consent", as the Nüremberg Code would have it, to participate, in a similar way that paternalistic medicine secured a *pro forma* agreement to what the doctor had in mind to do. It soon became obvious that individuals needed to know what they were consenting to, by being informed about the purpose of the research, the possible benefits they might expect, and the risks it entailed for them. Informed consent became the accepted standard of subject recruitment, based on the assumption that candidates were mentally competent to understand pertinent information and fully autonomous to decide. Investigators shied away from such a cumbersome procedure, and both Beecher in the US and Pappworth in the UK detected deficiencies in securing consent to be one of the most frequent ethical violations appearing in published papers (Beecher 1966; Pappworth 1967). Well into the 1980s, the issue of informed consent began to make a distinction between autonomy and mental competence, recognizing prisoners, soldiers, derelicts, the homeless and other captive groups as not free to consent or deny their participation. They were competent but hampered in their exercise of autonomy.

Unfortunately, as these fine points were being accepted, research began moving away from developed nations, and settling in areas where poverty, lack of education, chronic disease and malnutrition enfeebled the population and rendered them more susceptible to the additional risks of research. These people were wrongly labeled as vulnerable, for they were not merely predisposed to harm but actually harmed – vulnerated – (Kottow 2003). What made matters worse was Norm 13 of the CIOMS Guidelines for Biomedical Research in Human Beings (2002), which states: "Those persons are vulnerable who are absolutely or relatively incapable of protecting their own interests", adding that "individuals conventionally considered vulnerable are those with diminished liberty or capacity to consent or to refrain from consenting"(Council for International Organizations of Medical Sciences 2002). Thus, autonomy and informed consent in less developed countries have been severely curtailed by the simple expedient of labeling individuals and populations as vulnerable.

Autonomy was also battered in the developed countries (Kottow 2004). Some years ago, Veatch presented his doubts about the adequacy of informed consent in clinical settings (Veatch 1995). A still controversial area is biomedical research that claims exception to these ethical concerns when studying unproven, experimental methods in emergency situations, where informed consent is not available nor necessary, risks are unknown, and medical benefit is uncertain (Truog et al. 1999). Patients in emergency situation may be subjected to experimental therapy without direct or proxy consent (Truog 1999), as explicitly stated in a federal regulation in the U.S. (1996), and non-therapeutic research in incompetent individuals has been advocated in the name of medical progress, scientific knowledge, or the common weal (Rhodes 2005). Emergency room physicians may proceed under these circumstances, provided no reasonably effective therapy is currently in use, the innovative agent has some basis to recommend it, and potential risks do not exceed possible benefits (Dickert and Sugarman 2007).

THE ELUSIVENESS OF BENEFICENCE

A main concern of present day researchers is that patients entering a trial should not harbor the unsubstantiated belief that medical benefits might accrue. The so-called therapeutic fallacy reflects the all too frequent hope that entering a trial will in some way be of medical benefit (Appelbaum et al. 1987). Investigators fear that deception could lead to conflict, but on the other hand this fallacy occurs so often that it seems plausible that the therapeutic misconception is, in fact, a therapeutic misinformation ambiguously insinuating some benefits in order to gain subjects' confidence and consent. Another source of fallacious expectations could arise because patients simply cannot conceive that their doctors will refer them to a study that entails risks but no medical benefits. Insistence on the therapeutic fallacy as an erroneous perception of research subjects suggests that the concept is used as a smoke-screen to justify a no benefits policy (Stone et al. 2005). After all, the initial description of the therapeutic misconception was gleaned from "interviews with patients with psychiatric disorders that documented failure to appreciate the difference between research and treatment" (Henderson et al. 2007).

Patients do not participate in clinical trials in the neutral way investigators would have it. Although usually wary of major expectations, they do hope for some improvement in their medical condition. In addition to explaining risks and negative side-effects, informed consent procedures must assuage the perceived threats patient-subjects feel if they are to be taken off their current medication, and possibly randomized to a placebo group. If investigators fail to benefit their subjects directly, they should at least offer such prospective benefits as might accrue from the investigation, a request that is explicitly formulated in the Helsinki and in UNESCO's Universal Declaration of Bioethics and Human Rights. Nevertheless, this suggestion is "honored in the breach" and generally denied as being too onerous (Crouch and Arras 1998).

The incorporation of research subjects who will not benefit and are incapable of giving informed consent, has been justified by stating that, since the proper function of research is to accrue knowledge and attend the social good, "reasonable people should endorse policies that make research participation a social duty" (Rhodes 2005). Evans endorses a civil obligation for citizens to be entered "automatically" in clinical research protocols, whereas Harris prefers to call it a moral imperative that holds provided research is scientifically sound, of cognitive value, and only minimally risky or inconvenient, at the same time admitting that for profit research does not command such a moral imperative (Evans 2004; Harris 2005). This point has not been clearly taken by the Declaration of Helsinki when stating that "considerations related to the well-being of the human subject should take precedence over the interests of science and society"[2]. Admittedly, documents have been ambiguous in the matter of beneficence, and have failed to elaborate on the incongruity of evaluating risks to individual research subjects and then excluding them from any benefits by inconsistently referring to the social good. The much celebrated risk/benefit evaluation, which should carry special weight according to the Belmont Report, receives no more than lip-service, especially in the case of incompetent subjects. Vagueness about the social good is working here both ways, by postponing it in the name of the patient, or praising it beyond individual interests.

Not much needs to be said about risk in the research setting, where accurately assessing negative effects is intrinsically impossible precisely because of the investigation's imponderables. When studying a new drug, researchers do not know the probability, the magnitude, or the nature of eventual risks; consequently, a risk/benefit assessment becomes uncertain. The recently introduced idea of minimal risks, supposedly valid for subjects unable to give informed consent, is becoming an abridged version of risk evaluation, still in need of adaptation to different contexts and cultures (Wendler 2005).

The contingency of the traditional principles of bioethics have led to disruptive situations placing undue tension on the integrity and well-being of patients, often interfering with their therapeutic schedules. Researchers are increasingly interested in recruiting sick human beings, even if a direct therapeutic question is not posed, leading to conflict between scientific accuracy and clinical care. Healthcare professionals must be wary of having their patients enter clinical trials that entail unknown risks and discomforts without yielding any benefits for their medical condition.

[2] I owe this important point to an anonymous reviewer.

THERAPEUTIC VS. NON-THERAPEUTIC CLINICAL TRIALS

In its first version, the Declaration of Helsinki (1964) presented a clear and emphatic distinction between "research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research". H. Jonas wrote an influential paper demanding that no research be done on patients unless they were to obtain clear and direct medical benefits (Jonas 1965). There is no clear moral justification to subject sick people, whether competent or not, to trials that are of no value for them, more so considering the considerable amount of research protocols being carried out mainly for profit. Non-therapeutic research does not permit such flexibility, nor do third-party instances have the authority of consenting to research that will be of no benefit to autonomy-impaired subjects.

The distinction between therapeutic and non-therapeutic trials has been diluted and finally rejected by researchers who claim that clinical trials always carry elements of therapy, just as therapeutic efforts consistently contain research aspects. The so-called difference position aims at "recognizing the distinction between research and therapy and, accordingly, abandoning the distinction between therapeutic and non-therapeutic research" (Miller and Brody 2003).

The distinction between these different approaches has important consequences, especially with regard to informed consent. Autonomous subjects may well decide, for whatever reasons to enter a trial that will not benefit them, even if it entails certain risks. Ingelfinger observed many years ago that patients are never in full command of autonomy, not because they are confused by sickness, but because they are in a dependent position: "Incapacitated and hospitalized because of illness, frightened by strange and impersonal routines, and fearful for his health and perhaps life, he [the patient-subject] is far from exercising a free power of choice when the person to whom he anchors all his hopes asks [if he is willing to join a research project]" (Ingelfinger 1972). By becoming a research subject, the patient most probably will be discontinued from his routine medication and risk becoming a therapeutic orphan for the sake of scientific purity. Research ethics is intent on avoiding or reducing risks, but showing less concern for the well-being and protection of patients, or with the course of the underlying disease when it is not relevant to the investigation. Researchers like to insist that patients recruited for trials are no longer under the protection of clinical ethics (Miller and Weijler 2003). The staunch defense of placebos and the ambiguous but generally negative stance regarding equipoise, reflect the priority given by such reputed investigators to scientific purity above clinical care, and their firm belief that banning placebos would make the evaluation of new drugs almost impossible (Fried 1974; Macklin 2001).

EQUIPOISE

The term was coined by philosopher Charles Fried to define a clinical situation in which an individual physician is in genuine doubt about the merits of alternative therapeutic courses, consequently seeing no harm in entering her patients in a randomized controlled trial. If, however, the physician is convinced that the alternatives are not equivalent, she should discourage her patients from entering a trial where they might be assigned to the less active group. Such an understanding of equipoise might help physicians advise their patients to accept a trial or not, but it has no influence on whether initiating a research protocol is justified (Freedman 1987; Temple and Ellenberg 2000). Freedman suggested the concept of clinical equipoise, situation in which the medical community was in doubt as to the relative merits of alternative therapies. If 70% of clinicians favor one agent over the other one, equipoise is considered disturbed and no comparative trial is necessary, for a 70:30 discrepancy seems to settle the question by showing that one agent is clearly superior and should be preferred (Johnson et al. 1991).

Some writers conclude that equipoise is a "poor guarantor that participation in a study will not be bad for a particular patient", so that "if subjects want to enroll in a study that is bad for them, doing so should be their choice" (Menikoff 2003). At times, equipoise is dismissed as unimportant because "other considerations – informed consent, utilitarian tradeoffs, or some other – make such trials, or such sub-optimal treatment, acceptable despite the fact that therapeutic obligation is violated" (Gifford 2007). The ethics of such statements are more than debatable, and should be contrasted with the opinion that equipoise may be an indicator of clinical uncertainties that need to be cleared for the benefit of patients (Jansen 2005). Other scholars are better disposed to accepting equipoise as long as it serves to protect patients from unnecessary or harmful research, requiring "physicians conducting research always to place the interests of their patients before the interests of research" (Miller and Weijer 2003).

Controversial arguments on the subject have been presented by scholars who defend equipoise as a safeguard against redundant research, while others support investigators' neglect of equipoise when they are testing new "me too drugs" with the main purpose of gaining a niche in the pharmaceutical market (Angell 2004), or producing other benefits such as new patents, social prestige or academic privileges. The protection of patients from unnecessary clinical trials is undermined if equipoise is not employed as a litmus test of relevant research.

There are two varieties of equipoise that have not been sufficiently differentiated. Genuine equipoise exists when medical opinions agree that available evidence shows no substantial differences between alternative medical methods diagnostic, preventive or therapeutic. That is a state of sustainable equipoise and, since patients are equally well taken care of by any of the accepted alternatives, there is no reason to embark in a comparative study, nor should a new drug be tested unless preliminary studies suggest that the existing equipoise will be disrupted, either by gaining a more effective agent or by reducing unwanted side-effects.

On the other hand equipoise may be unstable, because a significant number of physicians rely on evidence denying that true equipoise exists, usually arguing that one of the apparently equivalent alternatives causes unwanted side effects. In such cases of intolerable equipoise, a clinical trial is mandatory to test these discrepancies in order to dissolve, or uphold, the equipoise situation. In sum, both sustainable and intolerable equipoise should be considered to the benefit and protection of patients, either by discouraging redundant research, or by disclosing possibly false equivalence of disparate therapeutic agents. Since equipoise is a comparative criterion between alternative medical agents, it tends to be incompatible with the use of placebos, which may be the main reason why researchers inclined to using them as comparators reject the idea of equipoise, under the assumption that "clinical equipoise provides erroneous ethical guidance for placebo-controlled trials" (Miller and Brody 2003).

PLACEBOS

Researchers prefer to use placebos when studying a new therapeutic agent, for an inactive arm is a very amicable comparator. As Robert Temple, a high official at the FDA approvingly remarks, using inactive substances in the control group makes the experimental drug look more effective than if compared to current medication (Macklin 2004), but the significance of such a result remains untested. Such a trial does not offer a reliable comparison of the new agent against currently employed treatments and, for the duration of the trial, patients randomized to the control arm will no longer receive the medication they need and were receiving before entering the study. This makes placebo trials unethical from the clinical point of view, the mark of scientific excellence being obtained at the cost of creating therapeutic orphans.

Placebos are also favored by researchers testing weaker doses of such therapeutic agents as are known to be effective but too expensive to be widely affordable (Grady 1998). The comparison of sub-medication against placebos has been recommended and employed in severely disadvantaged populations having no access to basic medical care. Since these subjects lack treatment for their diseases, they are considered to be natural placebo groups who will not be worse off if recruited for a study and randomized to the control arm, whereas they might benefit if the study shows the cheaper, less-than-best agent to be effective. If reasonably effective, sub-medication could be a possible answer, and placebos are conveniently used as a comparator to prove that

this cheaper agent is still better than no medication at all (Lie 2004), although placebo opponents will insist that lower-dosage alternatives be compared with the best proven method, hoping that the less costly agent will still be reasonably effective (Lurie and Wolfe 1997). This is of course wishful thinking, for the selected population is too poor to gain access to even the cheaper medical version, there being ample evidence that the availability of medical progress is strongly biased to the detriment of the disempowered (Rogers 2004).

A highly vocal defense for the use of placebos comes from policy-oriented randomized clinical trials, in which an affordable cost/benefit ratio is sought when the best proven therapy is too expensive, and an alternative with less but still reasonable effectiveness is sought. Trials of this kind are commissioned by public health care systems that believe they cannot afford some of the more expensive treatments in existence. Economic considerations usually prevail over the deliberation of ethics, purporting to be faced with inflexible contingencies that make it mandatory to ration resources.

The pro placebo lobby is inordinately strong, having imposed on Helsinki 2000 an addendum to paragraph 29, which had vigorously limited their use, finally concluding that placebos might be acceptable for scientific reasons a very flexible condition, or when research was done on minor conditions, "and the patients who receive placebos will not be subject o any additional risks or serious and irreversible harm" as the note of clarification on paragraph 29 states and ratified in Seoul (Declaration of Helsinki 2008).

ETHICS OF RESEARCH AND CLINICAL ETHICS

When patients are recruited for a clinical trial, it is to be expected that their medical care will continue to be fully honored, in addition to the protection they will gain within the research protocol. Unfortunately this does not happen, for the doctor-patient relationship is replaced by an investigator-subject interaction where the patients' well-being is no longer material and must make way to a neutral status of subjects to be quantitatively assessed. The patient is taken off his usual medication and becomes a therapeutic orphan whose medical treatment is now a matter of randomization. Since the opposition between protective clinical care and stringent research methods is not solvable, it may be advisable to uphold the distinction between therapeutic and non-therapeutic trials, and require that clinical research be well designed, cognitively promising, and minimally risky.

There is hardly any question in the mind of researchers, that their ethical concerns are basically restricted to avoiding unreasonable risks to their subjects, and that they are exempt from the burdens of clinical care: "Regardless of investigators' motivations, patient volunteers are at risk of having their well-being compromised in the course of scientific investigation. Clinical research involves an inherent tension between pursuing rigorous science and protecting research participants from harm" (Miller and Brody 2003). Statements of this kind would hardly pass Pappworth's rule: do not burden research subjects with risks you would not be willing to impose on your family (Pappworth 1967). Arguments on this and related issues are strongly biased and often come to contradictory conclusions. Whereas Moreno laments that too much regulated protectionism of research subjects has undermined the "researchers' discretion in governing their conduct with regard to human subjects" (Moreno 2001), Mastroianni and Kahn observe that protection has all but disappeared in the wake of including subjects who where previously were not eligible because they were either mentally incompetent, restricted in their autonomy because they were captive or dependent, or in a specially susceptible condition such as fetuses and pregnant women (Mastroianni and Kahn 2001).

Pressure on patients to participate in research is increasing: "society already accepts the idea that participation in the achievement of an important social goal can sometimes be made a condition of patient access to medical care" (Orentlicher 2005). Another unfortunate development has been the introduction of the term "ancillary-care", meaning that researchers are not bound to attend to the full medical needs a patient might develop during his recruitment, unless it can be demonstrated that his complications are directly due to the drug being tested (Richardson and Belsky 2004).

CONCLUSION

Medical ethics and the ethics of research are diverging to the detriment of patients, who lose protection as they are moved from the ward to the lab. Clinical research is no longer in the hands of patient-caring physicians, as biomedical investigations retreat from the lived body of the diseased subject, even neglecting the living body of the human organism, in order to concentrate on their research targets. Research revels in the scintillating world of drug trials, delving in the intricacies of the gene, the protein, the enzyme or the nanoparticle, where the patient merely serves as a donor of biological material or as experimental recipient of some novelty. Powerful interests make it improbable that this trend might revert. The physician is overruled in his care-giving endeavors as patients become research subjects that face new risks, have their therapies modified or suspended, and are submitted to tests their medical condition does not require. The loss of the therapeutic/non-therapeutic distinction puts the mentally incompetent at risk of being recruited for research they will not benefit from.

A perhaps far-fetched solution might be to let Phase II and Phase III clinical trials be managed by the same physicians who are taking care of their patients

and continue to follow the well-established norms of clinical ethics, overseeing that research methodology does not infringe upon the ethics of clinical care. Clinical research will be ethical if it abides by a comprehensive code encompassing both medical and research ethics, thus avoiding redundant trials, protecting research subjects, taking especial care of those that are dependent or mentally incompetent, and safeguarding that reasonable risk-benefit ratios are not trespassed.

Instead of purposefully widening the gap between clinicians and investigators, it might be more in line with medical ethics and the need of patients, to remember that bioethics was conceived as a bridge between knowledge and humane practice.

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