Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants

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Preface

This document has been developed for individuals and organizations involved in health-related research with human participants, including biomedical, behavioural, social science, and epidemiological research (throughout this document, the term "research" is meant to include, and refers to, all of these domains). In particular, this document is intended to provide guidance to the research ethics committees (RECs) on which organizations rely to review and oversee the ethical aspects of research, as well as to the researchers who design and carry out health research studies.

Ethics guidance for research involving human participants has been developed and disseminated by numerous organizations and agencies at international (see Annex 1), regional, and national levels over the past 50 years. Adherence to these guidelines helps to promote the ethical conduct of research and enhances and protects the rights and well-being of research participants and communities. A core component of all contemporary research ethics guidelines is that research should be subject to prior ethical review by a competent REC. Such review is intended to ensure that the ethical principles and practices put forward in the guidelines will be followed in the proposed research.

In 2000, the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) published *Operational guidelines for ethics committees that review biomedical research*, in response to requests from collaborating researchers throughout the world. These Guidelines were reviewed by multiple experts, stakeholders, researchers, and organizations, including officials of the African Malaria Vaccine Testing Network, the Council of Europe, the National Institutes of Health (USA), the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, and the World Medical Association. Since 2000, the Guidelines have been translated into more than 25 languages, widely disseminated, and used by RECs in more than 100 countries.

In 2006, the WHO Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) recognized the need for raising the capacity for ethical review of research, noting that "Further efforts should be made to strengthen the clinical trials and regulatory infrastructure in developing countries, in particular in sub-Saharan Africa, including the

improvement of ethical review standards."[1] The Commission further noted that the World Health Organization (WHO) has an important role to play in the improvement of ethical review standards. Under Resolution 61.21 in 2008, and 63.21 in 2010, while endorsing the Research Strategy for Health, the World Health Assembly further urged Member States to "establish governance mechanisms for research for health, to ensure rigorous application of good research norms and standards, including protection for human subjects involved in research", and requested the Director-General to support Member States in strengthening mechanisms for ethical review of research, especially in developing countries.[2]

In November 2009, WHO organized a consultation in Geneva of key international experts, including researchers, ethicists, members and chairs of ethics committees, and representatives of international organizations, to discuss what additional guidance, if any, was needed by RECs globally—given the observation of the CIPIH that RECs continue to be quite variable in terms of their experience, training, capacity, institutional support, human and financial resources, and expertise. Based on experience from the field, participants concluded that the 2000 WHO publication, *Operational guidelines for ethics committees that review biomedical research,* has been an invaluable resource but needs to be updated and strengthened. The meeting also recognized that Member States may find it useful to have a set of global standards for high quality decision-making against which RECs might measure their own performance. The meeting participants recommended that WHO coordinate efforts to draft standards for RECs and to revise the 2000 *Operational guidelines* to describe specific procedures to meet the standards. WHO also consulted widely during the course of revising these guidelines through open consultation at a number of international conferences, through list-serves, and with other agencies as listed in the Acknowledgements.

This second edition of the 2000 *Operational guidelines* was developed as a result of these global developments. It consists of a compilation of 10 standards that are applicable to the ethics review of health-related research with human participants. The term "standards" is

[1] http://www.who.int/intellectualproperty/documents/thereport/ENPublicHealthReport.pdf accessed on 21.06.2011

[2] http://apps.who.int/gb/ebwha/pdf_files/WHA61-REC1/A61_Rec1-part2-en.pdf and http://apps.who.int/gb/ebwha/pdf_files/WHA63-REC1/WHA63_REC1-P2-en.pdf accessed on 21.06.2011

used to delineate general principles and norms that all research ethics systems are expected to follow. Standards (set forth in bold type) in this document are intended to help RECs achieve high quality performance and to provide a common language that establishes specific outcomes or characteristics against which achievements can be benchmarked. The standards put forward in this document do not represent new ideas for REC functioning. Rather, they are based on requirements for RECs delineated in existing international guidance documents. Their purpose is to underscore essential considerations relevant to the ethical review of research, not to take a substantive position on how specific ethical dilemmas should be resolved. Accompanying the standards are a series of "operational guidance" points (set forth in regular type), which reflect commonly used strategies for implementing and fulfilling each of the standards.

In addition to delineating standards for the research ethics system, three other changes have been made in this edition. First, the title has been changed to reflect the purpose of the document. Second, the importance of a systems approach to research ethics—alluded to in the first edition of the book—has been further elaborated, and expanded to include and delineate the role of national governments and relevant legal and regulatory authorities. Third, the scope of the document has been enlarged to include all health-related research ethics committees, whether they review biomedical, social science, epidemiological, operational, or health systems research.

This document is intended provide guidance on the research ethics review process, not to take a substantive position on how particular ethical dilemmas in health-related research should be resolved. It is designed to complement existing laws, regulations, and practices and to serve as a basis upon which RECs can develop their own specific practices and written procedures. It is not intended to replace the need for national and local guidelines for the ethical review of research involving human participants, nor to supersede national laws and regulations. Indeed, it is hoped that this document will be useful to those charged with drafting national, local, and institutional regulations and policies, and that it will enhance the quality of RECs worldwide.

Standards for the research ethics review system

Standard 1: Responsibility for establishing the research ethics review system

Relevant authorities ensure that ethics review of health-related research is supported by an adequate legal framework that is consistent with the standards set forth in this document; that research ethics committees (RECs) capable of providing independent review of all health-related research exist at the national, subnational, and/or institutional (public or private) levels; and that an appropriate and sustainable system is in place to monitor the quality and effectiveness of research ethics review.

While this document focuses primarily on standards and guidelines for RECs, unless attention is given to the larger system of human research protections of which RECs are a part, these committees may become isolated or be unable to perform efficiently or effectively, despite their best intentions. A systems approach means the following.

1. All research with human participants is presumptively subject to REC oversight. Specific categories of research may be exempted from REC review or subject to expedited review (see Standard 8), as allowed by national laws and regulations and consistent with international guidelines.
2. RECs are part of larger research participant protection programmes that also include training for REC members and researchers, and mechanisms to ensure that RECs work efficiently and effectively. National governments have the primary responsibility for ensuring that RECs are subject to adequate oversight.
3. Procedures exist to ensure clear and efficient communication, harmonization of standards, networking, and cooperation among national committees and between different levels of committees, as applicable. These procedures enable RECs to learn about prior decisions by other RECs that may be relevant to the proposed research under review. In addition, procedures exist for the coordinated review of multi-site research, whether within a country or in more than one country.
4. Mechanisms exist to ensure that RECs' activities are coordinated with national regulatory authorities' oversight of drugs, biologics, and medical devices, as well as with national and/or international clinical trial registries.

5. Mechanisms are in place for obtaining community input into the ethics review system.
6. A system exists for registration of RECs that operate in a particular country.

Institutional, national, and regional committees

Different approaches to research ethics review exist in different countries. In some countries, review may occur only at institutional level, in others at both a national and institutional level, and in still others at a regional level. In designing systems for research ethics review, countries should take into account the volume of research conducted by various entities in the country.

Having a good systems approach and clear rules of how the various RECs within a country interact with each other can greatly facilitate the conduct of international health research.

Types of research studies

RECs may review different types of research studies, including, but not limited to, the following:

- clinical trials
- epidemiological research
- social science research
- research on medical records or other personal information
- research on stored samples
- health systems research
- implementation research

RECs should be familiar with the different methodologies and ethical considerations that apply to each type of proposed research they review.

Chapter II

Standards and guidance for entities that establish research ethics committees

Standard 2: Composition of research ethics committees

The research ethics committee (REC) is constituted according to a charter or other document that establishes the manner in which members and the Chair will be appointed. The appointing entity ensures that the REC has a multidisciplinary and multisectoral membership, that its composition is gender balanced, that it reflects the social and cultural diversity of the communities from which research participants are most likely to be drawn, and that it includes individuals with backgrounds relevant to the areas of research the committee is most likely to review.

The entity establishing the REC takes the following factors into consideration when appointing members.

1. Members include individuals with scientific expertise, including expertise in behavioural or social sciences; health care providers; members who have expertise in legal matters and/or ethics; and lay people whose primary role is to share their insights about the communities from which participants are likely to be drawn.
2. Lay people and other members, whose primary background is not in health research with human participants, are appointed in sufficient numbers to ensure that they feel comfortable voicing their views.
3. In order to enhance independence, committee membership includes members who are not affiliated with organizations that sponsor, fund, or conduct research reviewed by the REC (see also Standard 4).
4. Committees are large enough to ensure that multiple perspectives are brought into the discussion. To this end, quorum requirements provide that at least five people, including at least one lay member and one non-affiliated member, are present to make decisions about the proposed research.

Standard 3: Research ethics committee resources

The entity establishing the REC supports it with adequate resources, including staffing, facilities, and financial resources to allow the REC to effectively carry out its responsibilities.

As an integral part of a health research institution or health system, an REC receives:

1. support staff, adequate in number and training to enable the REC to carry out its technical and administrative responsibilities;
2. adequate resources for the staff to fulfil its assigned functions, including office space and equipment and supplies (e.g. computers, stationery, telephones, photocopying machines, shredding machine) to conduct administrative business, to store committee files, and to keep documents secure and confidential;
3. access to appropriate space for the committee to meet and adequate means for members to communicate as needed between meetings;
4. adequate financial resources to permit the committee to produce high-quality work;
5. if considered necessary by the entity establishing the REC, resources necessary to compensate REC members, unless they are already being compensated for their time and effort on the REC through other means.

Standard 4: Independence of research ethics committees

Policies governing the REC include mechanisms to ensure independence of the REC's operations, in order to protect decision-making from influence by any individual or entity that sponsors, conducts, or hosts the research it reviews. Such policies provide at a minimum that REC members (including the Chair) remove themselves from the review of any research in which they or close family members have a conflicting interest.

To ensure that the REC cannot be pressured to approve or disapprove particular protocols, the charter, by-laws, policies and/or procedural rules of the REC provide that:

1. the REC's membership includes at least one person with no connection to the organization that sponsors or conducts the research under review;
2. researchers, sponsors, and funders may attend an REC meeting to answer questions about their research protocols and associated documents, but they are not present when the REC reaches decisions about their proposed research;
3. senior decision-makers of the entity creating the REC, or of any organization that sponsors or conducts the research reviewed by the REC (such as the director of an institution, or his or her agent), do not serve as members of the REC or its Chair;
4. the entity that establishes the REC ensures that REC members are protected from retaliation based on positions taken with respect to REC-related matters or review of research projects.

Standard 5: Training the research ethics committee

Training on the ethical aspects of health-related research with human participants, how ethical considerations apply to different types of research, and how the REC conducts its review of research, is provided to REC members when they join the committee and periodically during their committee service.

The training provided to REC members, either directly by the appointing entity or through cooperative arrangements with other RECs and/or organizations that provide education on research ethics, focuses on:

1. the role and responsibilities of the REC, and its role vis-à-vis other relevant entities, according to relevant international guidelines (e.g. the Council for International Organizations of Medical Societies [CIOMS] International Ethical Guidelines for Biomedical Research, CIOMS International Ethical Guidelines for Epidemiological Research, International Council on Harmonization [ICH] Good Clinical Practice [GCP] guidelines in the case of clinical trials), national laws, and institutional policies;
2. the full range of ethical considerations relevant to research with human participants;
3. the application of such ethical considerations to different types of research;
4. basic aspects of research methodology and design (for members who lack such background);
5. the impact of different scientific designs and objectives on the ethics of a research study;
6. the various approaches for recognizing and resolving the tensions that can arise among different ethical considerations and modes of ethical reasoning.

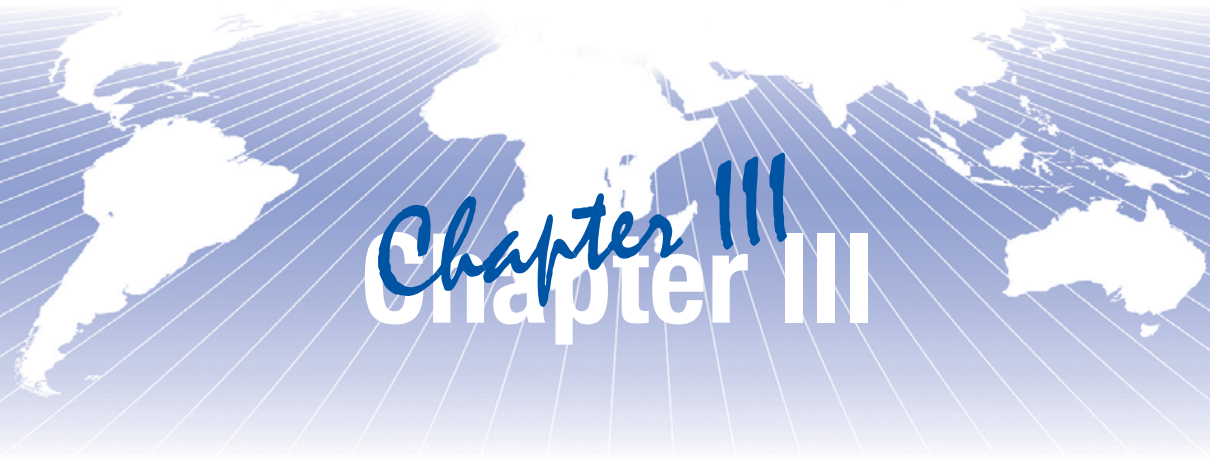
When training is supported by research sponsors, mechanisms are in place to ensure that the sponsor has no control, direct or indirect, over the content of the training.

Standard 6: Transparency, accountability, and quality of the research ethics committee

Mechanisms exist to make REC operations transparent, accountable, consistent, and of high quality.

The entity establishing the REC employs reliable means to evaluate whether the staff and members of the REC routinely follow the REC's policies, rules, and written procedures (see Standard 9), with special attention to whether the ethical considerations articulated in international guidelines and national standards are being considered and applied consistently and coherently.

1. Such evaluations are conducted by knowledgeable and unbiased people at regular, pre-defined intervals using a pre-defined format; internal assessments are supplemented periodically by independent external evaluations.
2. The entity establishing the REC is committed to consider and, when appropriate, follow up on the findings and recommendations of the internal and external evaluations.
3. The results of the evaluation are of a type that can aid the REC in reviewing its practice and appraising performance (rather than apportioning blame), while also assuring the public that research is being reviewed according to established standards.
4. Researchers, research participants, and other interested parties have a means of lodging complaints about the REC; such complaints should be reviewed by an entity other than the REC itself, and appropriate follow-up actions should be taken.
5. Researchers have a means of discussing concerns with REC members, both on general matters and in response to REC decisions on particular research studies.
6. REC decisions, excluding confidential information, are made publicly available, through mechanisms such as clinical trial registries, web sites, newsletters, and bulletin boards.



Chapter III

Standards and guidance for members of the research ethics committees

The primary task of an REC is the ethical review of research protocols and their supporting documents. Approval or disapproval is based on the *ethical acceptability* of the research, including its social value and scientific validity, an acceptable ratio of potential benefits to risks of harm, the minimization of risks, adequate informed consent procedures (including cultural appropriateness and mechanisms to ensure voluntariness), measures to ensure protection of vulnerable populations, fair procedures for selection of participants, and attention to the impact of research on the communities from which participants will be drawn, both during the research and after it is complete. The review take into account any prior scientific reviews and applicable laws.

Standard 7: Ethical basis for decision-making in research ethics committees

The REC bases its decisions about research that it reviews on a coherent and consistent application of the ethical principles articulated in international guidance documents and human rights instruments, as well as any national laws or policies consistent with those principles. The REC makes clear the specific ethical guidelines on which it relies in making decisions and makes them readily available to researchers and the public. When an REC develops reliance agreements for review of research under its jurisdiction by another REC, it is the responsibility of the delegating REC to assure that the same ethical principles serve as the basis of the other REC's decision-making.

To aid in determining the ethical acceptability of research protocols, an REC may utilize a checklist to ensure that all relevant criteria are considered during review and that, as a general rule, similar protocols are treated similarly. When an REC determines that an approach it has taken on a particular ethical issue in the past is no longer appropriate, it provides an explicit rationale for its change in position. In communicating decisions about particular protocols to researchers, the REC explains its analysis of any significant ethical issues that arose in the review.

As articulated in more detail in international ethics guidelines and the research regulations of a number of jurisdictions, key criteria include, but are not limited to, the following.

1. Scientific design and conduct of the study

Research is ethically acceptable only if it relies on valid scientific methods. Research that is not scientifically valid exposes research participants or their communities to risks of harm without any possibility of benefit. RECs should have documentation from a prior scientific review, or should themselves determine that the research methods are scientifically sound, and should examine the ethical implications of the chosen research design or strategy. Unless already determined by a prior scientific review, RECs should also assess how the study will be conducted, the qualifications of the researcher(s), the adequacy of provisions made for monitoring and auditing, as well as the adequacy of the study site (e.g. availability of qualified staff and appropriate infrastructures).

2. Risks and potential benefits

In ethically acceptable research, risks have been minimized (both by preventing potential harms and minimizing their negative impacts should they occur) and are reasonable in relation to the potential benefits of the study. The nature of the risks may differ according to the type of research to be conducted. REC members should be aware that risks may occur in different dimensions (e.g. physical, social, financial, or psychological), all of which require serious consideration. Further, harm may occur either at an individual level or at the family or population level.

3. Selection of study population and recruitment of research participants

Ethically acceptable research ensures that no group or class of persons bears more than its fair share of the burdens of participation in research. Similarly, no group should be deprived of its fair share of the benefits of research; these benefits include the direct benefits of participation (if any) as well as the new knowledge that the research is designed to yield. Thus, one question for research ethics review to consider is whether the population that will bear the risks of participating in the research is likely to benefit from the knowledge derived from the research. In addition, ethically acceptable research includes recruitment strategies that are balanced and objectively describe the purpose of the research, the risks and potential benefits of participating in the research, and other relevant details.

4. Inducements, financial benefits, and financial costs

It is considered ethically acceptable and appropriate to reimburse individuals for any costs associated with participation in research, including transportation, child care, or lost wages. Many RECs also believe that it is ethically acceptable to compensate participants for their time. However, payments should not be so large, or free medical care or other forms of compensation so extensive, as to induce prospective participants to consent to participate in the research against their better judgement or to compromise their understanding of the research.

5. Protection of research participants' privacy and confidentiality

Invasions of privacy and breaches of confidentiality are disrespectful to participants and can lead to feelings of loss of control or embarrassment, as well as tangible harms such as social stigma, rejection by families or communities, or lost opportunities such as employment or housing. RECs should therefore examine the precautions taken to safeguard participants' privacy and confidentiality.

6. Informed consent process

The ethical foundation of informed consent is the principle of respect for persons. Competent individuals are entitled to choose freely whether to participate in research, and to make decisions based on an adequate understanding of what the research entails. Decisions for children or adults who lack the mental capacity to provide informed consent should be made by an authorized surrogate decision-maker.

RECs should examine the process through which informed consent will occur, as well as the information that will be provided. RECs may waive the requirement of informed consent only when doing so is consistent with international guidelines and national standards.

While informed consent to research is important, the fact that a participant or surrogate may be willing to consent to research does not, in itself, mean that the research is ethically acceptable.

7. Community considerations

Research has impacts not only on the individuals who participate, but also on the communities where the research occurs and/or to whom findings can be linked. Duties to respect and protect communities require examining by the REC and, as far as possible, are aimed at minimizing any negative effects on communities such as stigma or draining of local capacity, and

promoting, as relevant, positive effects on communities, including those related to health effects or capacity development. Researchers should actively engage with communities in decision-making about the design and conduct of research (including the informed consent process), while being sensitive to and respecting the communities' cultural, traditional and religious practices.

Standard 8: Decision-making procedures for research ethics committees

Decisions on research protocols designated for review by the convened REC are based on a thorough and inclusive process of discussion and deliberation. Protocols involving no more than minimal risk and burden to research participants may be reviewed on an expedited basis by one or more members (rather than the full committee), if the REC has established written procedures permitting such a procedure.

1. During meetings of the REC, members engage in discussions to elicit all concerns and opinions related to the protocols and the associated documents under consideration. The REC's rules ensure that the discussions are respectful of all opinions and allow for varied beliefs to be aired. The Chair fosters a respectful and inclusive tone and allows adequate time for deliberation, during which only REC members participate and decisions are made only by those who were present during the entire discussion. The Chair is responsible for the decision-making process, in particular for determining when consensus is needed to achieve the decision. Researchers, funders, or others directly associated with the protocol in question are not present during committee deliberations.
2. REC members recognize the limitations of their knowledge and seek external input when necessary, particularly in relation to research that involves people whose life experiences may differ significantly from those of the committee members.
3. Decisions are arrived at through either a vote or consensus. Consensus does not require that all REC members support the decision, but that all members consider the decision at least acceptable and no member considers the decision unacceptable. A pre-defined method determines when votes will be taken and how many favourable votes will be needed for a proposed research to be approved.

Chapter IV

Standards and guidance for the secretariat, staff, and administration of the research ethics committees

Standard 9: Written policies and procedures

Written policies and procedures specify the REC's membership, committee governance, review procedures, decision-making, communications, follow-up, monitoring, documentation and archiving, training, quality assurance, and procedures for coordination with other RECs.

The entity that creates the REC has a responsibility to establish the necessary policies to govern the REC. The REC adopts its rules of procedure and—with the secretariat/staff—promulgates comprehensive, written procedures, which are distributed to all committee members and made publicly available. To the fullest extent possible, the hosting institution provides RECs with a Secretariat whose staff have the necessary knowledge, expertise and training to support the REC in performing its review and record keeping function (for further guidance on the Secretariat function, see Annex 2) . To ensure efficient operation, the policies, rules, and written procedures are reviewed periodically in the light of ongoing assessment of performance and outcomes to determine whether any revisions are needed. REC policies and rules typically address the following topics.

1. Membership of the committee

The REC's policies and procedures delineate the authority, the terms, and the conditions of appointment. Staggered, finite terms of appointment should be considered, allowing continuity of some members when other members are newly appointed. Having limited terms also promotes the development of research ethics expertise and greater knowledge of REC procedures among the larger community of individuals who may rotate through committee service, and allows for input of fresh ideas and approaches to committee deliberations.

2. Committee governance

The REC's policies and procedures define how the REC will establish its offices (e.g. Chair, Vice-Chairs). The Chair is someone respectful of divergent views, able to encourage and help achieve consensus, and with the time to prepare adequately for meetings. The Chair is not a person who has a supervisory relationship toward other members of the committee.

3. Independent consultants

The REC's policies and procedures define the circumstances under which an REC may call upon independent consultants to provide special

expertise to the REC on specific research protocols, populations, or topics.

4. Submissions, documents required for review, review procedures, and decision-making

The REC's policies and procedures describe the requirements for submitting an application for review, including the forms to be completed and the documents to be submitted. They also specify the process and procedure for review, process for coordinating review with other committees, process for setting up meetings, circulating documentation for the meetings, inviting non-members of the REC, approving the meeting minutes, and any related process issues. Procedures for deliberation and decision-making are clearly established and described. Specific quorum requirements for reviewing and making decisions or taking actions are clearly established in the standard operating procedures.

5. Communicating a decision

The REC's policies and procedures describe procedures for communicating the decisions of the REC and specify the maximum amount of time between the decision about the application and when the applicant is informed.

6. Follow-up reviews and monitoring of proposed research

Standard operating procedures describe the process by which RECs will follow up the progress of all approved studies—from the time that the approval decision is taken until the termination or completion of the research.

7. Documentation and archiving

All of the REC's documentation and communication is dated, filed, and archived according to the committee's written procedures. Records may be kept either in hard copy or electronically. In either case, sufficient safeguards are established (e.g. locked cabinets for hard copy files, password protection and encryption for electronic files) to maintain confidentiality. Members of staff are sufficiently trained to understand their responsibilities related to record-keeping, retrieval, and confidentiality. Procedures outline who is authorized to access committee files and documents.

Further guidance on REC written procedures is provided in Annex 3.

Standards and guidance for researchers

Standard 10: Researchers' responsibilities

Research is performed only by persons with scientific, clinical, or other relevant qualifications appropriate to the project, who are familiar with the ethical standards applicable to their research, who submit the necessary information to the REC for review (including both the research protocol and disclosures of any conflicting interests), and who carry out the research in compliance with the requirements established by the REC.

The person conducting research fulfils the following criteria in the conduct of ethical research.

1. Submitting an application for review

a. An application or review of the ethics of proposed health-related research is submitted by a researcher qualified to undertake the particular study, who is directly responsible for the ethical and scientific conduct of the research. In certain jurisdictions, the sponsor of a study is responsible for submitting the research protocol to the REC.

b. Student applications are submitted under the responsibility of a qualified advisor / faculty member involved in the oversight of the student's work or in the student's name, co-signed by the qualified faculty supervisor.

c. All information required for a thorough and complete review of the ethics of proposed research is submitted, including disclosures about researchers' conflicting interests, if any.

2. Conduct of research

a. The research is conducted in compliance with the protocol approved by the REC.

b. No deviation or changes are made to the approved protocol or in following it, without prior approval of the REC, except where immediate action is necessary to avoid harm to research participants. In such a case, the REC is informed promptly of the changes/deviations made, and the justification for doing so.

c. The REC is informed of any changes at the research site that significantly affect the conduct of the trial, and/or reduce the protections or decrease the benefits provided or increase the risk to participants (e.g. closing down of a health facility at the

research site or other impediments to obtaining access to health care that was originally available).

3. Safety reporting

a. All serious, unexpected adverse events related to the conduct of the study/study product or unanticipated problems involving risks of harm to the participants or others are promptly reported to the REC and/or other relevant authorities, as required by REC policies and applicable laws.

b. Any recommendations provided by the REC in response to such reporting are immediately implemented.

4. Ongoing reporting and follow-up

a. The researcher submits written summaries of the research status to the REC annually, or more frequently, if requested by the REC.

b. Researchers inform the REC when a study is completed or prematurely suspended/terminated.

c. In the case of the early suspension/termination by the researcher or sponsor, the researcher notifies the REC of the reasons for suspension/termination; provides a summary of results obtained prior to prematurely suspending or terminating the study; and describes the manner by which enrolled participants will be notified of the suspension or termination and the plans for care and follow-up for the participants.

d. If the REC terminates or suspends its approval of a study, the researcher informs the institution under whose authority the research is being conducted, the sponsor of the research, and any other applicable organizations.

5. Information to research participants

Researchers have a responsibility to keep the research participants and their communities informed of the progress of research by appropriate means, at suitable time-frames in simple and non-technical language, for example, when:

a. the research study is terminated or cancelled

b. any changes occur in the context of the research study that alter the potential benefits or risks

c. the research project is completed

d. results of the research are available.

Annex 1. 2. 3.
and Glossary

Annex 1

Guidelines and codes of best practice

1. Nuremberg Code (Available at: http://ohsr.od.nih.gov/guidelines/nuremberg.html, accessed 17 January 2009)
2. Declaration of Helsinki (Available at http://www.wma.net/en/30publications/10policies/b3/index.html, accessed 05 October 2011)
3. CIOMS: International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002) (Available at http://www.cioms.ch/publications/layout_guide2002.pdf, accessed 05 October 2011)
4. CIOMS: International Ethical Guidelines for Epidemiological Research Involving Human Subjects (2009) (For more information click http://www.cioms.ch/frame_ethical_guidelines_2009.htm)
5. UNAIDS/WHO, Ethical Considerations in Biomedical HIV Prevention Trials (2007) (Available at http://data.unaids.org/pub/Report/2007/JC1399_ethical_considerations_en.pdf , accessed 05 October 2011)
6. UNESCO Universal Declaration on Bioethics and Human Rights (2005) (Available at http://portal.unesco.org/en/ev.php-URL_ID=31058&URL_DO=DO_TOPIC&URL_SECTION=201.html
7. Nuffield Council on Bioethics: the Ethics of Research related to Healthcare in Developing Countries (2002) (Available at http://www.nuffieldbioethics.org/sites/default/files/Ethics%20of%20research%20related%20to%20healthcare%20in%20developing%20countries%20I.pdf)

Statutes and regulations

1. The Universal Declaration of Human Rights Available at http://www.un.org/en/documents/udhr/ accessed on 05 October 2011)
2. ICH Good Clinical Practice Guidelines (1996) (Available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf
3. ICH Guidelines on Choice of Control Groups and Related Issues in Clinical Trials (2000) (Available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E10/Step4/E10_Guideline.pdf , accessed 05 October 2011)

4. Council of Europe. Convention on Human Rights and Biomedicine, 1997 (Available at http://conventions.coe.int/treaty/EN/Treaties/Html/164.htm, accessed 05 October 2011)

5. Council of Europe. Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, 2005 (Available at http://conventions.coe.int/treaty/EN/Treaties/Html/195.htm , accessed on 05 October 2011))

6. 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. (Available at http://www.eortc.be/Services/Doc/clinical-EU-directive-04-April-01.pdf , accessed 05 October 2011)

7. The Common Rule (45 CFR Part 46) (Available at http://www.hhs.gov/ohrp/policy/ohrpregulations.pdf accessed 05 October 2011)

8. United States Food and Drug Administration regulations for the protection of human subjects CFR — Code of Federal Regulations Title 21, Part 50 (Available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50, accessed 15 August 2011

Annex 2

Guidance for developing terms of reference for the Secretariat of the research ethics committee

Institutions hosting RECs provide the RECs with a Secretariat that is adequately staffed to support them in their review and record keeping duties. At a minimum, the functions of the Secretariat include:

1. Informing and advising the principal investigators, sponsors, and new REC members of applicable regulations, guidelines, processes and procedures. In some cases the Secretariat maintains a website ensuring public access to this information.
2. Managing the timely progress of protocol review through initial and continuing contacts with Principal Investigators. This includes identifying and requesting missing documentation in applications and preparing the completed file for committee review.
3. Preparing the meetings of the REC, including the distribution of relevant documentation to the members, scheduling the meetings, and ensuring the quorum.
4. In close collaboration with the chair of the REC, preparing applications that will be evaluated through expedited review.
5. Following-up with tasks that the REC requests the principal investigators to perform such as progress reports, final reports, corrective actions, amendment of the approved protocol or consent documents etc.
6. In close collaboration with the Chair of the REC, preparing reports of REC meetings and annual reports of REC activities. The annual report includes information about sources of funding and expenses of the REC.
7. Record keeping, including maintaining research protocols and all correspondence in relation to their review, as well as records of any continuing oversight that may be required after approval. The Secretariat ensures that the confidentiality of REC records is maintained.
8. Facilitating access to literature and educational programmes useful to the members of REC.
9. Up dating information about REC membership, including declarations of potential conflicts of interests.

Additional responsibilities may be delegated to the Secretariat staff by the entity creating the REC and/or the REC Chair, as appropriate in light of the Secretariat's training, expertise, capacity, and resources; such responsibilities may include keeping abreast of developments in research ethics and regulation, engaging in community outreach and education, serving as a liaison between the REC and the research community, facilitating implementation of quality improvement and quality assurance programs etc.

Annex 3

Guidance for developing written procedures for the research ethics committee

REC written procedures address the following issues:

I. Membership of the Committee

a) Authority for appointment of committee members specifying the name or description of the entity responsible for making appointments and the procedures for:

1. selecting and appointing the REC Chair and members, including the method by which new members and the Chair are selected (e.g. by consensus or majority vote of existing members, by direct appointment of the Chair or other official)
2. managing conflicts of interest in making appointments (see Standard 4).

b) Terms of appointment, including:

1. the duration of an appointment
2. the policy for the renewal of an appointment
3. the disqualification procedure
4. the resignation procedure
5. the replacement procedure.

c) Conditions of appointment, including:

1. that an REC member shall agree to publicize his/her full name, profession and affiliations
2. whether a member receives any reimbursement for travel expenses and/or lost wages and that such reimbursements, if any, shall be recorded and information about such reimbursements made available to the public
3. that REC members and staff shall sign confidentiality agreements regarding sensitive aspects of protocols, meeting deliberations and related matters (e.g. information about trade secrets or personal information about research participants).

II. Committee governance

The REC establishes clearly defined offices for the good functioning of ethical review. The REC's policies and procedures define how the REC will establish its officers (e.g. Chair, Vice-Chairs, etc.). Terms of reference are established for officers that outline:

1. procedures for selecting and appointing officers
2. the requirements for holding the office
3. the terms and conditions of each office
4. the duties, responsibilities, and authority of each officer (e.g. running a meeting, setting the agenda, notifying decisions to applicants).

III. Independent consultants

Written procedures define the circumstances under which an REC may call upon independent consultants to provide special expertise to the REC on specific research projects, populations, or topics. Such consultants could include experts in ethics, law, or specific medical specialties or procedures, or they might be representatives of communities, patients, or other groups relevant to the deliberations required. Written procedures require terms of reference for independent consultants and confidentiality agreement, and clarify that—because consultants are not members of the REC—they do not have any voting or decision-making authority.

IV. Submissions, documents required for review, review procedures, and decision-making

a) Submission procedures

The written procedures describe the requirements for submitting a research project for review. Submission requirements and required forms should be readily available to prospective applicants. Application instructions generally include at least the following:

1. the name(s) and address(es) of the REC secretariat, officers, or member(s) to whom the application material should be submitted
2. all written documentation to be submitted as part of the application
3. the format for submission
4. the language(s) in which (core) documents are to be submitted
5. the number of copies to be submitted
6. the deadlines for submission of the application in relation to review dates
7. the means by which applications will be acknowledged and by which notices about the incompleteness of an application package will be communicated
8. the expected time for notification of the decision following review
9. the time-frame to be followed in cases where the REC requests supplementary information or changes to documents from the applicant
10. a fair and transparent fee structure, if any, for reviewing a research project

11. the procedure for seeking amendments to the protocol, or its related documents
12. the required format for recruitment material, information to be given to prospective research participants, and the informed consent form
13. if appropriate and necessary, a check list for the above procedures.

b) Documents required for review

All documents required for a thorough and complete review of the proposed research project should be submitted by the applicant, in the REC's working language. As applicable, this may include, but is not limited to:

1. signed and dated application form, including signatures of listed co-applicants and institutional officials (e.g. heads of departments) where relevant
2. the protocol for the proposed research project, clearly identified and dated, together with supporting documents and annexes
3. a project summary or synopsis in non-technical language
4. a description (which may be included in the protocol) of the ethical considerations involved in the proposed research
5. background information on previous research in the same area of work that justifies and/or supports the proposal
6. when the research involves an experimental product (such as a pharmaceutical or medical device under investigation), an adequate summary of all safety, pharmacological, pharmaceutical, and toxicological data available on the study product, together with a summary of clinical experience with the study product to date (e.g. recent investigator's brochure, published data, a summary of the product's characteristics)
7. current curricula vitae of the principle investigators
8. all data collection forms to be used in the research project, including but not limited to case report forms, diary cards, questionnaires, interview schedules, etc., clearly identified and dated
9. all forms, documents, advertisements to be used in recruitment of potential participants
10. a detailed description of the recruitment process and strategies
11. informed consent form(s) (with date and version number) in languages understood and at a reading level appropriate for the potential research participants and when required, in other languages

12. a description of the process that will be used to obtain and document informed consent
13. a description of measures that will be taken to ensure the protection of participants' privacy and the confidentiality of data
14. a statement describing any remuneration or other goods or services to be provided to study participants, including reimbursement of expenses and access to medical care
15. a description of arrangements for insurance coverage for research participants, if applicable
16. disclosure of all previous decisions (including those leading to a negative decision or modified proposal) by other RECs or regulatory authorities for the proposed study, whether in the same location or elsewhere, and indication of the reasons for previous negative decisions and modification(s) to the proposal made on that account
17. a statement that the researcher(s) agree to comply with ethical principles set out in relevant guidelines.

c) Review procedures

The REC's written procedures specify the process by which the REC will decide which projects should be reviewed by the full convened committee and which projects may be reviewed through an expedited procedure. The written procedures address who will have the responsibility of making this determination, as well as the number of reviewers required for expedited review and how those reviewers will be selected. The Chair regularly notifies the REC members of expedited reviews that have been conducted between convened REC meetings. The REC's written procedures state the procedures for coordinating with and/or relying on the reviews and decisions of other domestic RECs or RECs in other countries.

d) REC meetings

RECs should meet regularly as a committee on dates that are announced in advance. The written procedures should describe the process for setting up meetings, circulating documentation for the meetings, inviting non-members of the REC, approving the meeting minutes, and any related process issues. The following issues are outlined in the written procedures:

1. the frequency of meetings, which should be based on committee workload and regular enough to avoid undue delay
2. the maximum time-frame for review after receipt of complete applications, and a process or mechanism which provides justification if the time-frame is exceeded.

3. mechanisms to ensure that REC members receive all relevant documents in advance of the meetings with enough time to adequately review meeting materials
4. standards and procedures for inviting the researcher and/or sponsor of a particular project to present or comment on the project in question or on specific issues that relate to it during the meeting, at the discretion of the committee
5. standards and procedures for taking and approving meeting minutes.

e) Quorum requirements

Specific quorum requirements for reviewing and making decisions or taking actions on an application are clearly established in the written procedures, including:

1. the minimum number of members required to compose a quorum (e.g. half of the members, a simple majority—see Standard 2)
2. the distribution of committee composition requirements across the quorum; a quorum should consist of at least five members, including at least one lay member and one non-affiliated member (see Standard 2)

f) Deliberation and decision-making.

Procedures for deliberation and decision-making are clearly established and describe:

1. the ethical guidelines on which the REC will rely to make its decisions
2. the manner in which the project documents will be presented to the committee for discussion
3. the process by which the project will be discussed, including who may remain in the room during various components of the discussions and/or decision-making
4. quorum requirements for making a decision (see Standard 2, and quorum requirements above)
5. the pre-defined method for arriving at a decision and who may take part in decision-making
6. clear options for decisions, including approval, conditional approval, a request to revise and resubmit, or disapproval; criteria for each outcome should be described, as should any specific follow-up procedures associated with each option, including specific procedures for re-review, as applicable.

Committee correspondence should make clear to the applicant that no research project with human participants can commence before the relevant

REC's concerns have been satisfied and full approval has been granted.

V. Communicating a decision

Written procedures describe mechanisms for communicating the decisions of the REC and outline the maximum amount of time between the decision about the proposal and when the applicant is informed. The communication of the decision includes, but is not limited to, the following:

a) Specific identifying information about the project, including:

1. the exact title of the research project reviewed
2. the clear identification of the protocol of proposed research or amendment, date and version number (if applicable) on which the decision is based
3. the names and (where possible) specific identification numbers (version numbers/dates) of the documents reviewed, including the research participant information sheet/material and informed consent form
4. the name and title of the applicant and/or sponsor
5. the name of the site(s)
6. the date and place of the decision
7. the name of the REC making the decision.

b) A clear statement of the decision reached:

➥ *In the case of an approval,*

1. any significant ethical issues that were discussed during the meeting, and the resolution of those issues
2. the fact that approval is given only for the protocol and its associated documents as accepted by the REC, with compliance expected
3. the duration for which the approval is valid, and the procedures to be followed to renew the approval at the end of that period, if applicable.
4. a statement of the responsibilities of the applicant; for example,
   - confirmation of the acceptance by the researchers of the requirements imposed by the REC
   - submission of progress report(s) at predefined intervals
   - the need to seek further prior approval from the REC in cases of protocol and/or it's related documents amendments or deviations (other than logistical or administrative changes that may be made without permission of the REC, as authorized by local law and REC policies)

- the need to seek further prior approval from the REC in the case of amendments to the recruitment material, the prospective research participant information, or the informed consent form
- the need to report to the REC and/or other relevant authorities, all serious unexpected adverse events related to the conduct of the study or unanticipated problems involving risks of harm to the participants or others, as required by REC policies and applicable laws
- the information the REC would expect to receive in order to perform follow-up reviews
- the need to notify the REC when a study is completed (i.e. when interactions with participants have concluded) or prematurely suspended/terminated, and to provide the REC with a final report.

➥ In the case of a conditional decision, any requirements by the REC, including suggestions for revision and the procedure for having the application re-reviewed

➥ In the case of a negative decision, clearly stated reasons related specifically to ethical considerations

➥ Advice or suggestions that are non-binding may be appended to the decision but should clearly be marked as advice separate from any stipulations or determinations of the REC.

c) Signature (dated) of the Chair (or other authorized person) of the REC.

d) Written procedures provide mechanisms for researchers to request reconsideration of REC decisions, either by the REC itself or by other entities. If appeals to entities outside the REC are authorized, written procedures address the process for appeals, what materials must be submitted and to whom, and who will be the ultimate decision-maker.

e) Written procedures specify mechanisms for informing the public about REC decisions (e.g., bulletin board or Internet postings, newsletters, or use of registries).

VI. Follow-up reviews and monitoring of proposed research

Written procedures describe the process by which RECs will maintain ethical oversight of research by following up the progress of all approved studies, from the time that the approval decision is taken until the termination of the research. In addition, mechanisms exist to ensure that researchers fulfil any commitments they have made to engage in specific activities after the study is over (e.g. continuing to provide treatment to study participants).

The procedure for follow-up review takes the following into consideration:

a) documents to be reviewed, including but not limited to:

1. progress reports, final report
2. safety reports
3. audit reports, independent of the researcher and the sponsor (e.g. institutional internal audits)
4. experiences of the participants and potential participants (e.g. independent observation of the informed consent discussion, independent surveys of participants experiences)
5. notification from the applicant with regard to suspension/premature termination or completion of the study

b) quorum requirements, and communication procedure for follow-up reviews, which may vary from requirements and procedures for the initial review of the application

c) the intervals for follow-up reviews, which should be determined by the nature of the research project but should generally be at least once a year

d) circumstances that will trigger follow-up reviews, in addition to those that are regularly scheduled, including the following:

1. any protocol amendment likely to affect the rights, safety, and/or well-being of the research participants or the conduct of the study
2. serious unexpected adverse events related to the conduct of the study or study product
3. any event or new information that might affect the potential benefits or risks of harm involved in the study
4. decisions made by a data safety monitoring board (DSMB) or other monitoring or regulatory authorities to suspend a study in whole or in part

e) a decision resulting from a follow up review should be issued and communicated to the applicant, indicating either that the original decision is still valid or that there has been a modification, suspension, or withdrawal of the REC's original decision.

VII. Documentation and archiving

All of the REC's documentation and communication is dated, filed, and archived according to the committee's policies and written procedures. Such policies should be consistent with any relevant local laws or institutional policies. REC records may be kept in hard copy, electronically, or both. In either case, sufficient safeguards are established (e.g. locked cabinets for hard copy files, password

protection and encryption for electronic files) to maintain confidentiality. Members of staff are sufficiently trained to understand their responsibilities related to record keeping, retrieval, and confidentiality. Procedures outline who is authorized to access committee files and documents.

a) Committee-related documents

Committee-related documents that should be filed and archived include, but are not limited to:

1. any documents formally establishing the REC
2. the REC's standard operating procedures
3. the published guidelines for submission of documents to the REC
4. annual reports summarizing REC activities; such reports will promote transparency and will help raise awareness of the REC within its institution or jurisdiction, as well as serving as an ongoing reminder of the resources necessary to run the committee
5. curricula vitae of all REC members
6. record of all income and expenses of the REC, including allowances and reimbursements made to the secretariat and REC members and for what purposes
7. agendas of the REC meetings
8. minutes of the REC meetings
9. regulatory texts used by the REC

b) Project-related documents

All documents and materials related to the review of specific projects should be filed. Committee procedures should specify length of time documents must be archived—for example, with studies under ICH GCP, the documents are archived for a minimum period of 3 years following completion of the study. These include, but are not limited to:

1. one copy of all materials submitted by an applicant
2. any correspondence by the REC with applicants or concerned parties regarding applications, decisions, and follow-up
3. a copy of initial and follow up decisions and any advice or requirements sent to an applicant
4. all written documentation received during the follow-up, including any advice or requirements sent to the applicant
5. the notification of the completion, premature suspension, or premature termination of a study
6. the final summary or final report of the study

Glossary

Benefit: A favourable consequence arising from a study, for example the demonstration that a vaccine is effective in a randomized controlled trial or the identification of a workplace hazard in an observational study.

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

Compensation: That which is given in recompense, as an equivalent rendered, or remuneration.

Confidentiality: The obligation to keep information secret unless its disclosure has been appropriately authorized by the person concerned or, in extraordinary circumstances, by the appropriate authorities.

Conflict of interest: In the research context, scientists have a conflict of interest if they stand to achieve personal gain (money or the equivalent) by failing to discharge professional obligations, either to protect the welfare of participants or to uphold the integrity of the scientific process.

Consent form: An easily understandable written document that documents a potential participant's consent to be involved in research which describes the rights of an enrolled research participant. This form should communicate the following in a clear and respectful manner: research time-frame; 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; and declarative statement of understanding that the potential participant agrees to and signs. The consent form should be in a language that 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 be given.

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

Expedited review: Review of proposed research by the REC chair or a designated voting member or group of voting members rather than by the entire REC.

Informed consent: Is a decision to participate in research, taken by a competent individual who has received the necessary information; who

has adequately understood the information; and who, after considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation.

Multi-site research: A clinical trial conducted according to a single protocol but at more than one site, and, therefore, carried out by more than one investigator.

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.

Privacy: The state or condition of being alone, undisturbed, or free from public attention, as a matter of choice or right; seclusion; freedom from interference or intrusion; absence or avoidance of publicity or display; secrecy, concealment, discretion; protection from public knowledge or availability.

Quorum: A quorum is the minimum number of members that must be present to constitute a valid meeting where decisions can be taken concerning submissions put forward for ethical review. A meeting is quorate when a quorum is present.

Reimburse: To repay (a sum of money which has been spent or lost).

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

Research ethics committee (REC) (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 that provides the background, rationale, and objective(s) of a biomedical research project and describes its design, methodology, and organization, including ethical and statistical

considerations. Some of these considerations may be provided in other documents referred to in the protocol.

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

Risk: The probability that an event, favourable or adverse, will occur within a defined time interval. Although often contrasted to *benefit* (as in a "risk/benefit ratio"), the term "potential harm" is better for that context, leaving "risk" in its formal epidemiological sense to express the probability of a (typically adverse) event or outcome.

Sponsor: An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of research.

Voluntary: (1) Performed or done of one's own free will, impulse, or choice; not constrained, prompted, or suggested by another; (2) free of coercion, duress, or undue inducement. Used in the health and disability care and research contexts to refer to a consumer's or participant's decision to receive health or disability care or to participate (or continue to participate) in a research activity.

Vulnerable (research) participants: Vulnerable persons are those who are relatively (or absolutely) incapable of protecting their own interests. More formally, they may have insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests. Individuals whose willingness to volunteer in a research study may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate may also be considered vulnerable. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable persons include patients with incurable diseases, people in nursing homes, unemployed or impoverished people, patients in emergency situations, ethnic minority groups, homeless people, nomads, refugees, minors, and those incapable of giving consent.[3] This list may not be exhaustive as there may be circumstances in which other groups are considered vulnerable, women for example, in an orthodox patriarchical society.

[3] International Conference on Harmonization. Guideline for Good Clinical Practice E6(R1). Geneva, ICH, 1996.

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