Module 1 (2023)

Part 1 - Historical overview

1.1. Why research is important

Medical science and practice is constantly evolving. New diagnostic and therapeutic treatments appear every year, often replacing established treatments that are either not effective, indicated or accessible for many patients.

This implies that:

- established treatments need to be monitored and evaluated to determine when they are effective,
- the search for new treatments must be ongoing,
- medicine is inherently experimental,
- new diseases and conditions emerge that require novel treatments.

Research is a central and indispensable component of improving health. Over the past century, there has been great progress in medical research, including the development of many new drugs, devices and techniques such as surgical, transplant and transfusion procedures. The field of health research has expanded tremendously in the past half century in terms of both financial investment and diversity in epidemiology, genetics, sociology and anthropology, and health systems research.

Although much new knowledge has been generated, large gaps remain. The knowledge and tools available are not always adequate to tackle existing health problems and there is a constant and never-ending need to generate new information and develop improved and more effective ways of protecting and promoting health and reducing disease. Further advances in these areas require research involving human participants.

In low- and middle-income countries, the need for research related to the burden of diseases and the improvement of healthcare is urgent. Many products of research (for example, new drugs) are not readily available or accessible. In addition, it is important to continue expanding the quality and quantity of research that focuses on the health problems of poorer countries and of marginalized populations. Wherever possible, such research should be conducted in these countries with the full involvement of local researchers, with the goal of improving health services and alleviating suffering.

- Nuffield Council on Bioethics, 2002.
- Nuffield Council on Bioethics, 2004.
- Ijsselmuiden C., Matlin S., 2006.
- Williams J.R., Medical Ethics Manual, 2015.

1.2. The evolution of research ethics

Ethics, one the main branches of Philosophy, deals with the question of “What is good?”. It is also known as “Moral Philosophy”. The term is also used as a synonym for “morality”, or a set of moral rules; therefore an act can be identified as “unethical” if it does not comply with these rules.

“Research ethics” is a sub-branch of ethics. It includes a specific set of rules – which will be mentioned throughout this module - for protecting the life, health, and rights of persons who participate in scientific research. It also includes ethics studies which aim to justify the best, or least bad, action where there is a dilemma regarding research activities.

Research involving humans has been part of medicine for centuries. In the nineteenth century, the adoption of the experimental method in both science and medicine generated significant progress in research involving humans. However, when animal experimentation became current practice, some scientists, mainly physicians, began to question the necessity of research on humans. Various ethical debates arose within the scientific community regarding the appropriateness of such research.

By the beginning of the twentieth century, conducting research involving humans was becoming more acceptable as long as extensive studies were first conducted on animals. With the development of bacteriology and the rise of pharmaceutical companies, the number of animals and humans used in research increased significantly.

Research in bacteriology at the end of the nineteenth century and the beginning of the twentieth century involved some highly questionable practices across North America and Europe where, for example, infectious agents were injected in orphans, mentally disabled persons and prisoners without their consent or knowledge, and various other experiments involving the use of electroshocks on vulnerable individuals were reported.

Questionable research practices also occurred in Africa. For example, during the colonial period as researchers searched for much needed remedies against yellow fever, tuberculosis, the plague, small pox and measles, many people found themselves submitted to isolation, quarantine, segregation and other constraints for surveillance purposes.

At the time, there were some attempts to regulate human experimentation. For instance, the Prussian Minister of Religious and Medical Affairs promulgated a guideline on human experimentation in 1900 and the German Reich Ministry of the Interior issued regulations on new therapy and human experimentation in 1931. Yet, such guidelines were largely ignored and although medical and scientific associations condemned these practices, they did not result in any professional, disciplinary or criminal charges. It was only following the Second World War and the Nuremberg trials that such charges were laid.

Nuremberg

The Nuremberg trials in 1946 brought the issue of inhumane treatment of humans involved in research to the attention of the public. Twenty-three Nazi doctors and administrators were held responsible for the deaths of thousands of concentration camp prisoners who died during and after horrific experiments. The judges’ verdict in 1947 included a section entitled “Permissible Medical Experiments” which described ten principles to be followed in conducting research on humans. Known today as the “Code of Nuremberg”, it states as its first principle that “the voluntary consent of the human subject is absolutely essential.” Please take a few minutes to read the Nuremberg Code.

- The Nuremberg Code, 1949.

1.2.1. The evolution of research ethics - The emergence of rules specific to research

Following the Nuremberg trials and Code, more revelations about inappropriate treatment of humans in research continued to stimulate reflection about research ethics and raise awareness of the need to provide some form of public oversight of research involving humans.

The first requirement for independent review

In 1953, the United States established a federal funding requirement for institutional review of proposed research projects involving humans by an independent committee [Katz J., 1972]. This rule was limited to research conducted directly within the facilities of the National Institutes of Health (NIH) at Bethesda, Maryland. The lay membership on these committees signified that biomedical research is an activity of public interest and the public has important views to share on its ethical aspects.

The development of international guidelines

In 1964, the World Medical Association published its first version of the Declaration of Helsinki, which has been revised several times since. The first revision of the Declaration in 1975 stated that protocols for clinical research should be sent to a “specially appointed committee for consideration, comment and guidance,” making this the first international statement on review of research where the review is independent from the researcher, the sponsor or any other undue influence. However, under the Declaration of Helsinki, the ultimate duty to ensure the protection of human participants remains with the physician-researchers.

Unethical research practices

During the latter half of the 20th century, unethical research practices were reported in many different parts of the world. Some events were especially significant since they prompted regulatory activity and increased public scrutiny.

In 1966, Henry Beecher, an American physician and researcher, described 22 cases of American researchers conducting ethically dubious research involving humans. He concluded that “it must be apparent that [participants] would not have been available if they had been truly aware of the uses that were made of them.” [Beecher H., Ethics and Clinical Research, 1966] This was followed by other revelations of misconduct, most notably:

- The Brooklyn Jewish Chronic Disease Hospital study where researchers injected live cancer cells under the skin of non-consenting elderly patients to test their immune system [Encyclopedia of Bioethics, Vol.3, p.1274]; and
- The Willowbrook case involving the administration of hepatitis virus in institutionalized mentally retarded children in an attempt to understand the natural history of the disease and to test the effect of gamma globulin [Encyclopedia of Bioethics, Vol.3, p.1274].

Accounts of unethical research practices can be found in many countries around the world. For instance, in Canada, the CIA and American army sponsored secret brain washing experiments at the Allan Memorial Institute in Montreal in the 1950s and 1960s. The research participants were not informed of the nature of the experiments, which clearly were not in their best interests. It was only in 1977, some 14 years after the end of the trials, that the participants learned what had been done to them. Similar experiments using the hallucinogenic drug LSD and electroconvulsive therapy were conducted on women held at a Canadian federal prison, also without their consent.

- Katz J., 1972.
- WMA, Declaration of Helsinki, 2013.
- Beecher H., 1966.
- Encyclopedia of Bioethics, Vol.3. 2004.

1.2.2. The evolution of research ethics - The emergence of formal requirements for ethics evaluation

Some events in research ethics are significant historically because they prompted concrete actions. In the Tuskegee syphilis study [Encyclopedia of Bioethics, Vol.3. p.1275], researchers observed the effects of untreated syphilis in African-American men. Initiated in 1932, it was not until 1972 that revelations about the conduct of the study exposed the need for clearer guidance and increased measures that exceeded funding requirements. Amidst a flurry of regulatory activity that followed, a U.S. federal statute (National Research Act, 1974) was adopted and is still in force today. It formally requires research institutions to establish independent, local, multidisciplinary institutional review boards (IRBs) to protect human research participants. These institutional review boards in the U.S. have the same role as research ethics committees (RECs), as they are called in many other countries.

Publication of the Belmont Report

During the 1970s, a presidential commission was established in the United States to identify ethical principles to guide research on humans and to develop guidelines for researchers and institutions. Its 1979 report, commonly called the “Belmont Report”, identified three basic principles of research involving humans:

- respect for persons, which requires respecting people’s autonomy and protecting people with diminished autonomy;
- beneficence, which requires minimizing harms and maximizing benefits;
- justice, which requires fairness in the distribution of benefits and burdens of research.

These three principles correspond to the fundamental requirements for ethically acceptable research:

- consent, which flows from the principle of respect for autonomy;
- appropriate risk-potential benefit ratio, which flows from the principle of beneficence;
- equitable selection of research participants, which flows from the principle of justice.

Over the years, the Belmont Report has become the cornerstone of many normative documents that oversee ethical conduct in scientific research. The Belmont principles remain at the core of research ethics discussions today.

The regulation of research involving humans

In the past few decades, a number of countries have developed legislation that regulates research involving humans. In some countries, clinical trials with experimental drugs or other products are tightly regulated through specific legislation [See module 4; See also the U.S. Office for Human Research Protections (OHRP) International Compilation of Human Research Protections].

Towards international harmonization

The proliferation of normative documents nationally and internationally has resulted in varying requirements that researchers and sponsors must meet. Given this situation and the increase in international multi-centre clinical drug trials, a process for the harmonization of requirements for the conduct of clinical drug trials was initiated by the clinical trials industry in the United States, the European Union and Japan. This resulted in the International Council on Harmonization Good Clinical Practice Guidelines (ICH-GCP). The ICH-GCP aim at:

1. avoiding the duplication of studies by making data generated in trials in one country admissible in other countries and
2. accelerating the drug development process.

Need for continued vigilance

Despite the flurry of regulatory documents, recent history reminds us of the need for continued vigilance. For example, the 1999 VanTx case in Switzerland demonstrated the need to ensure RECs are free from conflicts of interest. VanTx was a small company conducting clinical trials for the international pharmaceutical industry. It was able to deliver quick results at the cost of gross violations of the basic rules of human research participant protection. Among others, one great advantage of VanTx was to use its own private Research Ethics Committee whose manager was the main investigator of the company. [BOX 1: VanTx case]

In 1997, controversy broke out over a placebo-controlled trial designed to test a low dose of AZT (azidothymidine) in HIV-pregnant women in Thailand and Africa. The lower dose was much cheaper but below the standard of care in high-income countries. [BOX 2: Placebos]

Around the same time, an outbreak of bacterial meningitis occurred in Tudun Wada, a very poor residential area in central Kano, Nigeria. A team of researchers came into the country and recruited over 200 children into a trial of a drug called Trovan or Trovafloxacin to treat meningitis, which had never been administered to children orally. Despite favourable results from the trials, the researchers are alleged to have left Kano once they had completed their studies in spite of the fact that the meningitis epidemic was still ravaging the community. [BOX 3: Trovan Trial]

These cases prompted debate about standards of care and shed light on the need to address the ethical issues raised by international or externally sponsored research.

- US, National Research Act, 1974.
- US, The Belmont Report, 1979.
- US, OHRP, International Compilation of Human Research Standards.
- ICH-GCP, 2016.
- Encyclopedia of Bioethics, Vol.3, 2004.

1.3. Why research ethics is important

Research involving humans is necessary for the advancement of human health worldwide. Many health care professionals participate in research as investigators or as members of research teams. Research ethics aims to promote high standards of behaviour in the conduct of research involving humans through an awareness of relevant values, principles and rules.

Why research gets evaluated?

As we have seen, there have been many examples of ethically questionable research. In some rare cases, significant violations resulted in criminal sanctions. These latter cases aside, many of the former mishaps were rooted in the “dual role” of physicians who were also researchers [BOX 4: The dual role]. This dual role is relevant to all health care providers who have a relationship of trust with patients and who also conduct research. There need not be any inherent conflict [BOX 5: Potential of conflicts of interests] between the two roles of health care provider and researcher, as long as the basic rules of research ethics are understood and applied.

In addition, it is generally accepted that participation in research may expose individuals to harm that they would not otherwise experience. This is one of the reasons why research involving humans requires review and approval by an independent research ethics committee according to accepted standards. This review serves to assess the ethical acceptability of research studies and helps researchers improve the quality of their projects.

Today, many researchers are not physicians. Yet, the potential for a “dual role” can still exist if there is a trust relationship; for example, if a nurse is also a researcher. Sometimes, researchers will not be health care professionals at all. Despite this, the requirement for ethics review still holds.

In the context of international collaborative research, there are often inequalities in resources between high-income countries, which often sponsor research, and low- and middle-income countries that host the research. This raises important ethical concerns, including the potential for exploitation. Given the need for research in low- and middle-income countries, awareness of the risk of exploitation reinforces the need for robust evaluation of research by RECs.

Part 2 - Overview of normative frameworks applicable to health research involving humans

The regulation of research involving humans has evolved over the past century and took the form of guidelines and even state regulations during the latter half of the 20th century and the first decades of the 21st century. It is important to understand that even if there is no single instrument that applies to all research involving humans worldwide, there are various instruments - some more and some less specific to research - that establish safeguards for the conduct of research involving humans. This section will focus on instruments that are relevant to biomedical and health research.

2.1. International instruments

2.1.1. World Medical Association (WMA)

The World Medical Association was founded in 1947. It showed concern over the state of medical ethics in general and took up the responsibility for setting ethical guidelines for the world's physicians. The WMA hoped that developing guidelines "would help to impress on newly qualified doctors the fundamental ethics of medicine and would assist in raising the general standards of professional conduct." [WMA History, https://www.wma.net/who-we-are/history/]

One of the early guidelines developed by the WMA is the Declaration of Helsinki, which provides recommendations to guide physicians from all over the world in biomedical research involving human participants. The original 1964 text of the Declaration of Helsinki has undergone several revisions over the years and has had "great impact on human experimentation and has served as a starter for establishing ethical committees in various countries to scrutinize research projects on human beings." [WMA History, Recommendations guiding physicians in biomedical research involving human participants] It is referenced in many other international and national documents that address biomedical as well as other types of research. As such, the Declaration of Helsinki sets the core values that guide biomedical research.

Specific sections of the Declaration of Helsinki will be referred to in Module 2.

In 2016, the WMA adopted the Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks. This Declaration is intended to cover the collection, storage and use of identifiable data and biological material beyond the individual care of patients. In concordance with the Declaration of Helsinki, it provides additional ethical principles for their use in Health Databases and Biobanks. The principles of the Declaration of Taipei are applicable regardless of the purpose of the health database or biobank (research, diagnostic or other).

2.1.2. World Health Organization (WHO)

The World Health Organization (WHO) is involved in many ways in supporting improved ethical standards and review processes for research with human beings. Guidance documents in this field have been developed directly by the WHO and cooperatively with other groups, particularly the CIOMS (Council for International Organizations of Medical Sciences).

Significant documents for researchers and ethics review include:

- Operational Guidelines for Ethics Committees That Review Biomedical Research (2000)
- International Clinical Trials Registry Platform (ICTRP)

The WHO has also adopted Good Clinical Practice guidelines that mirror the ICH-GCP discussed below.

2.1.3. Council for International Organizations of Medical Sciences (CIOMS)

The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, non-profit organization established jointly by the WHO and UNESCO in 1949 to represent the biomedical scientific community (medical research councils, for example).

The CIOMS has issued international guidelines, particularly used in low-resource settings, for the application of ethical principles in various key areas, including:

- International Ethical Guidelines for Health-related Research Involving Humans (2016)

The CIOMS guidelines cross reference the Declaration of Helsinki and add more specific guidance.

2.1.4. International Council on Harmonization (ICH)

Clinical studies should be carried out according to International Council on Harmonisation (ICH)/WHO Good Clinical Practice (GCP) standards. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use is a continuation (since 2015) of The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) which was created in 1990. Drug approval agencies in a number of countries require adherence to these standards. This provides a unified standard for the European Union (EU), Japan and the United States, along with Australia, Canada, the Nordic countries and the World Health Organisation (WHO). Thus, any country that adopts the ICH-GCP guidelines technically follows these same standards when conducting clinical trials. The ICH-GCP are relevant for ethics since they refer to the principles of the Declaration of Helsinki and include guidance on various ethics-related processes and procedures, such as ethics evaluation, investigator qualification, consent and confidentiality.

2.1.5. Other instruments

In addition to the texts described above, there are a number of other international instruments relevant to research involving humans that are broader in scope. For example, UNESCO has adopted several declarations including the Universal Declaration on Bioethics and Human Rights and the Universal Declaration on the Human Genome and Human Rights. Such declarations provide guidance by establishing fundamental principles in their respective fields.

In Europe, several normative texts have been adopted by various bodies. Perhaps the most noteworthy is the Convention on Human Rights and Biomedicine, with the Additional Protocol specific to biomedical research.

All of these documents should be considered within the broad framework of human rights protections in research.

- WMA, Declaration of Helsinki, 2013.
- WMA, Declaration of Taipei, 2016.
- ICH-GCP, 2016.
- WHO, Operational Guidelines for Ethics Committees, 2000.
- WHO, International Clinical Trials Registry Platform (ICTRP).
- CIOMS, International Ethical Guidelines for Health-related Research Involving Humans, 2016.
- TRUST, Global Code of conduct for research in resource-poor settings, 2018.
- UNESCO, Universal Declaration on Bioethics and Human Rights, 2005.
- UNESCO, Universal Declaration on the Human Genome and Human Rights, 1997.
- COUNCIL OF EUROPE, Convention on Human Rights and Biomedicine, 1997.
- COUNCIL OF EUROPE, Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, 2005.
- Williams J.R., Medical Ethics Manual, 2015.

2.2. National instruments

In addition to international instruments, many countries have also enacted legislation, guidelines, rules or procedures to regulate research involving humans conducted within the country. The regulatory frameworks of the TRREE on-line training course provide country-specific normative frameworks, so national frameworks are not addressed here. Rather, this section highlights the general characteristics of national normative frameworks. Depending on the type of research and on the type of participants, there may be more specific guidelines or regulations that apply.

2.2.1. Regulations or guidelines specific to research involving humans

In some countries, there are regulations or guidelines that apply to any type of research involving humans. Typically, such regulations or guidelines will cover requirements for prior ethics review and approval, including appropriate risk-to-potential-benefit assessments and respect for autonomy through consent and protection of confidentiality. In addition, some countries also have regulations that apply to clinical drug trials as part of the drug or device approval process. In some countries, specific types of research (such as research involving human reproductive material) will receive additional regulatory oversight. In other countries, privacy legislation will apply to research using personally identifying information.

2.2.2. Broader regulations

In many countries, however, there are no research specific regulations or guidelines. This does not in any way mean that there is a legal vacuum. Indeed, broader based legal frameworks will provide guidance and minimal standards that must be met. For example, in many countries with a civil code or a constitution, there will be broader provisions protecting individuals' physical integrity as well as requiring respect for autonomy. There may also be provisions that require consent to treatment. Similarly, privacy regulations are relevant. In addition, criminal law prohibitions could also be invoked in the absence of other more specific provisions. Finally, when researchers are also health care professionals (such as physicians, nurses, etc.), professional codes of conduct must be respected.

2.3. Institutional requirements

Institutions where biomedical research is conducted (for example, hospitals, research institutions and universities) also bear responsibility for the ethical conduct of research involving humans. In addition, when researchers conduct their research abroad in other countries, their home institution maintains responsibility over its affiliated researchers.

Governmental agencies that fund research, as well as many private and not-for-profit organizations, will often adopt research ethics guidelines that must be respected as a condition for funding. Well known examples of such guidelines include:

- US, National Institutes of Health (NIH): NIH Grants Policy Statement, 2015.
- UK, Wellcome Trust, Research involving human participants: guidance notes on research involving people living in low and middle income countries.
- EDCTP Guidelines on Ethics, 2008.

Part 3 - Core values and concepts of ethics for research involving humans

Ethics in research, like ethics in general, is based on values. Values are abstract concepts, like truth, dignity and fairness, that are widely considered to be of the greatest importance for human well-being. One of the most important statements of values is the 1948 U.N. Universal Declaration of Human Rights. The role of research ethics committees is to ensure that the human rights of participants in research are respected.

Values are often expressed as principles. For the purpose of this training material, the following is a list of principles of ethics that facilitate protection of human rights and dignity:

- the inclusion of humans in research must be justified,
- scientific value and validity of the proposed research must be demonstrated,
- the benefits of the proposed research must outweigh any harms that may result,
- the interests of humans who participate in research must prevail over the interests of science and society,
- participation in research must be voluntary - participants must be fully informed about, and be able to choose to take on, the risks of research,
- appropriate compensation and treatment must be provided to persons who are harmed as a result of participating in research,
- the risks and potential benefits of research must be distributed fairly,
- ongoing respect for persons must be shown, for example, by protection of their privacy,
- transparency and public accountability must be upheld during the research process.

Because principles of ethics are, by their nature, fairly general, they need to be interpreted and applied to specific situations. One role of ethics is to show how general principles apply in specific situations. When the principles appear to conflict, it is the role of ethics and ethics review committees to identify and manage such conflicts.

There is a rich literature on ethics and its application to research. The analysis and discussion of principles of ethics in these documents can be useful to research ethics committees faced with new or complex challenges in the review of research protocols or the application of regulations.

- Emanuel E.J., Lemmens T., Elliot C., 2006.
- UN, The Universal Declaration of Human Rights, 1948.
- WMA, Declaration of Helsinki, 2013.
- WMA, Declaration of Taipei, 2016.
- CIOMS, International Ethical Guidelines for Health-related Research Involving Humans, 2016, Guidelines 1, 3, 4, 9, 13, 14, 24.
- TRUST, Global Code of conduct for research in resource-poor settings, 2018.

3.1. Justifying the inclusion of humans in research: social value and scientific validity

Social value

In light of the ethical principle of respect for persons, the justification for including individuals in a research project depends on the social value of the proposed research. Research will be considered as having value when the hypotheses or questions being researched have potential benefits. These benefits may accrue to individuals, to the advancement of knowledge within a discipline, to society generally in relation to an important topic or issue, or to some combination of these.

To have social value, a research project should be designed to solve a problem that is relevant to community concerns or that has been identified by the community as a problem that needs to be addressed: “Information can be important because of its direct relevance for understanding or intervening on a significant health problem or because of its expected contribution to research likely to promote individual or public health. The importance of such information can vary depending on the significance of the health need, the novelty and expected merits of the approach, the merits of alternative means of addressing the problem, and other considerations. (…) Researchers, sponsors, research ethics committees and relevant health authorities, such as regulators and policy-makers, must ensure that a study has sufficient social value to justify its associated risks, costs and burdens. In particular, there must be sufficient social value to justify risks to participants in studies that lack the prospect of potential individual benefit to them.” (CIOMS, 2016)

For example, an anti-malarial drug called “malarone” was tested in a low- and middle income country but was intended for use by travellers going to malaria endemic area. Although the research burden was borne by the low- and middle-income countries, the drug turned out to be too expensive to be administered in those same countries. Conducting a research study to test new drugs that will not be affordable to the community that bears the burden of the research is an example of research that does not have social value and is exploitative.

Scientific validity or rigour

A project is scientifically valid if it has the potential to result in facts, reproducible observations or generalizable information in relation to the question under study. The phrase “scientific validity” is used here to refer to the need for sound methodology and protocol design that is likely to lead to reliable conclusions. In qualitative research, instead of scientific validity, research must strive to achieve scientific rigour.

Research involving human participants that lacks this characteristic is inherently unethical because it unnecessarily exposes participants to risks of harm or inconvenience. This contravenes the overarching principle of respect for persons and it is a waste of resources.

- Freedman B., Scientific value and validity as requirements for research: a proposed explication, 1987.
- WMA, Declaration of Helsinki, 2013, Para. 21.
- ICH-GCP, 2016, Sec. 2.5.
- CIOMS, International Ethical Guidelines for Health-related Research Involving Humans, 2016, Guidelines 1, 2.
- TRUST, Global Code of conduct for research in resource-poor settings, 2018.
- COUNCIL OF EUROPE, Convention on Human Rights and Biomedicine, 1997, Art. 16(i).
- COUNCIL OF EUROPE, Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, 2005.

- EU Directive 2001/20/EC on Clinical Trials, 2001, Art. 6(3).
- Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use, 2014.
- US 45 CFR 46 Protection of Human Subjects - Common Rule, 2018, Art. 46.111 (a) (1), (2).

3.2. Bringing about more good than harm

In an ideal world, research would always “do good” (i.e., beneficence) and “not do harm” (i.e., non-maleficence). However, in today’s world, a more realistic goal for research is to try to bring about more good than harm while avoiding unnecessary or disproportionate harm. Any harm caused by the research should be outweighed by the good that researchers hope to achieve. Thus, researchers should optimize the potential benefits of their research (e.g., health, safety, knowledge, satisfaction), and try to minimize the risks of unwanted effects associated with the research (e.g., reduced health, pain, exploitation, inconvenience, emotional burden). CIOMS recommends a two-step process for evaluating the potential individual benefits and risks of research: “First, the potential individual benefits and risks of each individual research intervention or procedure in the study must be evaluated. In a second step, the aggregate risks and potential individual benefits of the entire study must be assessed and must be considered appropriate.” (CIOMS, 2016)

Researchers have to take these principles into account when designing their projects in order to ensure that all risks have been minimized to the greatest extent possible and that remaining risks are justified in the context of the question being studied. The potential risks could be minimized, for example by:

- “monitoring the study and providing mechanisms for responding to adverse events;
- establishing a Data Safety and Monitoring Committee (DSMC) to review and decide on data on harms and benefits as a study progresses;
- instituting clear criteria for stopping a study;
- installing safeguards to protect the confidentiality of sensitive personal data;
- seeking exemptions, where possible, from requirements to report information about illegal activities of study participants (such as sex work in countries where prostitution is forbidden by law);
- avoiding unnecessary procedures (for example, by performing laboratory tests on existing blood samples instead of drawing new blood, where scientifically appropriate); and
- excluding participants who are at a significantly increased risk of being harmed from an intervention or procedure.” (CIOMS, 2016)

In conducting their review, research ethics committees should pay particular attention to the well-being of research participants. They should ensure that potential participants will only be invited to participate in research that is not unreasonable. However, they should also consider the potential benefits and risks for others, including those who may benefit from the results of the research. In practice, this involves conducting a “risk-benefit analysis”.

- US, The Belmont Report, 1979.
- WMA, Declaration of Helsinki, 2013, Para. 16, 17, 18, 19, 20.
- ICH-GCP, 2016, Sec. 2.2.
- CIOMS, International Ethical Guidelines for Health-related Research Involving Humans , 2016, Guidelines 4.
- COUNCIL OF EUROPE, Convention on Human Rights and Biomedicine, 1997, Art. 6.
- COUNCIL OF EUROPE, Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, 2005, Art. 3(a).
- US 45 CFR 46 Protection of Human Subjects, 2018, art. 46.111 (a) (1), (2).
- TRUST, Global Code of conduct for research in resource-poor settings, 2018.

3.3. The interests of humans who participate in research must come before the interests of science and society

Giving primacy to the interests of persons who participate as research participants is central to ensuring respect for human dignity. This means that patients should not be entered into studies, no matter how important, if they are likely to suffer an unacceptable or unreasonable level of harm.

This rule is often challenged, either directly or indirectly. For example, certain placebo-controlled trials or drug trials conducted in countries where a drug is not yet approved, while it is approved in the country sponsoring the trial, raise direct challenges to the requirement of giving priority to the interests of human participants. Sometimes the challenge is more subtle, for example, when inclusion and exclusion criteria are “tweaked” to ensure sufficient enrolment, or when ongoing trials continue despite mounting evidence of lack of efficacy or of emerging safety concerns.

- WMA, Declaration of Helsinki, 2013, Para. 8.
- WMA, Declaration of Taipei, 2016, Para. 20.
- ICH-GCP, 2016, Sec. 2.3.
- COUNCIL OF EUROPE, Convention on Human Rights and Biomedicine, 1997, Art. 2.
- COUNCIL OF EUROPE, Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, 2005, Art. 2.
- EU Directive 2001/20/EC on Clinical Trials, 2001, Art. 4(i), 5(h).
- Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use, 2014.

3.4. Voluntary participation: choosing to take on the risks of research

There is an important sense in which individuals are self-governing. Within limits set by society, people generally control or shape their own lives in significant and meaningful ways. They have personal goals, values and preferences. They can make and act on plans for themselves and their lives that take these goals, values, preferences, the options before them and other matters into account. This self-governing ability is called “autonomy.” It is often thought to be what sets humans apart from other beings and is considered valuable and worth protecting. Autonomy is held in such high regard that it is considered part of the integrity of a person, that is, part of what makes a person complete or whole.

Historically, this principle is connected to the idea that all persons possess intrinsic worth independent of any special circumstances that confer value. Actively showing respect for the autonomy of others involves due appreciation of their capacities and perspectives, including their rights to hold views, to make choices and take actions based on personal values and beliefs.

In research involving human participants, researchers must conduct studies in a way that demonstrates respect for autonomy. This includes facilitating a participant’s choice about whether or not to participate in research. Seeking a potential participant’s genuine consent must ensure that the autonomous choices of persons are respected and that coercion is avoided. Consent “should be understood as a process, and participants have a right to withdraw at any point from the study without retribution. Researchers have a duty to ensure that the potential participant has been given sufficient opportunity and time to consider whether to participate.” (CIOMS, 2016).

In some communities, individualism within a family and community is dependent on family and community values. Before a person can consent individually to participate in research, she needs to consult, inform, agree or reach a consensus with members of her family, parents or head of household, or spouse before agreeing or disagreeing. However, the consent of the individual is always necessary for participation in research.

Module 3 of the TRREE on-line course deals more fully with informed consent.

- WMA, Declaration of Helsinki, 2013, Para. 26, 27, 28, 29, 30.
- WMA, Declaration of Taipei, 2016, Para. 11, 12, 13, 15.
- ICH-GCP, 2016, Sec. 2.9.
- CIOMS, International Ethical Guidelines for Health-related Research Involving Humans, 2016, Guidelines 9, 10.
- TRUST, Global Code of conduct for research in resource-poor settings, 2018.
- COUNCIL OF EUROPE, Convention on Human Rights and Biomedicine, 1997, Art. 5.
- COUNCIL OF EUROPE, Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, 2005, Art. 14.
- EU Directive 2001/20/EC on Clinical Trials, 2001, Art. 3(2) (d).
- Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use, 2014.
- US 45 CFR 46 Protection of Human Subjects, 2018, Art. 46.116, 46.117.

3.5. Fair distribution of the risks and potential benefits of research

In research ethics, justice refers specifically to the fair distribution of the risks and potential benefits of participation in research. What is understood to be a fair distribution is often a matter of dispute. Yet typically, researchers respect justice by ensuring that those who share in the burdens of research participation (e.g., by taking experimental medication) also share in its potential benefits (e.g., by having access to that medication once it is approved and available). Also, “groups, communities and individuals invited to participate in research must be selected for scientific reasons and not because they are easy to recruit because of their compromised social or economic position or their ease of manipulation.” (CIOMS, 2016).

A more challenging aspect of justice is ensuring that research results will be accessible to those who will benefit from them. For example, Insecticide Treated Nets (ITNs) were first tested in rural areas. When there were promising results, the ITNs went into commercial production but were sold at prices that were not affordable to people living in rural areas. The urban population, on the contrary, was more likely to be able to afford the nets.

The systematic exclusion of groups of individuals can also result in unfair distribution of benefits. A group might be excluded or suffer adverse events due to the lack of specific research on their shared characteristics, such as gender, age, environment or nutrition.

Exclusion of an affected group from a single research study might not on its own be problematic, but their exclusion from an entire field or program of research is certainly problematic. Therefore “groups that are under-represented in medical research should be provided appropriate access to participate” (CIOMS, 2016), and it is important to take a global view on systematic exclusion of certain groups and give serious thought to the “90/10 gap”, as described below.

Quote from WHO: “The majority of biomedical research has been predominantly motivated by concern for the benefit of already privileged communities. This is reflected by the fact that the WHO estimates that 90% of the resources devoted to research and development on medical problems are applied to diseases causing less than 10% of the present global suffering. The establishment of international guidelines that assist in strengthening the capacity for the ethical review of biomedical research in all countries contributes to redressing this imbalance.” WHO, Operational Guidelines for Ethics Committees, 2000.

- WMA, Declaration of Helsinki, 2013, Para. 20, 34.
- WMA, Declaration of Taipei, 2016, Para. 17.
- WHO, Operational Guidelines for Ethics Committees, 2000.
- CIOMS, International Ethical Guidelines for Health-related Research Involving Humans, 2016, Guideline 3.
- TRUST, Global Code of conduct for research in resource-poor settings, 2018.
- COUNCIL OF EUROPE, Convention on Human Rights and Biomedicine, 1997.
- COUNCIL OF EUROPE, Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, 2005, Art. 15.
- EU Directive 2001/20/EC on Clinical Trials, 2001, Art. 4(e), 5(e).
- Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use, 2014.
- US 45 CFR 46 Protection of Human Subjects, 2018, Art. 46.111 (a) (3).

3.6. Showing ongoing respect for persons

In research ethics, respect for persons is promoted when projects are evaluated by research ethics committees to ensure they meet the highest ethical standards and are worthy of participant consent. Continued respect for persons is also shown during the conduct of a trial and after it is completed. This requires, for example, that any new information that comes up during a trial that may be relevant to a person's continued participation should be communicated to that person and that she should be given the opportunity to reassess her consent.

Another way of showing ongoing respect is to keep personal information about research participants secret - or confidential - and not share that information with outside persons. Also, the way in which research results are reported and published must be considered carefully to avoid stigmatizing groups and communities that participated in the research.

Demonstrating ongoing respect also involves considering what will happen once the research is over. For example,

- If there was a placebo arm, will participants of the control arm receive the experimental product if it is proven to the efficacious?
- Will participants in the trial continue to receive the tested product once the trial is complete?

In low- and middle income countries, consideration should also be given to whether the wider community will be provided with access to the benefits arising from research. This is a contentious issue with no easy answer. However, it is generally agreed that all of these concerns should be addressed before the research starts.

- Nuffield Council on Bioethics, 2002.
- Nuffield Council on Bioethics, 2004.
- WMA, Declaration of Helsinki, 2013, Para. 5, 7, 20, 24, 27, 33.
- WMA, Declaration of Taipei, 2016.
- CIOMS, International Ethical Guidelines for Health-related Research Involving Humans, 2016, Guidelines 6, 11, 12, 22.
- TRUST, Global Code of conduct for research in resource-poor settings, 2018.
- ICH-GCP, 2016, Sec. 2.11.
- COUNCIL OF EUROPE, Convention on Human Rights and Biomedicine, 1997.
- COUNCIL OF EUROPE, Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, 2005, Art. 27, 28.
- US 45 CFR 46 Protection of Human Subjects, 2018, Art. 46.111 (7).

3.7. Upholding transparency and public accountability during & after the research process

Transparency means that an individual or group does not conceal information from others who have a legitimate interest in knowing that information.

Transparency is important in the research context because there are many interests (scientific, corporate, financial, personal, etc.) involved. Some of these interests may compete with, and even hinder, research participants' interests and well-being. For example, a pharmaceutical company does not want its competitors to know the results of clinical trials on its experimental drugs, but the trial research participants have a right to know if the trial shows that a drug is ineffective or harmful. Without sufficient transparency, patients can be harmed and public trust in researchers and research generally may be hindered.

Striving to ensure a transparent research process is an ongoing task, as many factors may need to be addressed. For example, conflicts of interests are common among sponsors, governments, organizations hosting research, researchers and RECs. There are many types of conflicts of interests, some of which are more apparent than others, some manageable and others simply not. In dealing with such conflicts, researchers and research ethics committees should adhere to the principle discussed above, that the interests of research participants should take priority over other types of interests.

CIOMS recommends the following steps for identifying, mitigating, eliminating, or otherwise managing conflicts of interests (CIOMS, 2016):

- "Research institutions should develop and implement policies and procedures to mitigate conflicts of interest and educate their staff about such conflicts;
- Researchers should ensure that the materials submitted to a research ethics committee include a disclosure of interests that may affect the research;
- Research ethics committees should evaluate each study in light of any disclosed interests and ensure that appropriate means of mitigation are taken in case of a conflict of interest; and
- Research ethics committees should require their members to disclose their own interests to the committee and take appropriate means of mitigation in case of a conflict of interest."

One means of ensuring transparency and public accountability in health research is the requirement for registration of clinical trials, including both the existence of these trials and the results: "Researchers should prospectively register their studies, publish the results and share the data on which these results are based in a timely manner. Negative and inconclusive as well as positive results of all studies should be published or otherwise be made publicly available." (CIOMS, 2016). The suppression of negative results from clinical trials has resulted in drugs being approved for general use despite significant safety issues. Several groups, including the World Health Organization (WHO), have developed clinical trials registries that are accessible to the public. Research ethics committees should require that a trial be included in one of these registries before approving the trial.

- WMA, Declaration of Helsinki, 2013, Para. 35, 36.
  WMA, Declaration of Taipei, 2016, Para. 20.
  WHO, International Clinical Trials Registry Platform (ICTRP).
  CIOMS, International Ethical Guidelines for Health-related Research Involving Humans, 2016, Guidelines 24, 25.

Part 4 - Introduction to research ethics evaluation

4.1. What is research ethics evaluation?

Research ethics evaluation is a process by which a group of people representing different perspectives meet to review the ethical acceptability of a research project. The process used to conduct the evaluation involves 2 steps:

1. ethical deliberation,
2. decision-making.

Ethical deliberation refers to the reflection and discussion process about research projects that allows each member of the committee to express his or her own perspectives. When different principles of ethics and concepts appear relevant but lead to contradictory courses of action, a significant amount of deliberation may be needed to come to a satisfactory resolution.

After deliberating, the committee must reach a decision about the protocol being reviewed. Ideally, the committee will come to a consensus about how to resolve any ethical issues that is acceptable to all members. The committee's decision should be justified and communicated in writing to promote a common understanding of any issues raised.

4.2. Why research ethics evaluation is important?

During the 20th century, in response to multiple mishaps and scandals, there was a significant shift with respect to who would bear responsibility for assessing the ethical acceptability of research projects: independent and multi-disciplinary ethics committees with public representation. In practice, this meant that researchers would no longer make this assessment alone; the public was recognized as having important views on the acceptability of research projects.

Research ethics committees conduct ethics evaluation of research protocols. Research ethics evaluation is important because it ensures that a given project is ethically acceptable and properly protects participants. In the context of externally sponsored research that is conducted in low- and middle-income countries, RECs also play an important role in ensuring that “research has been properly planned, taking into account the local context, and effectively reviewed on scientific and ethical grounds.” [Nuffield Council on Bioethics, 2002] In short, ethics committees ensure that the project is consent-worthy before any potential research participants are invited to participate.

- Nuffield Council on Bioethics, 2002.

4.3. Role and mandate of research ethics committees (REC)

The primary role of RECs is to ensure the well-being, safety and protection of research participants. This involves working with researchers to ensure that research meets the highest standards. RECs ensure the protection of research participants by accomplishing a combination of the following activities:

- the prior ethics evaluation and approval of projects,
- the continuing review of ongoing research,
- the active promotion of principles of ethics through education and training.

- Nuffield Council on Bioethics, 2002.
- WMA, Declaration of Helsinki, 2013, Para. 23.
- WMA, Declaration of Taipei, 2016, Para. 19.
- ICH-GCP, 2016, Sec. 3.1.
- CIOMS, International Ethical Guidelines for Health-related Research Involving Humans, 2016, Guidelines 8.
- TRUST, Global Code of conduct for research in resource-poor settings, 2018.
- WHO, Operational Guidelines for Ethics Committees, 2000, Guidelines 2, 4.
- COUNCIL OF EUROPE, Convention on Human Rights and Biomedicine, 1997, Art. 16(iii).
- COUNCIL OF EUROPE, Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, 2005, Art. 9(2).
- EU Directive 2001/20/EC on Clinical Trials, 2001, Art. 2(k).
- Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use, 2014.
- US 45 CFR 46 Protection of Human Subjects - Common Rule, 2009, Art. 46.102 (g).

4.4. Authority of RECs

Generally, RECs can come to the decision that a given project:

- is acceptable as presented,
- needs to be modified as per the REC's comments before it can be accepted,
- requires more information to make a decision, or
- is unacceptable in its current form.

Typically, clinical trials need to receive several levels of approval, including regulatory approval, institutional approval and REC approval. In some countries a proposal needs to receive ethics approval before proceeding to other regulatory bodies for medicinal product registration, drug importation, and/or a clinical trial approval certificate.

REC decisions can be binding or advisory. Whether a REC decision is binding or advisory depends on applicable regulations and if there is a requirement for ethics approval. Requirements for ethics approval may not necessarily exist in the country hosting the research; a requirement may exist in the country sponsoring the research, or in the country where the clinical trial data will be submitted in support of a submission for market approval of the experimental drug. The decision of a REC is binding if a positive REC decision is required and a negative decision cannot be overridden by regulatory or institutional authorities. REC decisions will be advisory if there is no specific legal regulation in a certain country and they can be overturned by higher authorities, such as hospital administrators or ministry of health officials. Nevertheless, a regulatory or institutional authority should consider itself bound by a negative REC decision.

- WMA, Declaration of Helsinki, 2013, Para. 23.
- WMA, Declaration of Taipei, 2016, Para. 19.
- CIOMS, International Ethical Guidelines for Health-related Research Involving Humans, 2016, Guidelines 8.
- ICH-GCP, 2016, Sec. 2.6.