Ethics in Biomedical Research

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Abstract

Scientific research on human subjects or animals calls for meticulous ethical scrutinizing and approval of the study plan before any such research can be commenced. Modern techniques such as genetic biomanipulation have brought unforeseen ethical problems calling for special attention. In this chapter we briefly discuss the philosophical and historical basis of ethics with focus on medical research ethics. The process of ethical approval is also being described.

13.1 Introduction

Since the traumatic aftermath of World War II, ethical issues have become an essential part of any research project whether clinical study on patients or good research practice in animal or laboratory studies. In this chapter we briefly review research ethical principles in general and, more specifically, regarding oral health-related research.

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13.2 Ethics Is a Field of Philosophy

The word "ethics" has several meanings in English. In philosophy, it refers to philosophical ethics or moral philosophy, but in the ordinary language it merely can refer to common human ability to ponder ethical problems. Further, the word "ethics" may describe idiosyncratic principles or habits of a particular person. We first discuss the philosophical meaning of ethics and how the important values and principles influence the decision-making and actions in research.

Ethics as a branch of philosophy is interested in what is morally right or not. Typical questions are the following: "What is the best way for people to live?" and "What actions are right or wrong in particular situations or circumstances?" Ethics thus covers different ways of understanding and examining the moral life. In *metaethics* moral philosophers study abstract issues like the theoretical meaning and reference of moral propositions by asking how should truth values of moral propositions be determined, if ever it is possible to determine them at all. Other philosophers are more interested in the practical means of determining a moral course of action concentrating on the rightness and wrongness of actions. In this *normative ethics*, there are many traditions, for example, virtue ethics, deontology and

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consequentialism of which utilitarianism is a well-known example. *Applied ethics*, also called practical ethics, is the main concern in biomedical research. It aims to apply normative ethical theories to specific cases and situations of human life by telling what is right and what is wrong. Bioethics and professional ethics or moralities such as medical ethics are examples of applied ethics.

Ethics is pluralistic and what is ethical may differ in different societies. Philosophers may also give different answers to the same question. Even the concepts may be defined in divergent ways. Dissimilar and opposing views arise in philosophy which, in turn, lead to progress and improvement of ethical thinking. However, there is sufficient consensus about fundamental research ethics [1].

13.3 Ethics and Morality

The word "ethics" is often used interchangeably with "morality" [2], but in philosophy the meaning of the two words is not the same. Ethics is often defined as philosophical study of morality, and moral philosophy and ethics can indeed be used as synonyms. Ethics nevertheless has more to do with philosophical theories and can be defined as a matter of knowing, while morality is more connected with human character and acts as, for example, morally good and honest behaviour. Some philosophers argue that it would be possible to apply some kind of common morality to all persons in all places [3]. Moral philosophers debate whether or not there exists some or any kind of common morality, but this debate is not relevant in the context of research ethics. However, it is of utmost importance that every member of a research group, whether in laboratory, animal care unit or hospital, is familiar with research ethics. Since close collaboration between clinicians and researchers is an essential part of translational research, it is necessary to comprehend and share basic ethical principles.

13.4 Research Ethics

Research ethics is regulated in a different way than medical ethics [3]. Scientific research has for a long time been heavily regulated, while medical practice still is much less regulated. The physician's focus is on the best interests of the patient by relying on proven beneficial treatment choices with acceptable risk. Research on the other hand is hypothesis driven by investigating treatments and questioning diagnoses, which need to be confirmed. Principles like benevolence, beneficence and non-maleficence guide the physician's actions. Empathy should always be there in professional–patient relationship. For the researcher, however, the patient may primarily be research subject where the benefit cannot be guaranteed.

In all medical research, however, it is absolutely necessary to respect the basic ethical principles and protect the rights of the subjects. Furthermore, in order not to lose credibility, it is highly important to keep the confidence of the patients, research subjects and society. Understanding and following the codes and regulations of research ethics, and local legislation, also guarantee high quality of research in all areas.

13.5 From Hippocratic Oath to Bioethics

13.5.1 Hippocratic Tradition and Nuremberg Code

Throughout the history of mankind, medical practicing has been controlled. Both doctors themselves and sovereigns have regulated this action. The earliest written orders can be found from the Mesopotamian law code of Hammurabi, the king of Babylon. The code was written down in about 1750 BC, and it treats questions like the doctor's rights and duties and what kind of punishments should be prescribed for a doctor who due to negligence or unskillfulness caused death

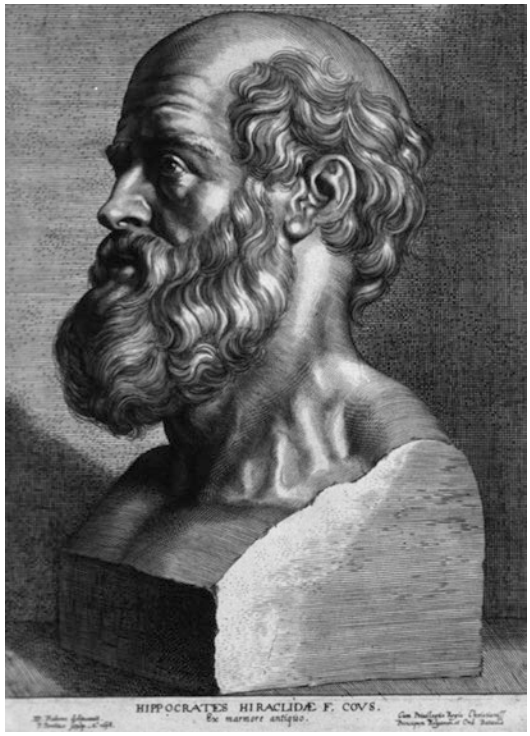

Fig. 13.1 Hippocrates 460–377 BC

of the patient or made other mistakes. Many religious scriptures also have regulations on practising medicine [4].

The Greek physician Hippocrates, who headed a medical school on the island of Cos around 500 BC, is regarded as the father of medicine and medical ethics (Fig. 13.1). The Hippocratic school mostly had writings about medicine, science and ethics [4]. It is thought that the concept of medicine as a profession comes from Hippocrates who emphasized that a physician must always place the interests of the patient above his own and that this promise must be made public: the *Hippocratic Oath* [5]. The Oath further demands collegiality, duty to render aid, refraining from causing harm or hurt and concealment. All these still are essential part of modern medical ethics. The Hippocratic Oath thus is the model of ethical codes in medicine, and it maintained its position until the middle of the twentieth century.

The need for something broader than the traditional Hippocratic medical ethics became apparent after World War II and the special tribunal at Nuremberg, Germany. Many Nazi physicians were tried and convicted because they had violated fundamental human rights in their research during the war. The trials began on December 9, 1946, and the verdict was delivered on August 20, 1947. During the trials ten important points in legitimate medical research, known as the *Nuremberg Code*, were compiled and were used as the basis of the judgement. The Nuremberg Code has been one of the fundamental documents of modern research ethics, and, for example, the request of voluntary informed consent is in the Code. Many are of the opinion that the Hippocratic tradition continues in the Nuremberg Code, which represents a new and expanded interpretation of the Hippocratic Oath endorsing the experimental approach to medicine but at the same time protecting the patient [6].

13.5.2 World Medical Association and the Declaration of Helsinki

In 1947, when the Nuremberg Code was set forth, the World Medical Association (WMA) was also established. A significant reason for establishing WMA was the need to ensure and reinforce the awareness of physicians of their ethical obligations after what had happened in Germany and some other countries during World War II. The WMA is "an international organization that seeks to represent all physicians, regardless of nationality or specialty". One of its roles is to establish general and globally applicable standards in medical ethics both for medical practice and research [5].

Soon after its establishment, the WMA had two important tasks: to define the duties of the physician pointing out also the humanitarian aspects of medicine and to specify the essential principles in medical research. The *Declaration*

of Geneva [7] and the *Declaration of Helsinki* [8] are the result of these attempts and are the most important declarations of WMA. Both have been revised several times already. In January 2005, WMA launched the *Medical Ethics Manual*, which is a comprehensive presentation of ethics and its role in medicine dealing also with medical research ethics (Table 13.1). In addition, many research institutes and organizations have formulated ethical guidelines. For oral health researchers, the International Association for Dental Research (IADR) Code of Ethics is essential [9]. However, the principal guidelines in different documents are mainly the same, and most of them refer directly to the Declaration of Helsinki as the basic code of internationally accepted guidelines in biomedical research.

Table 13.1 World Medical Association's declarations and codes of medical and research ethics

Declaration of Geneva
• The "Physicians' Oath"
• Adopted at the World Medical Association (WMA) 2nd General Assembly in 1948, revised latest in 2017
• The physician declares his dedication to the humanitarian goals of medicine
International Code Of Medical Ethics
• Adopted by the WMA 3rd General Assembly in 1949 and amended three times since then
• Describes the duties of physicians in general, to patients and to colleagues
Declaration of Helsinki
• A concise summary of research ethics as it is defined by the WMA in 1964
• Revised many times to meet the requests of the developments in research and in the technologies; latest revision in 2013
• Regarded as the most important document on research ethics
The WMA Medical Ethics Manual
• Launched in January 2005, 3rd edition in 2015
• A comprehensive presentation of ethics and its role in medicine and research
• Intended also for the use of medical schools throughout the world; translated in many languages

13.6 Biomedical Ethics

13.6.1 Bioethics

As noted before, bioethics is a field of applied ethics. It is interested in ethical questions arising from life sciences, i.e. medicine, biology (including genetics), biochemistry, biotechnology, ecology and many others. Bioethics is inter- and multidisciplinary, and bioethicists have different backgrounds, not only in life sciences but also in disciplines such as sociology, philosophy, theology, history and law. Bioethics began to develop during the second half of the twentieth century with historical background in medical ethics. Modern bioethics is commonly understood to consist of three main subdisciplines, namely, medical ethics, animal ethics and environmental ethics [1]. The need for bioethics arouse because traditional medical ethics was not able to respond to the new questions and challenges caused by technological progress. There were no appropriate tools to treat subjects and issues such as privacy and research involving human subjects in the larger perspective. Bioethics had first the human aspect in forefront. Animal ethics and environmental ethics have then become subdisciplines of bioethics, when the issues such as the responsibility for the nature and environment have emerged. Today, there are established centres dealing with issues of bioethics (Table 13.2).

The rational approach to the ethical issues is through different ethical theories and approaches. Most important in biomedical ethics including biomedical research are virtue ethics, deontology, consequentialism (especially utilitarianism) and principlism. However, none of these can fully answer even to the most usual ethical questions [5]. Hence, comprehensive ethical discussion should include the best features of each of these approaches, briefly described in the following.

Virtue ethics focuses in particular on the character of decision-makers: "What kind of person should I be?" Moral goodness of an action

depends both on the right action and on the right motive. Since antiquity, wisdom, courage, self-control and justice have been the central virtues, that is, types of moral excellence. Virtuous qualities of a physician, for example, are compassion, honesty, prudence and dedication.

Deontology or *duty theories* consider that the basis of morality lies on specific, foundational principles of obligation. Well-founded rules could then serve as the basis for moral decisions. One well-known foundational principle of duty is the "categorical imperative" of the German philosopher Immanuel Kant (1724–1804): "Treat people as an end, and never as a means to an end". People should always be treated with dignity. It is noteworthy that deontology is not interested in the consequences of an action but in motives and intentions. Therefore, an act is thought to be morally good, if the motive or intention, which leads to that act, is good.

Table 13.2 Examples of centres for bioethics

The Hastings Center (originally *The Institute of Society, Ethics and the Life Sciences*), New York
• Founded by Daniel Callahan and Willard Gaylin in 1969
• *The Hastings Center Report*—explores ethical, legal and social issues in medicine, healthcare, public health and the life sciences, both in print and online
• Visiting Scholar Program in collaboration with Yale University
The Kennedy Institute of Ethics (originally *The Joseph and Rose Kennedy Center for the Study of Human Reproduction and Bioethics*), Washington, DC
• Established at Georgetown University in 1971, backed by the Kennedy Foundation
• *The Kennedy Institute of Ethics Journal* is an interdisciplinary journal dedicated to philosophical bioethics, online
• Visiting Researchers Program
Eubios Ethics Institute
• Founded by Darryl Macer in 1990 in Christchurch, New Zealand and in Tsukuba Science City, Japan—Bangkok, Thailand added to the network in 2005
• Nonprofit group aiming to stimulate the international discussion of ethical issues and how to use technology in ways consistent with "good life" (eu-bios)
• Cooperation with many individuals and groups, including, e.g. UNESCO, UNU and Asian Bioethics Association
The European Association of Centres of Medical Ethics (EACME)
• Founded in 1985
• Network of academic and nonacademic centres
• Aim is to promote research, education and consultation in the field of biomedical ethics

Consequentialist theories are, according to definition, interested in the consequences or outcomes of the choices and actions. One of the best-known examples of this is *utilitarianism* where the good is measured by means of utility and may be defined as "the greatest good for the greatest number". The action which produces the best outcome is then the right one. Outcome measures obviously vary and, for example, in healthcare decision-making cost-effectiveness and quality of life are important. QALYs (quality-adjusted life-years) and DALYs (disability-adjusted life-years) are typical examples. From the physician's daily practice, an example could be health and well-being or lack of pain and suffering of a patient. It is, however, important to notice that although the principle "the end justifies the means" is a plausible deduction from utilitarianism, it can never be approved in research. Thus, for example, it is morally unacceptable to sacrifice individual human rights to attain a social goal.

Principlism is currently one important trend in approaches of bioethics. Its origin is connected with the Belmont Report (1978/1979), which, according to definition, is "a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects" [10]. The report defines three basic ethical principles in biomedical and behavioural research, namely, respect for persons, beneficence and justice [11]. Beauchamp and Childress have developed principlism further in the context of medical practice by adding to the list of principles also *non-maleficence*

("not doing wrong"), which in traditional medical ethics is usually expressed as the maxim primum non nocere ("above all do no harm"). Although principles indisputably play a central role in rational decision-making in biomedicine, principlism has been criticized for emphasizing the respect for autonomy over other principles, which is thought to reflect the Western liberal culture and hence not to be necessarily universal [3].

13.6.2 Principles in Applying Biomedical Ethics

Respecting human rights is the cornerstone of ethical assessment. This was proclaimed by the United Nations' Universal Declaration of Human Rights already in December 1948 and has ever since played an important role both in medical practice and in biomedical research. In the following we briefly describe the basic principles that should be taken into account when pondering biomedical issues of ethics.

Respect for autonomy. The word *autonomy* derives originally from Greek words *autos* ("self") and *nomos* ("rule", "governance"). In ancient Greece, it was connected to the independent city-states but now refers to individuals who should be treated as autonomous agents capable of deliberating their personal goals and acting accordingly. In medical context, a person or patient must be able to make his/her own decisions. This is the fundamental principle in biomedical research ethics and also prerequisite for an informed consent. Hence, particular attention is needed in situations where the research subject's autonomy is diminished, and he/she is unable to give consent (for details, see later).

Non-maleficence, "do no harm", was emphasized already in the Hippocrates era. Researches thus have an obligation to avoid causing harm to patients and research subjects. Careful risk assessment is thus a prerequisite in research planning.

Beneficence. While non-maleficence is merely refraining from doing, the principle of beneficence demands more, literally "doing good". Although some authors define the good end in medicine almost exclusively as healing, beneficence is usually thought to have broader sense. It means acting to the best interest of the patient or research subject which may represent different things, for example, development of new treatments, better understanding human physiology, etc.

Justice. The concept of justice is explicated with the terms fairness, entitlement and "what is deserved". In healthcare, it means that individuals and groups are treated in a fair manner which, in turn, may lead to complex questions when, for example, individual and community interests are taken into account. The importance of social value as a criterion, when deciding if a research project should be approved or not, has become more significant. Consequently, it is thought that justice demands that the results of the research should benefit the population in which the research in question is being carried out. Hence it is not fair that research subjects undergo risks and feel discomfort in one place while the beneficiaries are patients elsewhere [5].

13.7 Practical Principles in Science and in Medical Research Ethics

Clinical research on human subjects is necessary for the progress of medicine. Furthermore, animal studies are often regarded as an essential part of research, especially in translational health research. Many different local, national and international codes, rules and policies on research ethics exist both for research on human subjects and for animal experimentation (Fig. 13.2).

13.7.1 Research Ethics Committees

The researcher has not been left alone with the challenging issues of ethics. The Declaration of Helsinki describes the role and the responsibilities of research ethics committees (Table 13.3).

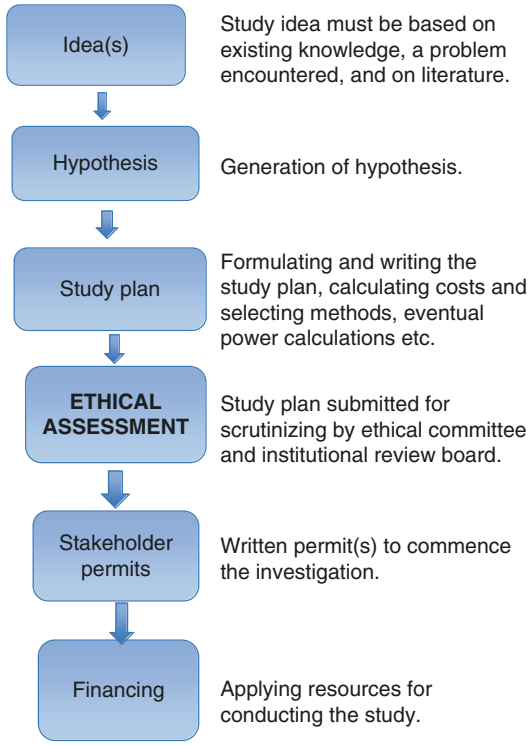

Fig. 13.2 Main steps for attaining permit(s) for scientific investigation. In life sciences approval by ethical committee has a central role

The committee's approval is necessary already before the study may begin, and its task continues in monitoring ongoing projects. The members of the committee should represent expert knowledge of different professions. The researchers have to demonstrate to the committee why that particular study is worthwhile and that they have enough competence to conduct it. Among other things, the committee reviews the research project's justifiability on scientific grounds and estimates the assessment of the risks and benefits made by the researcher. The researcher has to prove that the protection of potential research subjects is appropriately secured. Although the researcher may sometimes feel that the committee's only task is to delay the advances of science, the review and approval of independent research ethics committee actually guarantees the quality of research and is a necessity for the later publication process in any respectable forum.

Table 13.3 The role and responsibilities of an ethical committee

• The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins
• The committee must be transparent in its functioning; must be independent of the researcher, the sponsor and any other undue influence; and must be duly qualified
• The committee must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards, but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in the declaration
• The committee must have the right to monitor ongoing studies
• The researcher must provide monitoring information to the committee, especially information about any serious adverse events
• No amendment to the protocol may be made without consideration and approval by the committee
• After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions

13.7.2 The Concept of Informed Consent

According to the Nuremberg Code, "The voluntary consent of the human subject is absolutely essential". This indeed is the first requirement for research on human subjects. The person involved in a research as human subject must be capable of giving informed consent, and the participation in research needs be voluntary. The consent should be in written form and signed by the research subject. There are special guidelines for cases where subjects with diminished capability are not able to give consent, such as children, mentally handicapped or unconscious patients. There are three important elements in consent: information, comprehension and voluntariness. The research object has to be informed about the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provi-

sions and any other relevant aspects of the study (see Declaration of Helsinki). It is the responsibility of the researcher to ensure that the subject has understood the information. Voluntariness means that the subject has the right to refuse to participate and also to withdraw consent at any moment. Withdrawal must not affect the treatment of the patient. The ethics committee reviews also the "consent form" to secure its legibility.

13.7.3 Physician's Role as a Researcher

One possible ethical problem, which needs attention and which the research group should bear in mind, is the potential dual role of a physician or dentist as a researcher. The role in the physician–patient relationship differs from the role as a researcher in the researcher–research subject relationship. While the researcher is primarily interested in generation of knowledge, the physician's responsibility is always the health and well-being of the patient. The WMA states clearly that if there is conflict between the two roles, "the physician role must take precedence over the researcher". Similarly, a conflict of interest is another potential ethical problem, which a physician–researcher might encounter. One example of this are the rewards offered for the participating physicians. They may be remarkable causing obvious conflicts of interest. Again, the WMA's viewpoint is clear: when the physician follows the basic rules of research ethics, there will be no inherent conflicts since "the ethical values of the physician – compassion, competence, autonomy – apply to the medical researcher as well" [5]. Table 13.4 summarizes the ethical principles for biomedical research on humans here discussed.

Table 13.4 Central ethical principles in research

Respect
• Human dignity, privacy and autonomy must be guaranteed
• Collegiality, teaching and mentoring students and other individuals associated with the research are important to keep in mind
• Discrimination on the basis of sex, race, ethnicity or other factors not related to scientific competence and integrity is forbidden
• International codes of ethics must be literally followed
• Relevant national laws and institutional and governmental policies need to be followed
Confidentiality
• Confidential communications, personnel records, trade or military secrets and patient records must be protected
Do not harm
• Protect research subjects; take special precautions with vulnerable populations
• Carefully avoid errors and negligence, and keep good records of research activities
• Researcher is responsible of proper respect and care for animals used in studies—avoid unnecessary or poorly designed animal experiments
• Maintain competence and expertise in profession—lifelong education and learning is necessary; be open to criticism and new ideas; openness in sharing data, results, ideas, tools and resources promotes the important aims in science
• Remember social responsibility; strive to contribute to social good and prevent or mitigate social harms through research; strive to distribute the benefits and burdens of research fairly
Do not steal
• Honour patents, copyrights and other forms of intellectual property
• Do not use unpublished data, methods or results without permission
• Give proper acknowledgement or credit for all contributions to research
• Never plagiarize
Do not lie
• Strive for honesty in all scientific communications from reporting data, results, methods and procedures; fabricating, falsifying or misrepresenting data is not permitted
• Do not deceive colleagues, research sponsors or the public—capability of being objective is an obvious requirement in science, but maintaining objectivity in the competitive world of science may from time to time imply careful deliberation

Modified from Shamoo and Resnik [12]

13.8 Ethical Issues with Animal Experiments

It was not before the nineteenth century that animal experimentation in research became common. For a long time, it was thought that animals were more or less like machines and did not feel pain, as presented by the French philosopher, mathematician and scientist René Descartes (1596–1650). Since his days, animal behaviour studies have shown that not only animal species feel pain but also that at least some vertebrate animals have abilities to intend, understand and communicate. During the late twentieth century, the animal rights movement emerged, and this together with the new scientific discoveries on animals has given to the public cause for concern about the treatment of animals in research [13, 14].

The debate on the moral status of animals and how to justify their use as research objects is an ongoing process. Nevertheless, it is still difficult to think about biomedical research without animal studies. Many efforts have been made to limit the use of animals and to minimize the harm caused for them. Several countries have national laboratory animal protection laws, and there seems to be a general agreement that the housing conditions and care of captive animals need to reach humane standards. Wherever possible, the degree of animal pain and suffering must be minimized. Furthermore, the laboratory personnel should be competent in recognizing and alleviating pain in animals. It is recommendable that persons other than the investigator concerned should review the proposed experiments. One example of this is the monitoring committees, which serve to ensure legal compliance of the project. Their approval is needed for the research, and they can eventually modify the project to improve the animals' welfare [13–15].

Principles of refinement, reduction and replacement, referred as *The Three Rs*, are of concern regarding animal experiments (Table 13.5). These principles were first suggested by Russel and Burch [16]. *The Three Rs Declaration of Bologna*, signed in the Third World Congress on Alternatives and Animal Use on the Life Sciences in 1999, strongly reaffirms "the vigorous promotion and application of the Three Rs" [13, 17]. The principles have thereafter been successfully applied in many countries resulting in decline in the numbers of animals used in scientific experiments. Nevertheless, in recent years this downward trend seems to have been ceased especially because the use of genetically modified animals has increased [18, 19].

Table 13.5 The three "Rs" that guide animal experiments

Refinement
• Refining the experimental procedures to lessen the degree of pain or distress
Reduction
• The numbers of the animals used should be reduced as low as possible (without compromising the reliability of the research)
Replacement
• Animal studies should be replaced with non-animal methods wherever possible

The *Basel Declaration* is another important attempt in promoting the well-being of animals used in experiments. The Basel Declaration from October 2011 was been adopted by the Basel Declaration Society founded by biomedical researchers from both industry and academia. The Society emphasizes the importance of the three Rs and the transparency when using animals in biomedical research. It aims at bringing the scientific community together to further advance the implementation of ethical principles and trust for animal experiments. The Society strives for establishing the position of the Basel Declaration as a leading document in animal experiments [20].

From an individual researcher's point of view, planning animal experiments calls for corresponding procedures, applications and approvals as with human subjects. Both international and local guidelines need to be known.

13.9 Ethical Challenges Now and in the Future

Advances in research in life sciences have brought unforeseen ethical questions earlier generations could not dream about (Table 13.6). Cloning and stem cell techniques combined with gene manipulation in general, such as the CRIPSR-Cas9 method, opens up totally new avenues of research. Manipulating human germ cells and constructing totally new organisms are examples where science will take us. Ethical

Table 13.6 Current and future potential areas where ethical issues may arise

• Biomanipulation
• Stem cells
• Germ cells
• Biobanks
• Children's rights
• Population studies
• Animal rights
• Data management
• Financing and sponsoring
• Local, national and world politics

debate is absolutely necessary for formulating guidelines and international declarations for research with these and, in the future, even more advanced techniques. It is the responsibility of the research community to be transparent and provide accurate and legible information to political decision-makers and other stakeholders. At the same time the public must have trust on researchers and this trust can only be lost once. We nevertheless believe that the ancient principles of human ethics provide the best guidance also for future ethical problems—whatever they might be—as they have principally guided mankind more than the past 2000 years.

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Conflicts of Interest

The authors declare no conflicts of interest.

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