Research ethics committees

Basic concepts for capacity-building

World Health Organization

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Glossary

Assent:
A variation on consent where a person who does not possess full competence to give informed consent gives affirmative agreement to participate in research. For instance, a child or person with dementia should give assent before being enrolled in research. However, it is important to note that assent does not eliminate the need for obtaining the permission of a parent or other legally authorized decision-maker.

Bioethics:
A field of ethical enquiry that examines ethical issues and dilemmas arising from health, health care and research involving humans.

Competence:
Refers to a potential or enrolled participant's mental capacity to provide informed consent.

Consent form:
An easily understandable written document that documents a potential participant's consent to be involved in research and describes the rights of an enrolled research participant. This form should communicate the following in a clear and respectful manner: research timeframe; title of research; researchers involved; purpose of research; description of research; potential harms and benefits; treatment alternatives; statement of confidentiality; information and data to be collected; how long the data will be kept, how it will be stored and who can access it; any conflicts of interest; a statement of the participant's right to withdraw from participation at any point; declarative statement of understanding that the potential participant agrees to and signs. The consent form should be in a language the potential participant understands. For potential participants with limited literacy, the verbal communication of the consent-document details should be provided along with proper documentation of consent, if it is given.

De-identification and data linkage:
The process of de-identification (anonymization) and linking of collected research trial data and identifiable private information. This process ensures that items of data are not individually identifiable, but provides a mechanism for appropriate access to identifiable information.

Ethical guidelines:
Guidance documents which assist with decisions relating to the responsibility to adhere to established and relevant standards of ethical principles and practice.

Personal data:
Data that relate to a living person and contain personally identifying information.

Principal investigator (PI):
The main researcher overseeing or conducting the research process.

Researcher:
A person who engages in the methodical and systematic investigation of hypotheses with the goal of contributing to new knowledge.

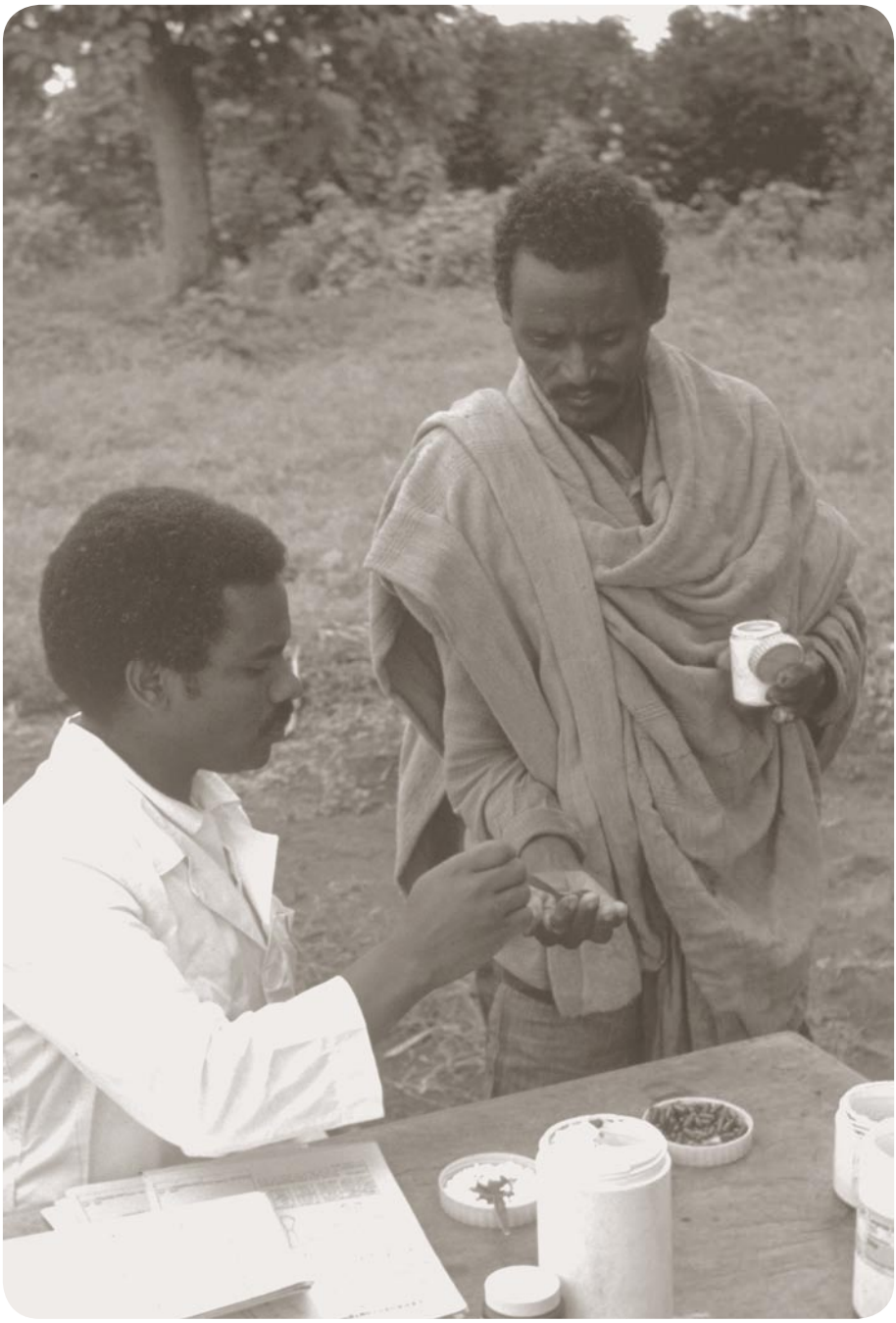
Research ethics committee (also known as ethical review board (ERB), ethical review committee (ERC), human research ethics committee (HREC), institutional review board (IRB)):
Group of individuals who undertake the ethical review of research protocols involving humans, applying agreed ethical principles.

Research involving human participants:
Any social science, biomedical, behavioural or epidemiological activity that entails systematic collection or analysis of data with the intent to generate new knowledge; in which human beings:

1) are exposed to manipulation, intervention, observation or other interaction with investigators, either directly or through alteration of their environment; or
2) become individually identifiable through investigators' collection, preparation or use of biological material or medical or other records.

Research protocol:
A document written by the investigator(s), which should contain a project summary; general information; background rationale; references and literature review; study goals and objectives; study design; methodology; safety considerations; follow-up; data management considerations and statistical analysis; quality assurance; expected outcomes of the study; dissemination of results and publication policy; duration of the project; problems anticipated; project management; ethical considerations; informed-consent documents; budget; funding organizations; collaborations; curriculum vitae of each investigator; list of all current projects; duration and percentage of time spent on this project; any financing or insurance.

Revision:
Requirement by the research ethics committee to alter the protocol in some way prior to approval or additional review by the committee.



Introduction

This manual and CD-ROM grew out of a training workshop organized by WHO in Ouagadougou, Burkina Faso in July 2007, with participants from seven Francophone African countries (members of research ethics committees and researchers). The workshop was prepared with a group of facilitators from Africa, Europe and North America and focused on the discussion of case-studies. Its main objective was to introduce basic ethical concepts useful for the ethics review of research protocols involving human participants.

The manual and CD-ROM are intended to help research ethics committees in low-income and middle-income countries to design training programmes for ethics committee members, researchers, national regulatory authorities, medical school faculty and other interested stakeholders from health care and research. The manual contains six introductory chapters on general topics: the role of research ethics committees, ethical analysis, training programmes, evaluation of risks and benefits, confidentiality and informed consent, with annexes covering financial conflicts of interest in medical research and international guidelines and regulations. The CD-ROM reproduces the printed manual and also provides an extensive bibliography, case-studies designed for use in training programmes and links to additional resources.

These materials are presented as a starting-point for a basic research ethics training programme. They are designed to draw attention to critical issues, without necessarily resolving them. They are not intended to be an exhaustive summary of all issues in research ethics. Moreover, they should not be viewed as “guidelines” that committees must follow in reviewing research protocols.

Research ethics committees

Research ethics committees review proposed studies with human participants to ensure that they conform to internationally and locally accepted ethical guidelines, monitor studies once they have begun and, where relevant, take part in follow-up action and surveillance after the end of the research. Committees have the authority to approve, reject or stop studies or require modifications to research protocols. They may also perform other functions, such as setting policies or offering opinions on ongoing ethical issues in research.

Review by a research ethics committee is required by international ethical standards governing research involving human participants, as well as by local law in many jurisdictions. In international cooperative research, review may be required by the laws of the country in which the research is being sponsored, even if it is not required by the host country's own laws. Review is also essential if the researchers intend to publish the results of their investigation, as most medical journals will not publish the results of research that has not received the approval of a research ethics committee.

The main responsibility of a research ethics committee is to protect potential participants in the research, but it must also take into account potential risks and benefits for the community in which the research will be carried out. Its ultimate goal is to promote high ethical standards in research for health.

Structure and functions of research ethics committees

Some research ethics committees operate within research institutions (where they may be known by different names, including "institutional

review board" (IRB)), while others operate on a regional or national basis. The advantage of research ethics committees that operate within research institutions is that they are familiar with the local conditions and can engage in closer monitoring of ongoing studies. The disadvantage is that the committee may feel inhibited from rejecting or requesting significant changes to studies, given the institution's financial interest in attracting externally funded research projects. Regional and national committees are further removed from the site where the research is conducted, but they may provide greater consistency and have greater legitimacy in the eyes of the research community and the public. In countries with multiple committees, it is important to develop mechanisms to promote consistency and avoid unnecessary duplication of work.

The functions of research ethics committees include identifying and weighing up the risks and potential benefits of research; evaluating the process and materials (printed documents and other tools) that will be used for seeking participants' informed consent; assessing the recruitment process and any incentives that will be given to participants; evaluating risks to participants' confidentiality (and the related risk of discrimination) and the adequacy of confidentiality protections; and examining any other issues that may affect the ethical acceptability of the research. In international research, the committee represents the interests of the local population. Thus, it should ensure that the participants and their communities will receive fair benefits from the arrangement. In studies involving medical interventions, research ethics committees must determine that adequate care and treatment will be provided for participants (see e.g. Guidance Point 14 in the UNAIDS/WHO publication *Ethical considerations in biomedical HIV prevention trials*[1]). This can be a significant issue in studies involving placebo controls (see Declaration of Helsinki, Section 32[2]). Committees should consider what will happen to participants who need medical attention

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[1] http://data.unaids.org/pub/Report/2007/jc1399-ethicalconsiderations_en.pdf, accessed 18 January 2009.

[2] http://www.wma.net/e/policy/b3.htm, accessed 17 January 2009.

during or after the study, either because they suffer injuries as a result of participation or because of the natural progression of a pre-existing illness. Sponsors' obligations to provide care in such circumstances should be clearly established before a study begins and made clear to potential participants during the informed-consent process.

Membership

In the light of their role in identifying and evaluating the risks and benefits of research, research ethics committees must include individuals with scientific and medical expertise. Without such expertise (supplemented, when necessary, by consultants in particular specialties), they will not be in a position to understand the procedures to be used in the study and their potential consequences for participants. In addition, committees must be able to assess the scientific validity of the study design to ensure that it is capable of producing reliable information. A badly designed study that will not result in usable data cannot support any level of risk. In some research oversight systems, the primary responsibility for scientific review rests with separate "scientific review committees", but even when this is the case, it is important for the members of the research ethics committee to have a basic level of scientific literacy.

Research ethics committees should not, however, be made up exclusively of scientific experts. Some types of risks and benefits may be more easily identified by non scientific members, particularly those related to social, legal or cultural considerations. In addition, once risks and benefits have been identified, determining whether the relationship between them is reasonable requires value judgements as well as scientific analysis. A diversity of backgrounds and qualifications (in medicine as well as law, social sciences, etc.) can help ensure that these judgements are not inappropriately dominated by a single perspective. Social diversity and gender balance should also be reflected in the committee's composition.

Committees also need broad community representation to identify relevant local attitudes or practices about which the researchers should be sensitive. For example, in some communities, it may be considered inappropriate to approach individuals about research participation before consulting community leaders. Input from community members will also enable the committee to assess the understandability of the information that will be provided to prospective participants as part of the informed-consent process.

The membership should be designed to minimize the potential impact of conflicts of interest on the decision-making process. For example, it is important for institutional research ethics committees to have members who are not affiliated with the institution and for Government-sponsored committees to have members who are not employed by the Government. In addition, members who have a conflict of interest with respect to a particular study should not participate in the review of that study.

Support and oversight

Research ethics committees need staff and funding to support their operations. It is not inappropriate to charge research sponsors a fee for review by the committee, but the fees should be based on the actual costs of review. Funding mechanisms should be designed to ensure that committees and their members have no financial incentive to approve or reject particular studies.

Members should receive training in the international and local ethical and legal standards governing research, as well as in the process the committee uses to review and approve protocols. Non scientific members should be given an understanding of medical terminology and research methodology sufficient to enable them to participate intelligently in the committee's discussions. A good knowledge of the social and cultural context is also important. Training should not be a single occurrence, but instead should be an ongoing process in which all committee members participate.

Committees should be subject to ongoing oversight, both to ensure that they are following applicable standards and procedures and to determine whether their actions are actually improving the ethical quality of research. Some committees may choose to undergo a formal accreditation process with national or international organizations. Other oversight mechanisms include regional or national meetings for the purpose of exchanging information about best practices, or partnerships between committees from different countries. Committees can also undertake initiatives to assess the impact of the review process on research participants – for example, by soliciting feedback through suggestion boxes or at community meetings, or by sending representatives to study sites to see if the committee's guidance to investigators is actually being followed.

Notes

Ethical analysis

Ethics does not prescribe a specific set of rules or policies. Instead, it provides a framework for evaluating problems and determining an appropriate course of action. Ethical analysis should reflect both internationally accepted norms and locally relevant cultural values.

One approach to ethical analysis is to identify a set of governing principles and then apply those principles to evaluate the appropriateness of particular behaviour. In bioethics, the most commonly identified principles are:

1) individual autonomy (the ability to make decisions for oneself);
2) beneficence (the obligation to "do good" for others);
3) nonmaleficence (the obligation to avoid causing harm to others); and
4) justice (the value of distributing benefits and burdens fairly).

These principles provide a general framework for analysis, which can then be applied to the facts of a particular ethical dilemma to reach a resolution.

For example, consider a study in which researchers propose to assign individuals randomly to an experimental HIV vaccine or a placebo. The principle of autonomy suggests that, as long as the individuals are adequately informed of the risks and benefits, they should be free to decide for themselves whether to participate or not. However, the principle of beneficence might lead a research ethics committee to require that the researchers offer participants counselling about risk-reduction methods and possibly care for individuals who become infected during the study. Based on the principle of nonmaleficence, the committee would have to consider whether participating in the study might harm individuals by leading them to think that they are protected from infection

and therefore do not need to use risk-reduction measures. Finally, the principle of justice would require consideration whether the burdens of the study fall disproportionately on particular populations.

The principle-based approach to ethical analysis has been criticized as overly vague. This vagueness is due not only to the open-ended nature of each of the principles, but also to the fact that, in many situations, some of the principles may point in different or even obviously conflicting directions. In the example above, a research ethics committee might be inclined to approve the proposal based on the principle of individual autonomy, but the other principles might suggest that the methodology should be modified or the target population altered. Some people also assert that the principle-based approach to ethics inappropriately prioritizes the cultural values of Western societies, particularly the principle of individual autonomy.

An alternative to principle-driven ethical analysis is a process known as "casuistic" reasoning. Instead of starting with abstract principles, the casuistic decision-maker begins by evaluating illustrative prior cases. Through the process of inductive reasoning, a judgement is made about the implications of these cases for resolving the particular issue at hand. For example, in evaluating the HIV vaccine trial, a research ethics committee might start by looking at other studies in analogous areas, such as vaccine trials related to other diseases, HIV studies not related to vaccines, or placebo-controlled studies involving preventive interventions. It would then seek to identify ways in which these other studies are both similar and different from the vaccine study under consideration.

It is not necessary to choose between principle-based and casuistic ethical analysis. In fact, most research ethics committees rely on a combination of both methods. Thus, they may consider not only whether a proposed study is consistent with abstract principles like autonomy and justice, but also how it compares with other studies the committee has reviewed in the past.

Ethical analysis in the context of vulnerable populations

Some individuals or communities face a greater-than-usual risk of being enrolled in research in violation of basic ethical standards. These risks can arise from a variety of sources. For example, some individuals face limitations in their ability to provide informed consent to research because of factors like immaturity or cognitive impairment. Vulnerability can also stem from individuals' relationships with others, such as when an employee is asked to participate in research being conducted by a supervisor, or when a student is asked to participate in a study being conducted by an instructor or mentor. Social factors, such as poverty and lack of access to health care, can also make individuals vulnerable to coercion, exploitation or other risks.

International regulations and guidance documents on research require additional protections in studies involving vulnerable participants. For example, the CIOMS guidelines[1] provide that "special justification is required for inviting vulnerable individuals to serve as research subjects and, if they are selected, the means of protecting their rights and welfare must be strictly applied". "Special justification" exists when:

1) the research could not be carried out as well with less vulnerable subjects;
2) the research is intended to obtain knowledge that will lead to improved diagnosis, prevention or treatment of diseases unique to the vulnerable class;
3) subjects will be assured reasonable access to any diagnostic, preventive or therapeutic products that will become available as a consequence of the research;
4) the risks will not exceed those associated with routine medical examination of such persons; and

[1] Council for International Organizations of Medical Sciences/World Health Organization. International ethical guidelines for biomedical research involving human subjects. Geneva, World Health Organization, 2002.

5) when prospective subjects are either incompetent or otherwise unable to give informed consent, their agreement will be supplemented by the permission of their legal guardians or other appropriate representatives.

The process of ethical deliberation

In ethics, the process by which a decision is made is as important as the outcome. For a decision to be ethically legitimate, it must be made in an open and inclusive process that takes into account the views of all stakeholders. Thus, research ethics committees should be encouraged to include individuals from diverse professional and social backgrounds and, where appropriate, to solicit input proactively from the community.

Most committees make decisions through a process of consensus. This means that, instead of taking a vote and following the decision of the majority, they strive to make decisions that most people in the committee feel comfortable accepting. While there may be situations in which a few members disagree with the committee's judgement, it should avoid making decisions to which a significant number of members strongly object.

Notes

Organizing a training programme

The first step in organizing a training programme on research ethics is to decide on the intended participants. One option is to have a programme designed solely for committee members. Such a programme could focus on general ethical principles, the roles and responsibilities of members and the process of protocol review. Another option would be to expand the audience to include other stakeholders, including researchers, national regulatory authorities, patient organizations, community representatives or academics. If the audience is expanded, the content of the programme should be modified accordingly. For example, a programme that includes regulatory authorities could include sessions on the role of legislation and regulation in research ethics oversight, as well as sessions on general ethical issues and the process of protocol review.

Whether the group is confined to members of a single committee or brings together interested stakeholders from a variety of organizations, it is a good idea to ensure that the participants represent a diversity of backgrounds and perspectives. Thus, even if the programme is limited to committee members, it should include individuals with both medical and nonmedical backgrounds, persons who are affiliated with research institutions and those who are not, and persons who represent a variety of cultural perspectives. Having a diverse audience will help ensure that all points of view are included in the discussion.

While it would be possible to create a comprehensive training programme lasting several days that addresses all of the issues discussed in these materials, it can also be valuable to offer shorter sessions limited to one or a few issues. For example, a short programme could

be devoted solely to informed consent or confidentiality. Committees that meet on a regular schedule could consider holding short training programmes on selected topics at the beginning of each meeting.

Training methodologies

Training programmes are most effective when they rely on a combination of lecture and discussion. For the lecture portion, it can be useful to have more than one speaker presenting on each issue, so that the participants can hear different perspectives. For example, in a session on informed consent, an academic ethicist could discuss general ethical principles, a researcher could talk about the process of communicating medical information to prospective research participants and a community representative could talk about cultural issues relevant to the informed-consent process.

For the discussion portion of the programme, one effective method is to break the audience up into smaller groups (ideally, no more than eight people per group) to discuss a case-study. The case-studies can be taken from the CD-ROM or adapted from other sources. If you use a real protocol to create a case-study, make sure you eliminate any references to confidential information. Case-studies should be relatively short, so that the participants can read them quickly, and they should focus on issues that have no obviously right or wrong answer. Before groups begin discussing the case-studies, they should select rapporteurs who will take notes on the discussion.

After the small-group discussions, the large group should reconvene so the rapporteurs from each group can give brief presentations of each group's observations and conclusions. The purpose of this process is not to determine which group has come up with the "correct" response, but to highlight areas of consensus and disagreement. The programme moderator can use the areas of disagreement as a springboard for further discussion.

Notes

Evaluation of risks and benefits

Key points

- The complexity of the notion of risk, as well as the uncertainty of the potential benefits of research, make the process of risk/benefit assessment a significant challenge for research ethics committees.
- Risk/benefit assessment does not stop at the individual; it must also take into account communities and health systems.
- The risks of research are not limited to potential physical harms, but can also include psychological, social, legal and economic ramifications.
- Evaluation of the benefits of research must distinguish between direct benefits for the individuals who participate in the study, expected benefits for the community in which the study will take place and potential benefits to science and the world at large.
- Identifying and evaluating risks and benefits is not a purely scientific endeavour. It requires the involvement of all stakeholders in research, including investigators, community and civil society representatives, lawyers, health authorities, etc.

Typology of research risks

For subjects

- Risks to physical integrity, including those associated with experimental drugs and treatments and with other interventions that will

be used in the study (e.g. procedures used to monitor research participants, such as blood sampling, X-rays or lumbar punctures).

- Psychological risks: for example, a questionnaire may represent a risk if it concerns traumatic events or events that are especially stressful.
- Social, legal and economic risks: for example, if confidential information collected during a study is inadvertently released, participants may face a risk of discrimination and stigmatization.

For the community

- Certain ethnic or population groups may suffer from discrimination or stigmatization as a result of research, particularly if members of those groups are identified as having a greater-than-usual risk of having a particular disease.
- The research may have an impact on the existing health system: for example, human and financial resources devoted to research may divert attention from other pressing health care needs in the community.

What are the different phases of risk/benefit assessment?

Identifying risks

This is first and foremost a task for the investigator, who must specify the nature, characteristics and scale of the risks in the research protocol submitted to the research ethics committee. The committee should carefully consider the description of risks contained in the protocol, but it should not assume that this description is necessarily accurate or complete. This is particularly true with respect to social risks, which may stem from local conditions or attitudes of which the investigators and sponsors may not be aware.

Example

After having given their consent, participants in a study about treatments for HIV/AIDS are treated for a specific period during which they are required to attend a hospital regularly for monitoring purposes.

The protocol stipulates that if the participants fail to attend for their appointment, they are to be contacted by phone and if necessary a member of the research team will go to their home. The informed-consent materials failed to mention this procedure. In the small town concerned, where everyone knows everyone else, a visit by health workers who are known to work in services treating persons with AIDS gives rise to suspicion. The participants may find themselves victims of exclusion by their family or workmates. In this example, the research ethics committee should have suggested to the investigators alternative measures for monitoring that would not subject participants to a risk of stigmatization.

Identification of the expected benefits

Medical research involves different types of interventions.

- Interventions that hold out the prospect of a direct diagnostic, therapeutic or preventive benefit for the individual participants. Some ethical guidance documents state that these types of interventions should not be provided in the context of research unless there is a reasonable basis for expecting that they will be "at least as advantageous to the individual subject ... as any available alternative" (CIOMS Guideline 8).
- Interventions that do not hold out the prospect of direct benefit for the subject, but are expected to produce scientific information that may benefit society in the future. The risks presented by such interventions must be "reasonable in relation to the importance of the knowledge to be gained" (CIOMS Guideline 8).

These two types of benefits must be clearly distinguished from benefits ("perks") participants may receive in exchange for their participation, such as payments for time spent participating in the study. While study participants may value these perks, the research ethics committees should not consider them "benefits" of the study for the purposes of the risk/benefit assessment.

Evaluation of the risk/benefit ratio

Any type of research must be preceded by a scrupulous evaluation of the relationship between the risks and the potential benefits for the participants and/or their communities. This evaluation requires a thorough and up-to-date knowledge of the scientific literature.

Comparison of the risks and benefits of research must avoid two pitfalls:

- underestimating the risks and/or overestimating the potential benefits, either of which can result in exposing participants to unjustified harm
- overestimating the risks and/or underestimating the potential benefits, thereby holding back potentially beneficial research.

Example

Risk evaluation for a study of a vaccine against rotavirus infections

According to the epidemiological data, in the United States rotavirus infections are responsible for 500 000 consultations, 50 000 hospital admissions and 20 deaths each year whereas, in developing countries, they account for 25 million consultations, 2 million admissions to hospital and 400 000- 500 000 deaths. The potential benefits of the study are greater in countries where the need for the vaccine is higher.

For research ethics committees, evaluation of the risk/benefit ratio is a complex task resulting in a decision which, even when based on precise data, cannot completely exclude uncertainty. In addition, differences

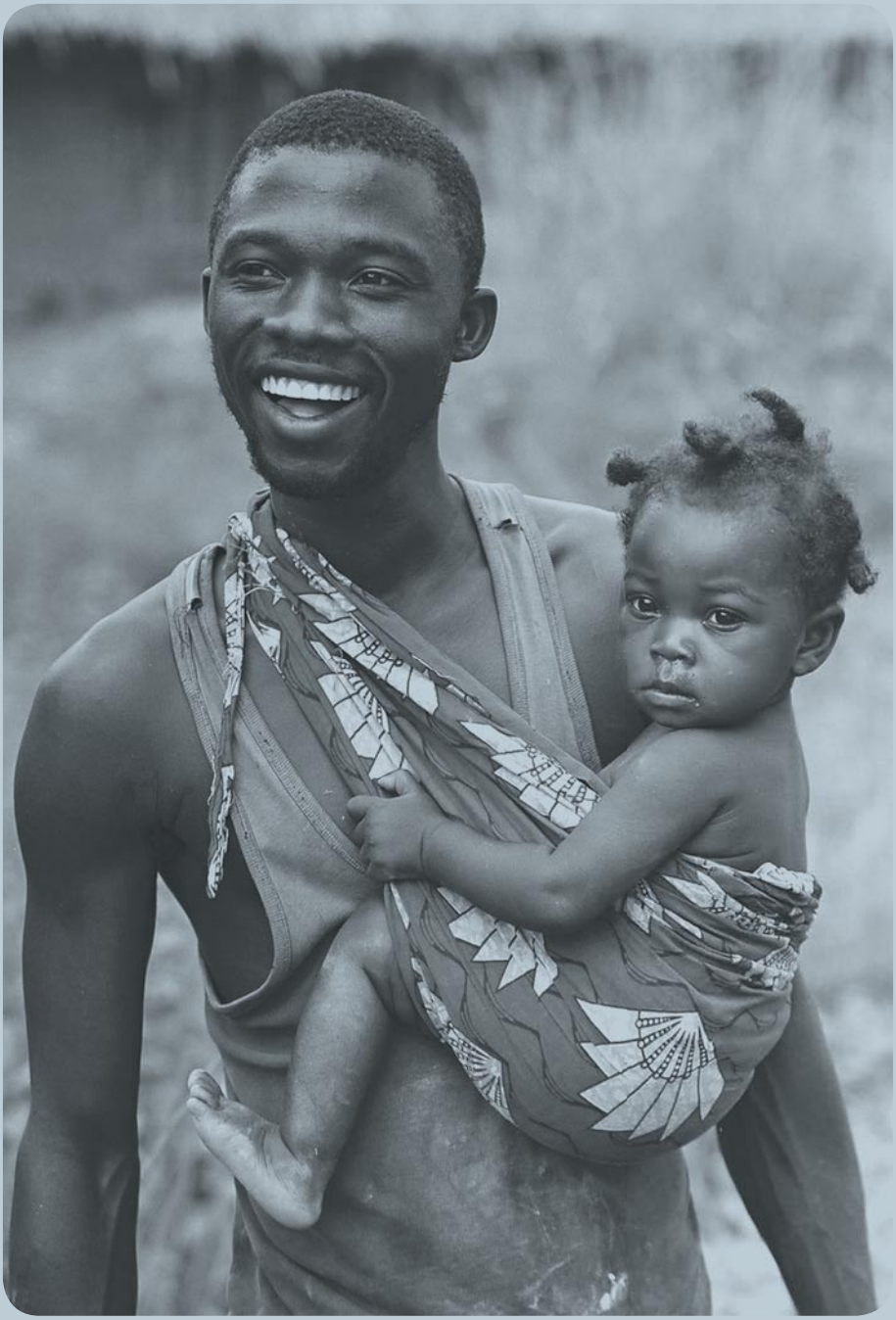
deriving from the different social and cultural environments in which the research is carried out have to be taken into account, further complicating this evaluation.

In order for the committee to perform an adequate risk/benefit assessment, the level and type of risks to which participants may be exposed must be described in detail in the protocol. Committee members should not, however, base their assessment solely on the information in the protocol, but should also actively seek out additional information, consulting experts and exchanging information with other committees when appropriate.

Quantitative and qualitative evaluation of the risks and benefits for participants and their community presupposes that the members of the committee are properly trained and well-acquainted with the social, cultural and economic context. A multidisciplinary approach is essential to the quality of the evaluation, and the composition of the committee must ensure that the required skills are represented. Continuing education for committees, together with sharing and critical analysis of experiences with other committees, help considerably in enhancing their skills.

In the field of research, there is no such thing as zero risk; however, ethical review of research must contribute to a practical solution in order to minimize risks and maximize benefits, while ensuring respect for persons and providing the best possible response to the health needs of populations.

Notes



Confidentiality

Key points

- Confidentiality is a fundamental principle in health-care ethics. It applies not only to medical treatment, but also to medical research with human participants.
- It is necessary to safeguard all personal information from unauthorized disclosure.
- Research ethics committees must ensure that basic standards of information protection are guaranteed.
- Confidentiality issues must be taken into account in the informed-consent process.

Confidentiality in medical ethics

The ethical principle of confidentiality, already mentioned in the Hippocratic Oath, forms a cornerstone of the relationship between the patient and his or her physician. While the relationship between researchers and research subjects is different from the traditional physician/patient relationship, protecting confidentiality remains an important goal.

Confidentiality is emphasized in medical ethics to build up trust, allowing individuals to reveal all information necessary to treat their medical condition, no matter how sensitive it may be, without having to fear public disclosure. This trust is paramount not only in guaranteeing appropriate medical treatment, but also in protecting public health, as untreated conditions may pose a significant threat to other persons. The obligation of nondisclosure is protected by law in many countries.

Participation in research may lead to information disclosure that could have a negative impact on the participant and/or his or her family and community. Therefore, all personal information must be safeguarded, whether or not the researcher and participant are in a formal physician/patient relationship. This applies even to personal information that the researchers would not consider particularly "sensitive".

In limited circumstances, physicians and/or researchers may be permitted, or even required, to reveal confidential information. Generally, these involve situations in which an individual poses an immediate danger to third parties, such as when mentally ill patients make credible threats of violence against specific individuals.

What information is safeguarded?

All personal information must be safeguarded. Personal information includes all information "relating to an identified or identifiable natural person ('data subject'); an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity" (Chapter 1, Article 2a of European Parliament and Council Directive 95/46/EC[1]).

This includes all information by which an individual can be identified, including but not limited to the following: name, social security number, address, phone number, etc. identifying features, information that reveals that an individual is a member of a small group of people, such as the fact that a person works in a particular office or lives in a particular apartment building, a combination of information, such as physical appearance, date of birth and place of work, that together can reveal the individual's identity.

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[1] Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data (http://europa.eu/scadplus/leg/en/lvb/l14012.htm, accessed 18 January 2009.

All information related to an identified or identifiable person must be safeguarded, but particular care should be taken with respect to sensitive information such as the following:

Medical information: medical history, current diagnoses and treatments (especially for potentially stigmatizing conditions), mental status, substance abuse, genetic characteristics.

Social status: level of education, family status, employment status, financial information, such as income level.

Other information: sexual orientation and practices, religious beliefs, political affiliation, risky behaviours.

Confidentiality issues that ethics review committees must consider

Ethics review committees must look closely at how information obtained during the trial will be protected from disclosure and ensure that the risk that patients will suffer negative consequences due to information disclosure is reduced to a minimum.

This includes information related to an individual's participation in a certain trial (e.g. an HIV vaccine trial), information uncovered during the research (e.g. HIV test results) or information uncovered after the research (e.g. when researchers use participants' identifiable tissue samples in subsequent research projects).

Ways to minimize confidentiality risks

- Only collect data that can lead to the identification of research participants if this information is necessary for the successful completion of the research project. In some cases, confidentiality risks can

be avoided by not collecting any identifiable information.

- When identifiable information must be collected, consider replacing individuals' names with code numbers and storing the key to the code in a secure location accessible only to a limited number of persons. Destroy the key code when it is no longer necessary to link data with identities for the purpose of research. If linkable information (that is, potentially identifiable data) is held, the purpose of this storage, its duration and the persons who will be granted access to it must be made explicit.
- Increase researchers' awareness of confidentiality issues by providing guidance and training.
- Ensure that information is secured by limiting access, using safe storage methods (e.g. locked drawers and password-protected computer access) and using protected means of communication (e.g. encrypted electronic messages).
- Destroy information as soon as it is no longer needed.

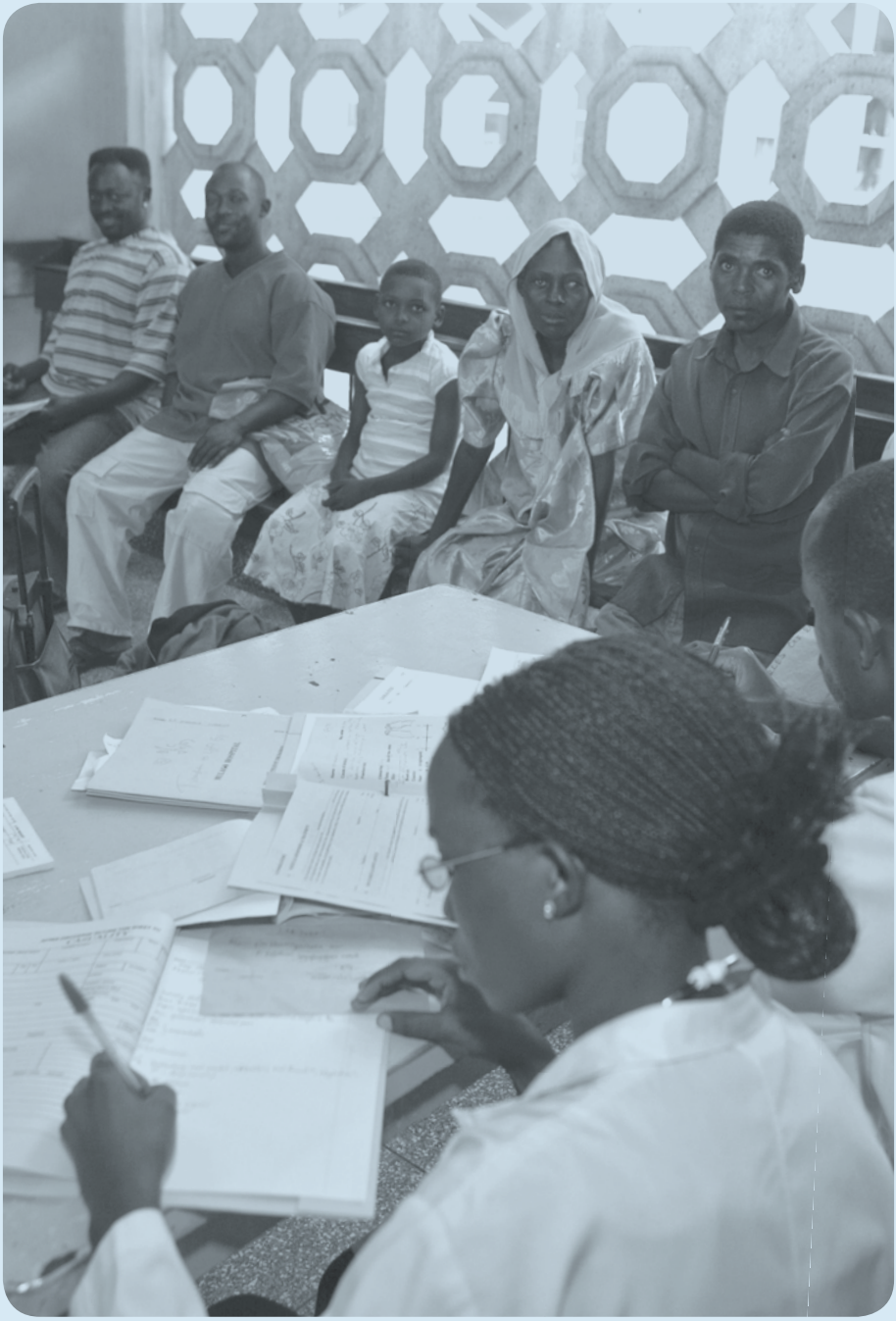
Confidentiality and informed consent

The duty to safeguard participants' information has consequences for the way the process of informed consent is handled.

Firstly, participants should be informed about any personal information that will be collected, who will have access to that information, the confidentiality protections that will be implemented and the risks that could arise if the information is improperly disclosed.

Secondly, in some circumstances, it may be impossible to guarantee full confidentiality protection. For example, in a study of a serious communicable disease, researchers may be required to report individuals who test positive for the disease to the public health authorities. Absolute confidentiality should not be promised if it cannot be guaranteed, and full transparency about data-sharing must be the rule.

Notes



Informed-consent process

Key points

- Consent is both a dynamic and an interactive process.
- Informed consent is the process whereby a person decides, free from any form of coercion or undue influence, to participate in research after having been apprised of information relevant to the decision.
- Individuals cannot provide informed consent to research unless they are legally capable. Individuals who do not have the legal capacity to provide consent, such as children or cognitively impaired adults, should not be enrolled in research without the consent of a parent or other surrogate decision-maker.
- The social and cultural context must be taken into account in designing and implementing the informed-consent process.

The process of informed consent: its meaning and origins

Informed consent to participate in research is related to fundamental ethical principles: respect for the persons, their dignity and autonomy. This process is set forth in the first provision of the Nuremberg Code, which was developed in response to the atrocities committed under the guise of medical research in Nazi Germany:

The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching [deception], or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity[1].

What elements are required in order for the consent process to be valid?

In order to be valid, the consent process must:

- precede any intervention
- be based on adequate information that the subject is capable of understanding
- be freely given, i.e. not the result of coercion or undue influence
- be clearly given and recorded.

[1] Available online at: http://ohsr.od.nih.gov/guidelines/nuremberg.html, accessed 17 January 2009.

What information must be given to prospective participants as part of the informed-consent process?

Before consenting to participate in research, individuals should be informed of the following:

- that it is a research activity designed to produce scientific knowledge and the ways in which participating in research differs from receiving medical treatment in the context of an individualized physician/patient relationship
- the duration of the study and the procedures to be employed
- the risks and inconveniences associated with participating in the study
- the potential benefits for the participants and/or the community; if there are no potential direct benefits to participants, that fact should be made clear
- alternative treatments that exist, if applicable
- measures taken to protect the confidentiality of personal information
- the voluntary and reversible nature of consent, i.e. of their right to withdraw at any time from the study without any penalty
- what they should do in case they experience adverse effects from the research
- whether they will be compensated in the event they experience harm from the research
- whether they will be able to continue receiving the interventions provided in the research after the study ends.

Consent and risk

Even if the potential participant is likely to give consent in any case, disproportionate risk-taking is not justified. Investigators must ensure that reasonable measures are taken to minimize the risks involved in the research and to enhance its benefits.

What are the key points for evaluating informed-consent procedures?

- Identification of all the information that must be provided to potential participants.
- Verification that all the necessary information is included in the information document and the information aids used.
- Assessment of the comprehensibility of the information, taking into account the persons for whom it is intended.
- Evaluation of the methods/procedures that will be employed to convey the information.
- Evaluation of any constraints that might influence consent.
- Evaluation of the specific social and cultural circumstances and of how they affect the validity of consent.

Compliance with the process of informed consent within the framework of multicentre trials poses new challenges for investigators and research ethics committees. Special attention needs to be given to those factors that might undermine the validity of the process:

- the social and economic context: illiteracy, inadequate access to care
- the cultural environment: the role of the community and family and of different sets of values
- the asymmetrical nature of the knowledge of the investigators and that of the participants, which puts the latter in a subordinate relationship
- the tendency of individuals to confuse being a participant in research with receiving individualized medical care (the "therapeutic misconception").

The tenofovir trial in Cameroon

This placebo-controlled trial involving a group of seronegative illiterate prostitutes in Douala in Cameroon was designed to demonstrate the preventive capacity of the molecule in tenofovir. Despite its importance, the trial generated considerable debate regarding its ethical legitimacy. The consent process was potentially jeopardized by the vulnerability of the participants and their difficulty in understanding the notion of a placebo. This trial has shown that certain situations of vulnerability require special efforts to convey information.

Notes

Annex 1

Financial conflicts of interest in medical research

Trudo Lemmens, Associate Professor, Faculties of Law and Medicine, University of Toronto, Canada[1]

Introduction

A conflict of interest (COI) in research exists when researchers or institutions in which the research takes place have specific interests which might affect the primary obligations associated with research. It is not necessary to prove that the conflict will inevitably influence a person's behaviour. Conflict-of-interest strategies are preventive: they aim at avoiding situations that could have a negative influence on researchers' most important duties, or that could reasonably be perceived as having such an influence.

The following questions have to be asked in the context of research: what are the primary professional obligations of researchers? What secondary interests can affect these obligations? What is the appropriate measure to deal with a conflict of interest, in the light of its potential impact?

Identification of conflicts of interest in medical research

Professional obligations of researchers

In research involving human subjects, the protection of the rights and well-being of the research subjects remains the most important concern

[1] Specially commissioned for this document; not discussed at the workshop.

(Declaration of Helsinki, principle 6). Researchers also have a primary obligation to conduct good research. Sometimes, patients do better when enrolled in a clinical trial than in ordinary clinical care. Yet participation in research also involves risks. When there is a tension between the obligation to conduct good research and the protection of research subjects, the obligation to protect the subjects takes priority.

Types of financial conflict of interest in medical research

In clinical research, per capita payments are often used as a financial incentive to stimulate or speed up subject recruitment. Researchers are often paid for time spent with research subjects, for filling out questionnaires and research forms, for blood and tissue collection and for administrative procedures. Payments given for the sole purpose of recruiting patients are termed "finder's fees", and they often form a hidden part of general payments for services provided. Researchers are sometimes paid more generally per project. They are sometimes paid per annum as consultants to a sponsor. Researchers may receive expensive research equipment, books or payment for speaking at conferences. Many researchers are members of speakers' bureaux or sit on advisory boards of pharmaceutical sponsors, and are paid for these services. Indirect benefits can also result from research participation, such as paid participation at conferences. Additional benefits of such participation are air-miles which can then be used for personal travel. Researchers may own shares in the company that produces the product they are studying, or may receive stock options for their participation in research.

Potential impact of conflicts of interest

Financial interests may have a negative impact on the protection of the rights and well-being of the research subjects. Financial interests may push researchers to disrespect inclusion criteria, to disrespect informed-consent procedures, to pressure research subjects to remain in a trial, or to continue a trial which should be stopped.

Money can influence behaviour in medical research, as in other walks of life. There is rarely, if ever, clear proof of such influence. It may be subtle

and is often unconscious. It seems impossible to measure concretely how much impact financial interests have on someone's actions.

Financial interests may threaten the integrity of the research process. They may influence the design of the study, the way it is conducted, the interpretation of research data and the presentation of the final results. Empirical studies have established a statistically significant link between source of funding and research outcome. Industry-sponsored research is more likely than non-commercially-sponsored research to lead to a conclusion that a new therapy is better than the standard therapy. There is systematic evidence of under-reporting of negative studies. There is also evidence of conscious manipulation of research questions and dissemination of results. Unfortunately, financial interests have also led academic researchers to put their name on publications written by specialist agencies working directly for the sponsor of the study.

The availability of strong financial incentives in industry-sponsored research may make it harder for non-industry-sponsored trials (e.g. on neglected diseases) to find sufficient researchers or research subjects, or to obtain institutional support for a study, thus distorting the research agenda.

Remedies for financial conflicts of interest

Regulatory remedies
Academic institutions, funding agencies, professional organizations and regulatory agencies should adopt conflict-of-interest policies and procedures.

Disclosure
Researchers should disclose any financial interest in the subject of their research to the research ethics committee. The committee should consider whether these interests should be disclosed to prospective participants as part of the informed-consent process. Researchers should

ensure that all conflicts of interest are disclosed in publications and presentations related to the research. The disclosure should contain complete information on the nature and extent of the conflict of interest.

Review procedures

Financial interests should be evaluated by a sufficiently independent and publicly accountable research ethics committee or by a specialized conflict-of-interest committee (COIC). The committee should have access to the research budget and receive information about all other relevant financial interests of investigators and of the institution. If a conflict-of-interest committee reviews the financial interests, it should report any conflicts to the research ethics committee for final evaluation. The research ethics committee should determine how to inform research subjects of these interests and whether other conflict-of-interest measures are needed.

Within academic institutions, review of all research contracts is necessary, to avoid that researchers enter into contracts with sponsors that limit their academic freedom or that may create contractual obligations that can affect the protection of research participants. Academic institutions should not allow researchers to enter into contracts that give a sponsor a right of veto over publication.

Ensuring independent oversight of the research process

Research ethics committees may impose some or all of the following conditions on research in order to deal with identified conflicts of interest:

- Appointment of an independent consent monitor,
- Appointment of an independent investigator to monitor the research process,
- Appointment of an independent data-monitoring committee, particularly in research that involves patients and may expose patients to significant risks. The data-monitoring committee should review all adverse events and can recommend to the research ethics committee that the research should be stopped. It should also review the proposed statistical methodology, the analysis, the presentation of findings and the final publication of results.

The conditions selected should be proportionate to the risk that the conflict of interest may affect the research or the protection of human subjects.

Prohibitions

A financial conflict of interest may be deemed so significant that an individual or institution should be prohibited from participating in a study. There should be a rebuttable presumption that researchers with significant financial interests ought not to be involved in the research and institutions with significant conflicts of interest ought not to have research take place in that institution. What constitutes a "significant" conflict of interest obviously depends on the social and economic context in which the research takes place, for example on the salary or consultation payments that health-care workers receive in their daily professional practice. National or regional regulatory agencies, funding agencies or professional organizations should provide guidance on this by means of regulations or guidelines, to ensure that this concept is not misused and avoid too many different interpretations at the local level.

In addition, some types of conflict of interest may be the subject of specific prohibitions. For example, research ethics committees may conclude that the payment of finder's fees, i.e. payment for the mere recruitment or referral of subjects, should not be allowed. Academic institutions, which have a clear public mandate, should also be strict with respect to potential financial interests among their researchers. An institution may, for example, prohibit researchers who receive full-time salaries from receiving additional payments for recruiting participants for research projects that are related to the researcher's salaried job.

Registration of clinical trials and results reporting

Mandatory registration of all clinical research and mandatory reporting of all research results are important to ensure the integrity of medical research. The Declaration of Helsinki now explicitly requires that

all clinical trials must be registered in a publicly accessible database before recruitment of the first subject (DOH principle 19); and that authors have a duty to make the results of research publicly available and to report accurately (DOH principle 30). Research ethics committees should impose trial registration as a condition for final approval of the research protocol. They also should ensure that there are no contractual clauses preventing appropriate results reporting and that all research results will be reported at the end of the research.

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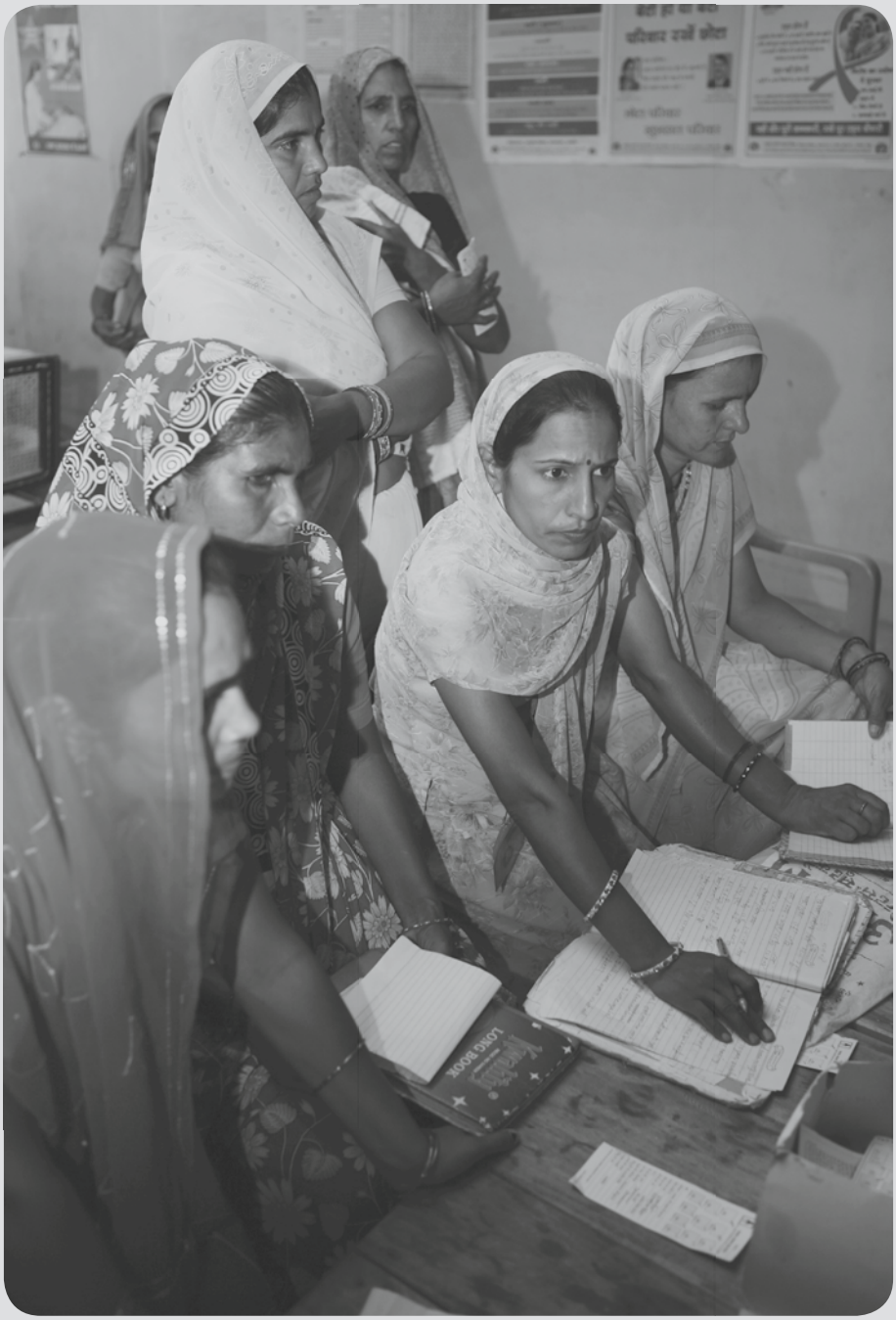
Notes



Annex 2
Guidelines and regulations

Guidelines and codes of best practice

Nuremberg Code[1]
Established in 1947 in the aftermath of the Second World War to avert future atrocities in the name of science, the Nuremberg Code is a 10-point declaration framing key principles that have become the backbone of research ethics, including the following:

- voluntary, informed consent
- absence of coercion
- opt-out possibility at any time during the experiment
- scientific justification and necessity of the experiments
- protection of the research subject against grievous bodily harm
- proportionality of risk.

Declaration of Helsinki[2]
The declaration was first adopted in 1964 by the World Medical Association, an international organization of physicians. There have since been six revisions, the last in the year 2008. Some of these revisions have been controversial, particularly with respect to the issues of placebo use in clinical trials and access to post-trial care. In addition to reiterating the principle of respect for research subjects, the Declaration of Helsinki underlines the importance of protecting vulnerable populations not capable of giving voluntary consent. Moreover, it stresses the obligation to offer the best proven care to trial participants after the end of the research project. Unlike the Nuremberg Code, the Declaration

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[1] Available online at: http://ohsr.od.nih.gov/guidelines/nuremberg.html, accessed 17 January 2009.

[2] Declaration of Helsinki, 6th revision (http://www.wma.net/e/policy/pdf/17c.pdf, accessed 17 January 2009).

allows surrogates to consent to research on behalf of individuals who lack decision-making capacity.

Belmont Report[1]

Outcry over the United States Public Health Service's study of untreated syphilis among African-American men in Tuskegee, Alabama led to the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, whose findings were published in the Commission's 1979 report "Ethical Principles and Guidelines for the Protection of Human Subjects of Research", also known as the Belmont Report.

The report identified three major ethical principles that must be observed when conducting research with human beings.

I. **Respect for the research participant:** Protecting individual autonomy was identified as a central value of research ethics. As a consequence, informed consent must be obtained before the study may be started. Persons not capable of autonomous decisions must be given special protection.
II. **Beneficence:** This concept refers to the obligation to secure the participant's well-being by maximizing possible benefits while minimizing risks. This requires an adequate assessment of risks and benefits.
III. **Justice:** Ensuring that the benefits and burdens of research are fairly distributed throughout society.

CIOMS: International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002)[2]

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[1] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont report: ethical principles and guidelines for the protection of human subjects of research. Washington, DC, Department of Health, Education and Welfare, 1979.

[2] Council for International Organizations of Medical Sciences/World Health Organization. International ethical guidelines for biomedical research involving human subjects. Geneva, World Health Organization, 2002.

The Council of International Organizations of Medical Sciences (CIOMS) was established jointly by WHO and UNESCO in 1949. This document, issued in 1993 and updated in 2002 by CIOMS, consist of 21 guidelines addressing ethical issues related to research involving humans.

It addresses the basic principles of research ethics, such as informed consent, risk/benefit assessment, protection of vulnerable groups, equitable distribution of burdens and benefits in groups of research subjects and confidentiality.

It differs from earlier documents by extending the concept of vulnerability to persons or communities with limited resources. Furthermore, it addresses issues such as compensation and access to post-trial care for participants, women and pregnancy in research and the obligation of external research sponsors to provide health care for participants.

WHO Operational Guidelines for Ethics Committees that Review Biomedical Research (2000)[1]

As stated in the preface: "These Guidelines are intended to facilitate and support ethical review in all countries around the world". They aim to complement national legislation in increasing the quality of research ethics review in order to create a high international standard. They deal with all aspects of research ethics review, from the role of an ethics committee and its functioning to the monitoring of approved studies.

UNAIDS/WHO,
Ethical Considerations in Biomedical HIV Prevention Trials (2007)[2]

The aim of this joint WHO/UNAIDS publication, consisting of 19 guidance points, is to encourage HIV/AIDS research in the countries most affected by the disease while ensuring the protection of research participants.

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[1] World Health Organization. Operational guidelines for ethics committees that review biomedical research. Geneva, 2000.

[2] Joint United Nations Programme on AIDS. Ethical considerations in biomedical HIV prevention trials.Geneva,2007(http://data.unaids.org/pub/Report/2007/jc1399-ethicalconsiderations_en.pdf, accessed 18 January 2009).

It addresses bioethical matters related to HIV/AIDS research, including informed consent, gender and vulnerability, as well as issues such as capacity-building and the standard of HIV prevention.

UNESCO Universal Declaration on Bioethics and Human Rights (2005)[1]

In 2005, UNESCO adopted the Universal Declaration on Bioethics and Human Rights, which aims to guide Member States in implementing national legislation relevant to these issues. The Declaration frames fundamental principles in the field of bioethics, such as informed consent and confidentiality, as well as their application.

Nuffield Council on Bioethics: The Ethics of Research related to Healthcare in Developing Countries (2003)[2]

This report's aim is to frame ethical standards of research in the particular context of developing countries with a particular emphasis on ethical review, standard of care, informed consent and post-trial care. It analyses the socioeconomic and cultural context of research in developing countries, frames ethical principles and gives recommendations on how these principles can be applied in particular settings.

Statutes and regulations

ICH Good Clinical Practice Guidelines (1996)[3] and Guidelines on Choice of Control Groups and Related Issues in Clinical Trials (2000)[4]

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[1] United Nations Educational, Scientific and Cultural Organization. Universal declaration on bioethics and human rights. Paris, 2006.

[2] Nuffield Council on Bioethics. The ethics of research related to healthcare in developing countries. London, 2003.

[3] International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Steering Group. ICH harmonised tripartite guidelines for good clinical practice. Richmond, Brookwood Medical Publications, 1996.

[4] International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Steering Group. ICH harmonised tripartite guidelines – choice of control group and related issues in clinical trials – E10 (http://www.ich.org/LOB/media/MEDIA486.pdf, accessed 18 January 2009).

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a group composed of United States, European and Japanese regulatory authorities, as well as representatives from pharmaceutical companies. Its purpose is to harmonize the registration process for pharmaceuticals, thus reducing duplication of effort and ensuring a high standard of quality and safety for the end-user as well as research trial participants.

For this purpose, ICH issued good clinical practice (GCP) guidelines in 1996, intended to serve as a reference for national legislation protecting the safety and the rights of trial participants.

In 2000, ICH amended the GCP guidelines by adding a section on the choice of control groups and related issues in clinical trials, addressing the scientific output which can be obtained from different types of control groups, as well as ethical considerations associated with the choice of a control group.

Council of Europe Convention on Human Rights and Biomedicine (1997)[1] and Additional Protocol on Biomedical Research (2005)[2]

The Council of Europe, an organization founded with the aim of furthering European integration, human rights and high legal standards, issued the Convention on Human Rights and Biomedicine in 1997, to "safeguard human dignity and the fundamental rights and freedoms of the individual with regard to the application of biology and medicine". It has a wide scope, dealing not only with ethical issues in clinical research, but also with more general themes such as equity in access to health care, confidentiality and the protection of embryos.

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[1] Council of Europe. Convention on Human Rights and Biomedicine, 1997 (http://conventions.coe.int/treaty/EN/Treaties/Html/164.htm, accessed 18 January 2009).

[2] Council of Europe. Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, 2005 (http://conventions.coe.int/treaty/EN/Treaties/Html/195.htm, accessed 18 January 2009).

It was complemented in 2005 by an additional protocol on biomedical research, which addressed issues related to ethics committees, informed consent, the protection of vulnerable persons and confidentiality.

European Parliament and Council Directive 2001/20/EC (2001)[1]
This directive of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduction of clinical trials on medicinal products for human use.

The aim of this directive was to protect the rights and the safety of clinical trial participants, to harmonize and simplify the administrative procedures of clinical trials and increase transparency of clinical trials within the European Union, thus ensuring greater consistency in trial procedures and greater scientific credibility.

United States regulations
The Common Rule[2] (45 CFR Part 46) is a set of Federal regulations applicable to research conducted or funded by 17 different Federal agencies, including the Department of Health and Human Services. In addition to applying to federally supported research, the Common Rule applies to some privately funded projects conducted by universities and other institutions that have contractually agreed to apply the Common Rule to all their research activities. The Common Rule requires most studies involving human participants to be reviewed and approved by ethics review committees (referred to as "institutional review boards" – IRB) and sets forth standards regarding risk/benefit assessment, informed consent and other issues.

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[1] European Union. Directive of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official Journal of the European Communities, 2001:L121/34.

[2] United States Department of Health and Human Services. Title 45 – Public welfare, Part 46 – Protection of human subjects, 2005 (http://www.hhs.gov/ohrp/documents/OHRPRegulations.pdf, accessed 18 January 2009).

United States Food and Drug Administration regulations for the protection of human subjects:

The United States Food and Drug Administration (FDA) has its own set of regulations regarding ethical principles in research, which are similar in most respects to the Common Rule. The FDA regulations apply to clinical research related to products regulated by the FDA, including drugs, medical devices and biologicals. The regulations apply regardless of whether a study is supported by Federal funds.

In order for the results of research conducted outside the United States of America to be used as part of an application for FDA approval, the study must have been approved by an independent ethics review committee and be in compliance with good clinical practice guidelines.

Notes

Research ethics committees
Basic concepts for capacity-building

Research ethics committees review and monitor research studies involving human participants to ensure that they conform to internationally and locally accepted ethical guidelines. Their main responsibility is to protect potential participants in the research, particularly the most vulnerable, but they also take into account potential risks and benefits for the community in which the research will be carried out.

This manual and the accompanying CD-ROM are intended for use in a basic research ethics training programme for members of research ethics committees, researchers, national regulatory authorities, medical school faculty and other interested stakeholders in health care and research. The manual describes basic concepts, including ethical analysis, risk/benefit evaluation, confidentiality and the informed-consent process, along with the role of the research ethics committee, the organization of a training programme and the issue of financial conflicts of interest. Finally, it lists the most relevant international guidelines and regulations. The CD-ROM reproduces the printed manual, along with case-studies for use in training programmes and an extensive resource list.

World Health Organization
Ethics and Health Unit
Department of Ethics, Equity, Trade
and Human Rights
20, avenue Appia
1211 Geneva 27
Switzerland

ethics@who.int
www.who.int/ethics/en

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