The Ethics Review Committee
(WPRO-ERC)

# Standard Operating Procedures

World Health Organization
Western Pacific Region

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**WHO Library Cataloguing in Publication Data**

The Ethics Review Committee (WPRO-ERC) standard operating procedures.

1. Ethics committees, Research. 2. Ethics, Research. I. World Health Organization. Regional Office for the Western Pacific.

ISBN 978 92 9061 517 0 (NLM Classification: WX 150 )

# Acknowledgements

We are pleased to present Standard Operating Procedures (SOP) for the Ethics Review Committee of the WHO Regional Office for the Western Pacific (WPRO-ERC). These SOP were approved by the Regional Director, Dr Shin Young-soo, in December 2010.

These SOP were created and reviewed by WPRO-ERC Secretariat and member of WPRO-ERC. The discussions and consultation on the SOP were coordinated by the WPRO-ERC Secretariat, housed within the Health Information, Evidence and Research (IER) technical unit in the Division of Health Sector Development. We would like to acknowledge the contributions by the Secretariat of the WHO's Ethics Review Committee and PAHO-ERC. Your comments and feedback are welcome and can be submitted to wproerc@wpro.who.int. Updates and additional information will be provided through the electronic research registry portal of WPRO-ERC (http://researchportal.wpro.who.int) once it becomes functional.

Dr John Ehrenberg, Chairperson, WPRO-ERC
Dr Susan Mercado, Vice-Chairperson, WPRO-ERC
Dr Manju Rani, Secretary, WPRO-ERC

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# List of Acronyms

| | |
|---|---|
| CIOMS | Council for International Organizations of Medical Sciences |
| ERB | Ethics Review Board |
| ERC | Ethics Review Committee |
| ID | Identifier |
| IER | Health Information, Evidence and Research |
| IRB | Institutional Review Board |
| SOP | Standard Operating Procedures |
| UNESCO | United Nations Educational Scientific and Cultural Organization |
| WCO | WHO Country Offices in the Western Pacific |
| WHO | World Health Organization |
| WMA | World Medical Association |
| WPRO-ERC | Ethics Review Committee of the WHO Regional Office for the Western Pacific |

# I Overview of the Ethics Review Committee

These Standard Operating Procedures (SOP) delineate the structure, functions and process (including the review criteria) to be followed by the Ethics Review Committee of the WHO Regional Office for the Western Pacific (the Committee or WPRO-ERC) for ethical review of research proposals submitted to it. The SOP will override any other administrative rules or procedures specified elsewhere before October 2010. The relevant section of the WHO Western Pacific Regional policy handbook dealing with this issue will be revised accordingly.

## A. The Purpose of WPRO-ERC

The key functions of WPRO-ERC will include:

1. Ensuring that any research involving human participants with whom the WHO Regional Office for the Western Pacific or the WHO Country Offices (WCOs) in the Western Pacific are involved either as funder, manager, technical assistance partner or collaborator meets ethical standards in accordance with three basic ethical principles: respect for people, beneficence and justice.

2. Ensuring that the proposed research design is scientifically sound and appropriate for addressing research questions and will not unnecessarily expose research participants to risk.

## B. Fundamental Ethical Standards

WPRO-ERC follows the guidelines set by World Medical Association in Declaration of Helsinki and by The Council for International Organizations of Medical Sciences (CIOMS). It also will be guided by other international and regional human rights treaties and standards as relevant, abiding with the ethical principles research involving human subjects, including research on identifiable human material and data.

# WPRO-ERC Structure

II

## A. Members

The Committee shall consist of at least 15 members excluding the Senior Technical Officer (Health Research Policy), who serves as an ex-officio member and Secretary to WPRO-ERC. The Regional Director will appoint two of those members to serve as Chairperson and Vice-Chairperson of the Committee.

1. The Committee shall have an appropriate gender balance, and at least two members (a single member may have multiple expertises) must have the following expertise or background in each of the following areas:

   a) biostatistics, epidemiology and research methodologies;

   b) social or behavioural research;

   c) health systems, preferably also with health economics background;

   d) communicable diseases;

   e) noncommunicable diseases; and

   f) human rights, gender and/or law

2. At least one of the appointed members will be from a nonhealth background.

3. Members who are Regional Office staff shall serve in an individual capacity and not as official representatives of any unit or programme of the organization. They may not be able to delegate their responsibilities as member of the Committee to any other technical staff in their unit or programme.

4. There shall be at least one Committee member not employed by the Regional Office for the Western Pacific. These members shall be known as "nonaffiliated members". These members also will serve in an individual capacity and not as an official representative of their organization.

5. Neither affiliated nor nonaffiliated members will receive any remuneration or compensation for specifically serving on the Committee or attending its meetings.

## B. Appointment of Members

Members shall be appointed by the Regional Director for a two-year term, renewable once for a maximum of two consecutive terms.

1. Members shall be appointed based on but not limited to:
    a) Their willingness to commit the time required for their duties on the Committee.
    b) Their expert knowledge in medicine, science, or another field, as appropriate.
    c) Their willingness to acquire knowledge of research ethics through appropriate training and education within two months of beginning service on the Committee.
2. Notwithstanding their term of appointment, the service of Regional Office staff on the Committee shall end when their employment terminates. For Regional Office staff members on short-term contracts, breaks between contracts of up to one month shall not be considered termination of appointment for the purposes of this rule, although during such a break they shall not perform functions for the Committee.
3. Members unable to fulfill their responsibilities may submit a letter of resignation to the Regional Director (copying the Secretariat) for the consideration of the Regional Director.
4. Each member shall attend at least 50% of the meetings.
5. To ensure the independence of the Committee and the ability of its members to exercise their judgement concerning matters coming before the Committee, they only may be removed from the Committee by the Regional Director in the event of:
    a) Failure to attend three consecutive meetings for which they had previously committed, without informing the Secretariat in advance of the meetings.
    b) Failure to attend at least 40% of the Committee meetings in any given year.
    c) Failure to perform the functions expected of Committee members, including serving as primary reviewer of assigned research proposals.
    d) Flagrant departure from Committee SOP.

6. Except in the case of removal for cause, members shall serve until their successors are named.

## C. Chairperson and Vice-Chairperson

1. Appointment

   a) The Regional Director shall appoint a Chairperson and a Vice-Chairperson of the Committee from among its members on the recommendation of the Director, Division of Health Sector Development.

   b) Appointment as Chairperson and Vice-Chairperson shall be for a maximum two renewable terms of two years each, or for the duration of the membership, whichever is shorter.

2. Responsibilities

   The Chairperson or, when the Chairperson is absent or unable to carry out the responsibilities of the office, the Vice-Chairperson, shall, in addition to such other functions provided for in these Rules:

   a) Preside at Committee meetings.

   b) Sign, on behalf of the Committee, the review outcomes and recommendations on the proposals reviewed by the Committee.

   c) Name the members of any subcommittees or ad hoc committees.

   d) Convey to the Regional Director the Committee's advice on matters related to the ethics of research involving human participants or to the activities and responsibilities of the Committee.

   e) Work with and provide general direction to the Secretary regarding the operation of the Committee and the Secretariat.

   f) Recommend to the Regional Director possible new members, endeavoring to ensure appropriate balance of expertise, gender, geography, and cross-division involvement.

3. The Chairperson will hand over the responsibility of the office to the Vice-Chairperson whenever proposals from the Chairperson's immediate area of work are being

reviewed or discussed. Similarly, the Vice-Chair shall not act as the Chair if proposals from their immediate area of work are being reviewed or discussed. (See section VI for more details regarding conflict of interest). In the event that neither the Chairperson nor the Vice-Chairperson is available, the Chairperson will designate in writing, the Committee member who will be authorized to act on behalf of the Chairperson.

References hereinafter to the Chairperson in these Rules shall refer to whichever officer is fulfilling the role of Chairperson.

## D. Secretary

1. The Secretary of the Committee shall be the Senior Technical Officer (Health Research Policy) in the technical unit of Health Information, Evidence and Research (IER) in the Division of Health Sector Development in the Regional Office for the Western Pacific. The Secretary shall be assisted by an administrative staff as required to fulfil the function of the Secretariat of the Committee. When necessary, the Secretary can delegate representation for meetings and administrative issues to another member of the IER. However, neither the Secretary nor the delegated people will count towards quorum.

2. Responsibilities

   In addition to such other functions as are provided in these Rules, the Secretary shall:

   a) Serve as an ex-officio member of the Committee.

   b) Certify, on behalf of organization, which research proposals have been duly approved by the Committee in accordance with these procedures.

   c) Make available to WHO staff and new Committee members the information and educational materials and training on ethical issues relating to research with human participants.

   d) Take appropriate steps to make the standards employed by the Committee in reviewing research known and accessible to Regional staff and to investigators who conduct research involving human participants funded or otherwise supported by WHO Regional Office for the Western Pacific.

e) Ensure that the Secretariat operates in an efficient, accountable and transparent manner, specifically by:

   i) Liaising with the Chairperson and the Committee members on policy issues relating to WPRO-ERC.

   ii) Ensuring access to any administrative assistance that may be needed by the Chairperson and members in carrying out the Committee's functions.

   iii) Maintaining a registry of research proposals involving human participants submitted for Committee review (Regional Office Research Registry).

   iv) Undertaking a preliminary review of all submitted proposals to assess whether they are complete and, if not, to liaise with the Regional Office Technical Officer in order to bring them up to the required standards.

   v) Scheduling, coordinating and organizing Committee meetings at such intervals and in such a manner as specified in these rules or as otherwise directed by the Committee to ensure prompt reviews of new and pending research proposals.

   vi) Informing the Responsible Regional Office Staff Member in a timely manner of the Committee's decision for each research proposal reviewed.

   vii) Timely drafting of meeting minutes, the annual report and other reports as may be required regarding the work of the Secretariat and of the Committee.

   viii) Work with the Chairperson and other officials to obtain for the Committee such approvals, evaluations, or accreditation of its research ethics review processes as are necessary and appropriate.

f) Maintaining and archiving the following documentation:

   i) a copy of these SOP and any amendments;

   ii) an up-to-date list of all Committee members, with their terms of service, titles and curriculum

vitae or other biographical information sufficient to describe their qualifications (e.g. educational background, current employer and relevant area(s) of expertise);

iii) a full set of minutes of Committee meetings and decisions and such additional detailed records as the Committee may require;

iv) the Regional Office Research Registry data documenting the status of all research proposals submitted to the Committee (e.g. whether exempt from review, approved, awaiting changes before action, or not approved); and

v) copies of all research proposals submitted to the Committee, including comments from any scientific or technical bodies and any other research ethics committees that reviewed any such proposal.

2. All project-related documentation shall be retained for of three years after the closure of the project and all Secretariat-related documentation (meeting agenda, minutes of meetings, annual reports, reports etc.) shall be retained for five years unless otherwise advised by the Records and Archive Department of WHO.

## E. Ad hoc Committee Members

The Secretariat of Committee shall maintain a roster of ad hoc members with expertise on specific health issues and their expertise shall be called upon by the Committee depending on the need and the topic of the research proposal in review. When called upon by the Committee, ad hoc members are expected to participate in the review process and make recommendations but not to vote on research proposals. Their attendance will be recorded but will not contribute towards the quorum of the meeting.

# Committee Meetings

III

## A. Frequency

1. Committee meetings shall be convened and organized by the Secretariat ad hoc, depending upon the number and timing of research proposals received by the Secretariat for review.

2. The Secretariat will ensure a Committee meeting will be held within three weeks of receiving the proposal by the Secretariat.

3. The Secretariat shall provide the Committee members with at least one week's notice of all meetings together with a copy of the proposed agenda and required meeting materials.

## B. Attendance

1. Committee meetings may only be attended by members, the Secretary and the Secretariat staff and such additional people who are permitted under these rules to be present for a particular meeting or a portion thereof.

2. Committee members are responsible for attending the meetings they agree in advance to attend or, if they are unable to do so, for notifying the Secretariat as far in advance as possible to enable the Secretariat to arrange for alternate dates of the meeting if the required quorum is not obtained.

3. The responsibility of attending and participating in Committee meetings shall be borne equitably by all members and the Secretariat shall keep records of the service of each member and distribute assignments accordingly.

4. At the invitation of the Chairperson, the Regional Office staff member responsible for a submitted proposal (or in his or her absence such other person(s) designated by the

Responsible Staff Member) may attend meetings at which the proposal will be reviewed for the purposes of offering additional information and clarifications requested by the Committee.

5. The Chairperson may invite additional staff of WHO, other United Nations agencies or experts to provide advice on special issues when the Chairperson considers that their expertise is needed for the review of a research proposal or for other matters before the Committee. When consulted on a research proposal, such experts may attend those portions of the meeting at which the proposal is being reviewed and participate in the discussion.

6. In the interest of transparency and improving the wider understanding of the work of the Committee, the Chairperson may also, at his or her discretion, invite a limited number of individuals as observers to the Committee meetings. Observers may attend the entire meeting to which they have been invited, but may not take part in discussions unless explicitly invited by the Chairperson to do so. The Chairperson at his or her discretion may decide to request the invited observers to leave the meeting room during specific portions of the discussions.

## C. Confidentiality

1. The project documentation and the deliberations of the Committee are confidential and all Committee members are bound to respect such confidentiality.

2. All experts and observers invited to any Committee meeting must commit to maintain confidentiality regarding the Committee's work for each meeting that they are invited to attend.

3. In order to ensure that the Committee is able to engage in a candid evaluation of research proposals, the minutes of its meetings and all other Committee records shall be kept in such a manner that the points discussed are recorded without ascribing the views or conclusions to particular members of the Committee. (Annex 5 for template for recording minutes.)

4. In all communications from the Committee and Secretariat, reasonable steps will be taken not to reveal confidential or proprietary information concerning any research proposal or investigator. Such measures, however, shall not interfere with the ability of the Committee to fully perform its function.

## D. Quorum

At least seven members, including the Chairperson, must be present to constitute a quorum. A meeting can only commence once a quorum is obtained. If at any time during the meeting the quorum is lost, the meeting must be concluded. Members of the Secretariat and other experts or observers do not count towards the quorum.

## E. Meeting records

Minutes shall be recorded by the Secretariat following the template provided in Annex 5 for all meetings and shall be submitted to the Chairperson and subsequently to the Committee for approval.

# IV Submission of Research Proposals

## A. Responsible Person for Submission

All proposals, including those coming from the WCOs, must be submitted by a Regional Office staff member, who is associated with the research in any capacity—either as principal investigator, co-investigator, manager of the research at Regional office level, the relevant technical counterpart (for research proposals initiated by WCOs) or providing technical assistance to the principal investigator. The responsible Regional Office Staff Member has the responsibility to ensure that the required documentation, as outlined in Subsection B of this section, for each proposal is complete. He or she also will ensure that such research has been authorized by the relevant health authorities in the country where the research will be conducted when so required in the countries concerned. He or She will become the contact person for the Committee regarding the proposal.

## B. Documentation Required at the Time of Submission

Each research proposal must include all the information listed below to be considered for review:

1. Proof of approval by a local Ethics Review Committee (ERC) or Institutional Review Board (IRB) from the country where the research is proposed to be conducted. The letter should be issued by the ERC or IRB in the country where the research project will be conducted. In cases of involvement of more than one country in the proposed research, a letter from the local ERC of each participating country will be required by the Committee. If the approval has not yet been obtained, a proof of submission of the proposal to the local ERC should be provided. All research proposals will include the name and complete contact details of the local ERC in the country that had reviewed or will review the research proposal.

2. A structured abstract (less than 300 words) should provide a succinct summary of the research question, the population and interventions involved, main outcomes, methods, potential risks for subjects and names of participating

institutions and countries. The abstract briefly should mention the potential value of this research for public health.

3. Disclosure by researchers of their funding sources, sponsors, institutional affiliations and other possible sources of conflicts of interest: real, apparent or perceived or incentives for people participating in the study. The Principal Investigator and co-investigators also shall submit a written declaration disclosing any conflicts of interest affecting the research and/or the research team or about the emergence of material conflicts of interest that may arise during the course of the project. (See Section VI-D about procedures for how the Committee will address potential conflicts of interest.)

4. A complete research proposal that includes (See Annex 1 for the recommended format of research proposal and summary sheet):

    a) a brief background and justification;

    b) Objective/purpose of study and a brief statement as to why the research question(s) is relevant;

    c) Methodology (including sampling methodology and sample size), procedures and analysis plan;

    d) Limitations, if any.

    e) Significance of study with a careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation;

    f) Plans for dissemination of research results to the relevant stakeholders;

    g) Budget and timelines; and

    h) References

5. Curriculum vitae (abbreviated, two pages) of the Principal Investigator and any co-investigators.

6. Disclosure of previous reviews by other ethical or scientific boards or committees or independent peer reviewers and a copy of the conclusions, recommendations and changes that were incorporated.

7. Informed consent documentation (Annex 3 provides examples); forms that will be used in the study and a description of how the subjects will be protected, including how data safety and monitoring will work and how deaths and unexpected events will be prevented or analysed and dealt with. The process of informed consent is one of the most important parts of planning a research study. It is important that human participants exercise their right of free will when deciding to participate. It is equally important that participants be given the correct information, comprehend what is being said and read to them and be given time to make their own decision about participation. The language of the informed consent must be comprehensible to the research participants or their guardians. In most cases this may include a document written in a language that the participant can understand at a fifth-grade reading level. The following should take place during the consent process:

   a) review of recruitment materials;

   b) verbal instructions;

   c) written material (when appropriate);

   d) questions and answer sessions; and

   e) agreement by documented signature when appropriate (most situations).

   Participants must be informed that it is their right to withdraw from a study at any time. The consent form must be communicated in suitable and effective ways to any participant including those with disabilities. Children and other vulnerable subjects may need information presented as simply and straightforwardly as possible (see Section VI).

   In cases in which the potential participants cannot read the consent form, it must be read to the individual and a witness' signature is required on the form, indicating that he or she was present during the reading and interpreting of the consent form and that it was presented in a manner that was comprehensible to the subject. If for any reason the informed consent process is waived (e.g. studies in some vulnerable populations such as those listed under Section VI-A), a clear justification has to be provided as well as any alternative arrangements.

8. A certification that all required documentation is attached which may take the form of items checked off on a cover sheet provided by the Committee (Annex 1), and if not, an explanation for any missing documentation and when such documentation will be made available to the Committee.

9. Other documentation as listed in Annex 2 relevant to a research proposal in specific situations.

## C. Submitting a Research Proposal

All research proposals must be submitted electronically by the Responsible Regional Office Staff Member using its Research Registry http://researchportal.wpro.who.int; Other communications should be addressed to wproerc@wpro.who.int. The research registry electronic portal is likely to be functional by March 2011. Until then, proposals can be submitted by email to wproerc@wpro.who.int. Once a proposal has been submitted, the Committee Secretariat will inform the Responsible Regional Office Staff Member whether the documentation is complete or incomplete within two working days of submission of the proposal. Incomplete submissions will not be reviewed.

**Note:** *When the study design corresponds to a clinical trial, the Committee requires submission of proof of registration in a database that is linked to the Search Portal of the International Clinical Trial Register Platform of WHO (http://www.who.int/ictrp/), before recruitment of the first research participant. If a trial already has been registered, the relevant identification number should be provided at the time the proposal is submitted.*

# V Review of Research Proposals

## A. Identification Number

A unique identifier (ID) automatically will be assigned to the proposal on electronic submission and an automated confirmation for successful submission along with unique ID will be sent to the Responsible Regional Office Staff Member. Once the required documentation is verified by the Secretariat, a written confirmation about complete documentation and the future course of action, including the review date, will be sent by the Secretariat to the Responsible Regional Office Staff Member.

## B. What is Subject to Review: Scope of Review

All research that uses human participants, tissues and specimens from humans, data and records from human participants, or surveys of human participants funded or technically supported by the Regional Office or the WHO country offices requires review and approval from Committee. Research involving humans includes, but is not limited to:

1. studies of a physiological, biochemical, pathological or social process among human populations;
2. response to a specific intervention including diagnostic, preventive or therapeutic measures, or studies designed to determine the consequences for individuals and communities of implementing preventive or therapeutic measures;
3. studies concerning human health-related behaviour in a variety of circumstances and environments;
4. research involving children or other vulnerable populations;
5. research involving quasi-experimental or experimental intervention, drugs and devices;
6. research involving invasive procedures;
7. research involving deception; and

8. research involving sensitive questions or information that can result in stigmatization, discrimination, persecution, prosecution or indictment or unnecessary stressful situations to participants.

## C. What may not necessarily require review?

Proposals that may not require review by the Committee include but are not limited to:

1. research does not involve human participants;
2. data (including healthcare records and specimens) being studied already exist and are either publicly available or are recorded by the investigator in such a manner as to be unidentifiable;
3. public officials who are interviewed in their official capacity on issues that are in the public domain;
4. intervention is limited to the observation of public behavior;
5. intervention is limited to public health surveillance or routine evaluation of health programmes carried out pursuant to statutory or regulatory authority; and
6. proposals registered in the Regional Office Research Registry when the study has been reviewed and approved by World Health Organizations's Ethics Review Committee (WHO-ERC). WHO-ERC approval needs to be uploaded in the Regional Office Research Registry.

## D. Authority to decide on exemption of review

1. The Secretariat, in consultation with the Chairperson, will decide after reviewing the proposal whether the proposal is exempt from review or needs to be submitted to a full review by the Committee.
2. If the Secretariat and Chairperson decide that, in accordance with the criteria set forth in Section V-C, a proposal does not require review by the Committee, the proposal shall be classified as "does not require review by the Committee". An official letter will be sent to the Responsible Regional Office Staff Member by the Secretariat, and an appropriate notation will be documented and reflected in the Regional

Office Research Registry. Such notification shall include a brief explanation of the grounds for the exemption and a reminder that the Secretariat must be consulted in the event that material changes are made in the design or execution of the activity in question.

3. If the Secretariat and the Chairperson cannot agree whether a research proposal qualifies as exempt from review, the proposal will be submitted for review to the Committee. The Chairperson may also decide to ask the Responsible Regional Office Staff Member to submit research proposals, e.g. multi-regional studies, to the WHO-ERC rather than to the Committee for ethical review.

4. The Secretariat will submit the list of all the proposals that have been reviewed by it in consultation with the Chairperson and were considered exempt from review to the next meeting of the Committee. Any member of the Committee may request a re-assessment of the proposals that were deemed to be exempt or eligible for expedited review.

   a) When such a request has been made, the Secretariat shall immediately notify the Responsible Regional Office Staff Member not to proceed further with the research project until the Committee has reviewed the matter and he or she has been informed of the outcome.

   b) If the Committee decides to override the determination made by the Chairperson and the Secretariat, it shall then determine the type of review the proposal shall undergo.

## E. WPRO-ERC Review: Basic Procedures

1. All proposals for research involving human participants funded or otherwise supported by the Regional Office or WHO Country Offices that are not determined to be exempt by the Secretariat in consultation with Chairperson (please see section V-D) will be subject to a review by the Committee at a convened meeting. Two members of the Committee scheduled to be present at the meeting where a research proposal will be discussed shall be assigned by the Secretariat as "primary reviewers", based on the expertise required to adequately assess the research proposal. Such primary reviewers shall summarize the proposal at the Committee meeting and provide their opinions on its

ethical aspects, including recommendations for action by the Committee. In the event a primary reviewer determines that additional material is needed for review, or that the presence of the Responsible Regional Office Staff Member at the Committee meeting would be desirable, he or she should promptly notify the Secretariat, who shall then attempt to obtain the needed information.

2. Notwithstanding the informational role of the primary reviewers, all members present at the Committee meeting shall be familiar with each proposal and shall participate in the discussion and in the decision to be taken with respect to each proposal.

3. A Committee decision on research proposals shall be made by consensus. When consensus cannot be reached, the Chairperson can at his or her discretion exercise the following two options:

   a) He or she may ask the Committee to vote. Committee action shall require a two-thirds majority.

   b) He or she may decide that additional information or expert advice is required. If that is the case, consideration on the proposal shall be postponed until the next meeting in order to seek additional information or expert advice. If consensus cannot be reached at the second meeting, then a vote on the Committee decision shall be taken. Committee action shall require a two-thirds majority.

## F. WPRO-ERC Review: Criteria for Review

The evaluation of research proposals by the Committee shall be guided by the Declaration of Helsinki (WMA 2008) (Annex 6), the International Guidelines for Biomedical Research Involving Human Subjects (CIOMS, 2002)(Annex 7), and the International Guidelines for Ethical Review of Epidemiological Studies (CIOMS 2009). The Committee officially also may recognize other statements on research ethics or formulate its own standards for particular topics (where such standards do not already exist) in addition to these documents. The committee will use following criteria for review (Annex 4):

1. The proposed research design is scientifically sound (the hypotheses and objectives are clear and the study design is appropriate to prove the hypothesis) and will

not unnecessarily expose subjects to risk. In addition, the research is relevant and will contribute to generalizable knowledge and is worth exposing the research participants to risk and inconvenience, even if minimal, involved in the study.

2. Beneficence: risks to subjects are minimized and a sound research design is implemented without exposing participants to avoidable risks. The benefit-risk balance seems reasonable and safeguards are included to protect human rights, fundamental freedoms and the welfare of participants, with particular care being paid to vulnerable subjects (see Section VI).
3. Fairness of subject selection.
4. Voluntariness: recruitment practices do not involve coercion.
5. Confidentiality: provisions are made to protect the privacy of subjects and the confidentiality of data.
6. Informed consent process and forms are presented in a comprehensible and suitable manner for the population where the research is being conducted. Informed consent sought and documented prospectively for each subject or his or her legally authorized representative.
7. Data monitoring procedures are in place to provide for the reasonable safety of all involved in the research, including the subjects.

   Please see Annex 4 for minimum regulatory requirements for Committee review, discussion and documentation in the meeting minutes.

## G. Decisions of Committee Review

The review of a research proposal will result in one of the following actions:

1. **Approved:** The research proposal is approved as submitted. This does not preclude the Committee from sending comments for the consideration of the research team or requesting proof of approval by the local ERB, IRB or ERC or proof of clinical trial registration in the international trial registry when appropriate.

2. **Conditionally approved:** The research proposal has not yet been approved; it requires the completion of one or more requirements before approval can be granted. When the requirements are met, a letter of approval will be issued. The Committee will determine who will review the response submitted (i.e. Secretariat, Chairperson, special reviewers or the Committee) and will be so recorded in the decision and meeting minutes. If the assigned reviewers are not satisfied with the response, the Secretariat will request the Responsible Regional Office Staff Member to provide further clarifications. Notwithstanding the manner of a final review of a proposal that has been conditionally approved, the Secretariat shall confirm a final approval in writing and have the approval signed off by the Committee Chairperson.

3. **Not approved:** The research proposal is not approved as submitted either because there is insufficient information to make a decision or the proposal is not ethically sound. However, the proposal can be re-submitted for the review by the full Committee after addressing all those concerns.

4. **Does not require review by the Committee**

## H. Reporting the Outcome of a Review

The outcome of a review shall be communicated by the Secretariat to the Responsible Regional Office Staff Member in writing with an explanation of the reasons for the decision. Each communication must include:

1. Committee's research proposal ID and date the proposal was received;
2. name of the Responsible Regional Office Staff Member;
3. names of investigators;
4. title of the research proposal;
5. date(s) of review and decision and the name of reviewing body (i.e. Secretariat in consultation with Chairperson, full Committee);
6. the decision; and
7. comments, questions, or suggestions (if applicable).

## I. Continuing Review of Approved Research Proposals

1. When an approved research proposal is planned to extend for more than one year, the research project shall be reviewed by the Committee 12 months after the date of the initial approval, unless the Committee determines that a more frequent review is needed. This review shall occur even if, for administrative or other reasons, work on the project has been delayed or no participant has been recruited. When the Committee determines that continuing review of an approved project should occur more frequently than once every 12 months or should occur after the accrual of a specified number of participants, the timing of the continuing review shall be set accordingly.

2. Assuming that no substantive changes have been made in the proposal or consent documents, a continuing review may be conducted as an expedited review. Such an expedited review may be carried out by the Secretariat, on behalf of the Committee and will be reported for information at the next Committee meeting.

3. If any substantive changes have been made in the protocol or consent documents, the continuing review shall be conducted as a Full Review.

4. Should the process of review lead to a disapproval of the continuation of a previously approved study, this determination shall be communicated immediately to the Responsible Regional Office Staff Member, who shall in turn convey it to the Principal Investigator and to any other people, funding agencies or other bodies with whom such reports must be filed pursuant to the terms and conditions agreed by WHO. The Responsible Regional Office Staff Member promptly shall report back to the Committee concerning the date the enrolment of new participants was halted and the manner in which the research project is dealing with the previously enrolled participants.

## J. Review of Special Categories of Proposals

1. **Multi-Centre Studies:** Research projects that are to be conducted at more than one centre require review in the same manner as any other research funded or supported by the Regional Office for the Western Pacific that involves

human participants, but the multi-centre nature of such projects can lead to two variations in the process of approval.

a) When the Regional Office is the lead agency funding or organizing the research, an expedited review by the Secretariat in consultation with Chairperson may be used to add new centres to an approved research project.

   i) Once the Committee has approved a research proposal for the first centre as a "master protocol", the review and approval of additional research centres as sites for the same project can be undertaken on an expedited basis by the Secretariat and the Chairperson. But each proposed new site shall be given a new ID in the Registry, with a notation that it is derivative of a particular master protocol. The Secretariat, however, will report about all these proposals to the Committee at its next meeting, for the information of all the members.

   ii) In such a situation, an expedited review can be limited to determine whether the research proposal remains unchanged from the master protocol; whether any variations in the local circumstances (in terms of the characteristics of the population, the local manifestation or nature of the disease, etc.) could adversely affect the benefit-risk ratio, the minimization of risk, or the validity of informed consent; and whether any translation of information and documentation has been prepared in an adequate and culturally appropriate fashion.

   iii) If the Secretariat and the Chairperson conclude on initial review that the benefit-risk ratio is adversely affected, the proposal will be submitted for full review by the Committee and the Responsible Regional Office Staff Member shall be so informed.

b) When WHO staff or people under contract to Regional Office for the Western Pacific are involved in only one or a few sites of a multi-centre study being led by scientists unaffiliated with the WHO and when another

institutional review board or research ethics committee has been designated as the "lead ethical review board" for the study with the aim of promoting consistent and uniform conditions for the research at all sites, the Committee may choose to postpone review of the research proposal until such board has completed its review.

i) The decision to postpone review should be made in a manner that will not unduly delay the final decision on Regional Office involvement in the study.

ii) A decision to postpone review is dependent upon a determination by the Committee that the lead ethics review board for the study is capable of providing a review of comparable scope and quality to that which the Committee would otherwise provide.

iii) The Responsible Regional Office Staff Member for the research proposal shall submit to the Secretariat the results of the review by the lead ethics review board (including any explanations, requirements, or other comments). When this documentation is received, the Committee will commence its review of the proposal.

2. **Nested Studies:** Any study which is part of another, i.e. "nested" within another study, shall be subject to the procedures and criteria for review as set forth in these rules. However, the Responsible Regional Office Staff Member shall also submit the protocol for the main study. While the main protocol need not be formally reviewed by the Committee, it should be satisfied with the ethical aspects of the main study before approving the nested study.

## K. Continuing Oversight and Monitoring

WHO's obligation to ensure continuing oversight of approved research projects with human participants which it funds or otherwise supports, creates responsibilities for the Responsible Regional Office Staff Member and for the Committee beyond the obligation to perform continuing reviews.

1. The Responsible Regional Office Staff Member for each approved research shall promptly report to the Committee any developments in the project that might have ethical implications.

2. Principal Investigators shall inform the Responsible Regional Office Staff Member of any changes in an approved research proposal or consent documentation proposed to be made before implementation, and these shall be reported immediately to the Committee by the Responsible Regional Office Staff Member.

    a) When the Secretariat receives a report of changes that are proposed to be made in the protocol or consent documentation of a research project that the Committee has previously approved, a determination shall be made by the Chairperson and the Secretariat in accordance with Section V-D whether the proposed changes should be subject to review by the Committee in accordance with these rules.

    b) Pending the Committee's decision, which it shall endeavor to produce in a timely manner, the changes proposed for the research project shall not be instituted, with the exception of any modifications urgently needed to protect the well-being or important interests of participants already enrolled in the study.

3. Any deaths as well as any serious adverse events or unexpected events that occur to participants during their participation in any approved research project shall be reported immediately by the Principal Investigator to the Responsible Regional Office Staff Member and to any other people, ethics review bodies, funding agencies or other bodies with whom such information must be filed pursuant to national regulations and the terms and conditions agreed by WHO. The Responsible Regional Office Staff Member must in turn promptly convey such

reports to the Secretariat, including the feedback from other review bodies.

a) The Secretariat shall review all such reports and determine whether the information reported warrants another review of the research project, with particular attention to the benefit-risk ratio, the adequacy of the steps taken to minimize risk and the information provided to prospective participants. Such determinations will be reported to the Committee at its next meeting.

b) If the Secretariat determines that another review should occur, it shall take place as soon as possible (including through an extraordinary Committee meeting, if necessary under the circumstances).

c) The results of the second review will be promptly conveyed to the Responsible Regional Office Staff Member.

d) It shall remain the obligation of the Responsible Regional Office Staff Member, rather than of the Committee, to ensure that adverse event reports, and the determinations reached by the Committee in a second review, are filed with all appropriate people and agencies, pursuant to terms and conditions agreed by WHO.

4. Procedures on completion of research project:

a) The Principal Investigator is requested to submit a final report and a financial report (if financially supported by the Regional Office) upon completion of the research project, if it had been reviewed by the Committee earlier, to the Responsible Regional Office Staff Member in the relevant technical unit. The final report also should include information about how the results have been used and disseminated to relevant stakeholders.

b) The Responsible Regional Office Staff Member shall report the final research project outcome (completion or discontinuation) and submit a final report on the study to the Secretariat. A notation shall be made in the Registry accordingly.

c) The Responsible Regional Office Staff Member also will submit a copy of any reports that were published in the public domain or any publications in any peer-reviewed journals, which will be linked with the project ID in the electronic registry.

# VI

# Special Considerations for Vulnerable Populations

## A. Definition of Vulnerable Populations

1. Vulnerable populations are those that are relatively (or absolutely) incapable of protecting their own interests, either because of insufficient power, intelligence, education, resources, strength or other needed attributes to protect their own interests (CIOMS, 2002). They may include but are not limited to:

    a) Children, including newborns and minors who are (under 18 years old) (see Section VI-C).

    b) Fertilized ova, pregnant women and viable fetuses (see Section VI-D).

    c) People whose judgement or capacity to make free-willed, informed decisions is limited or compromised. This includes cognitively-impaired people with conditions that affect their decision-making abilities.

    d) Participants with limited civil freedom, such as wards of the state, residents or clients of institutions for the mentally ill, populations under judiciary care and people in long-term care facilities, among others.

    e) Participants recruited from emergency medical facilities, intensive care units, older people in long-term care facilities, life threatening situations or the like.

    f) Participants whose economic conditions predispose them to certain incentives (see Section VI-D).

    g) Populations subject to stigma and discrimination.

## B. Research Involving Vulnerable Population:

The Committee will be guided by Article 17 and Articles 26-29 of the Helsinki Declaration and Guideline 13 "Research Involving

Vulnerable Persons' (CIOMS, 2002) in reviewing proposals involving vulnerable populations. Article 17 of Helsinki Declaration clearly states that *"medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research".*

## C. Research Involving Children

In accordance with the United Nations Convention on the Rights of the Child, special considerations must be made when performing research on children (those under 18 years old). These include the use of additional forms and signatures, including those adequately informing their parents or other legally authorized representatives or guardians. The Committee will be guided by Guideline 14 "Research Involving Children", of the International Guidelines for Biomedical Research (CIOMS, 2002) in reviewing proposals involving children.

## D. Research Involving Women

In a manner consistent with the United Nations Convention on the Elimination of All Forms of Discrimination against Women, pregnant and lactating women are classified as a vulnerable population because their condition leads to risk for both the mother and the fetus or breastfeeding offspring. The Committee will be guided by Guideline 16 "Women as Research Subjects" and Guideline 17 "Pregnant Women as Research Participants" of the international Guidelines for Biomedical Research (CIOMS, 2002) in reviewing proposals involving women.

## E. Vulnerability Because of Economic Status or Other Factors

Research participants should not be coerced into participating in a research study because of inappropriate inducements. The Committee will review the consent process and other forms to ensure that inducements offered are appropriate. It additionally will be guided by Guideline 7, "Inducement to Participate", and Guideline 10 of the International Guidelines for Biomedical Research (CIOMS, 2002) and Article 17 of Helsinki Declaration (2008) in reviewing proposals involving research in population and communities with limited resources.

# VII Conflicts of Interest

The avoidance of conflicts of interest or the appearance thereof is important to ensure both the quality and credibility of research ethics review. The Committee will therefore take necessary steps to avoid conflicts of interest and the appearance of conflicts of interest for investigators, Responsible Regional Office Staff Members, the Committee members and the Secretariat.

1. It is important that all people participating in the submission and review of proposals involving human research avoid situations that could affect their ability to provide objective guidance for, or review of, research proposals regarding particular drugs, devices, vaccines, or other interventions.

2. The Committee shall ensure that its resolution of any situation involving a potential conflict of interest avoids not only the occurrence of unacceptable interests but also the appearance of such conflicts of interest.

3. In all cases in which a conflict of interest is revealed, but is not so material as to warrant not approving the project, the Committee shall determine the type of description of such interest that needs to be included in the information provided to prospective participants in the research and shall ensure that the consent documentation also includes an appropriate disclosure.

## A. Investigators

1. The Principal Investigator who will conduct the research should not have any material conflict of interest or any other interests that may damage the scientific objectivity of the research.

2. All Principal Investigators involved in the proposed research proposal have to clearly mention in the proposal cover page that they do not have any conflict of interest with the proposed research.

3. The Committee shall approve a research proposal only if it concludes that the Principal Investigator does not have

any material conflict of interest or that such interests are not sufficient to damage the scientific objectivity of the research (in light of other means such as the independence of other investigators or the oversight of a monitoring board to counterbalance the interest).

## B. Committee members: Financial Conflict

1. Regional Office staff members on the Committee and the Committee Secretariat are bound by Staff Rule 110.7.1 to inform the Regional Director of any interest they, as well as their spouses and dependent children, may have in any entity that has a commercial interest or a common area of activity in the work of WHO. In the case of an interest in an entity having a commercial interest or common area of activity involving a research proposal submitted to the Committee, all such staff members shall inform the Secretariat.

2. Nonaffiliated members shall agree to be bound by the same obligation of disclosure to the Secretariat with respect to interests in an entity having a commercial interest or common area of activity involving a project submitted to the Committee.

## C. Committee: Role Conflicts

A Committee member who is also a Responsible Regional Office Staff Member for a proposal under review or is connected closely to a proposal (such as being on the same team as the responsible officer submitting the proposal or being in a supervisory position with the submitting Responsible Staff Member) would have a conflict of interest if he or she participated in the ethics review of the proposal.

## D. Resolution of Conflict

1. When asked to perform an expedited review or to be a primary reviewer, a Committee member that has a financial or role conflict shall disclose such a conflict and decline to undertake the review.

2. Committee members having reported a financial or role conflict may, unless the Chairperson determines otherwise,

comment on the matter before the Committee but may not participate in the Committee's decision on the matter. The Chairperson (subject to being overruled by the Committee) may impose additional restrictions (such as requesting the member to leave the meeting while the matter is discussed) as he or she believes are warranted under the circumstances. The conflict of interest shall be announced during the meeting and the minutes of the meeting shall record the declared conflict of interest and the steps taken to deal with the situation with regard to the Committee's deliberations and decisions.

3. Similarly, the Chairperson will hand over his or her responsibility to the Vice-Chairperson whenever he or she has a role conflict and the minutes of the meeting shall record the declared conflict of interest and the steps taken to deal with the situation with regard to the Committee's deliberations and decisions.

# Evaluation and Improvement

VIII

## A. Quality Improvement

1. All members of the Committee and the Secretariat are charged with scrutinizing the operations of the Committee in order to identify problems and to offer suggestions for improving the quality of the Committee's work.

2. Such suggestions should typically be presented to the Secretary, who will review the suggestions and consult with the Chairperson. If they conclude that a suggestion would improve the functioning of the Committee, the Secretariat shall either place the suggestion on the agenda of the next meeting for discussion or, if it merely amounts to an administrative adjustment, institute it and provide appropriate notification of the change to all affected parties.

3. Suggestions requiring formal changes in these SOP shall be considered under Section IX, Subsection B below.

## B. Independent Evaluation

1. The Secretariat shall arrange for the work of the Committee and Secretariat to be evaluated periodically, at least once in three years, by one or more persons who are knowledgeable about research ethics and the functioning of ethics review committees, provided such evaluators are not members of the Committee and are not in a supervisory or subordinate role to the Secretary or any Committee member.

2. The evaluator(s) should be given complete access to the records of the Committee and Secretariat. They may attend one or more meetings of the Committee as authorized observers and may interview members of the Committee as well as the Responsible Regional Office Staff Member and Principal Investigators whose research proposals have been reviewed by the Committee during the period under review.

3. The evaluator(s) should endeavor to compare the operations of the Committee in terms of the quality of its work, the efficiency and effectiveness with which the Secretariat and the Committee carry out their functions and the relationship between the resources available for the work and the workload to recognized standards or benchmarks for ethical review of research with human participants.

4. The conclusions of the evaluator(s) shall be submitted to the Chairperson and the Secretary, with a copy to the Regional Director, for appropriate action.

# IX

# Adoption and Amendment of the Standard Operating Procedures

## A. Adoption of Standard Operating Procedures

The SOP will be approved by the Regional Director, Western Pacific Regional Office for adoption by the Committee. These will be available publically on the WHO Regional Office for the Western Pacific external website under the "Health Research" web page. These SOP will supersede any other publications in this regard, including the provisions mentioned in the Regional Office for the Western Pacific Policies and Procedures, Part XV, Section 2, paragraphs 10-120.

## B. Amending Standard Operating Procedures

Any member of the Committee and Secretariat can propose an amendment to these SOPs. The proposed amendment shall be submitted in writing to the Secretariat to be placed on the agenda of the next available Committee meeting for consideration and possible adoption by a majority of the Committee members present and voting. The amendment shall come into effect once approved by the Regional Director.

# Glossary

**Adverse events:** Undesirable and unintended consequences of, or reactions to, procedures experienced by the research participant and subject.

**Annual Report:** An annual synoptic document that outlines and analyses activities, especially summarizing the research proposals reviewed over the last year.

**Beneficence:** Ethical obligation to maximize benefits and to minimize harms (CIOMS).

**Clinical trial:** Any research study that prospectively assigns human participants or group of humans to one or more health-related interventions to evaluate the effect on pre-defined health outcomes.

**Conditionally approved:** The research proposal has not yet been approved; it requires the completion of one or more requirements before approval can be granted.

**Conflict of Interest:** A conflict between a person's private interests and public obligations.

**(The) Council of International Organizations of Medical Sciences (CIOMS):** An international, nongovernmental, not-for-profit organization established jointly by WHO and UNESCO in 1949. CIOMS serves the scientific interests of the international biomedical community in general and has been active in promulgating guidelines for ethical conduct of research, among other activities. CIOMS promulgated guidelines entitled "International Ethical Guidelines for Biomedical Research Involving Human Subjects" for the first time in 1982, revised in 1993 and 2002, and are designed to be of use, particularly in low-resource countries, in defining national policies on the ethics of biomedical research, applying ethical standards in local circumstances, and establishing or redefining adequate

mechanisms for ethical review of research involving human subjects. The latest version published in 2002 supersedes that of 1993 and consists of a statement of general ethical principles, a preamble and 21 guidelines which address issues including informed consent, standards for external review, recruitment of participants, and more. Website:
http://www.cioms.ch/

**Declaration of Helsinki:** Adopted in 1964 by the 18th World Medical Association (WMA) general assembly at Helsinki, Finland, as a set of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The original guidelines have been revised six times since then, with the latest revision in 2008 by the 59th WMA General Assembly for Physicians conducting biomedical research. The declaration outlines clinical trial procedures required to ensure patient safety, consent and ethical committee review in human subjects. The declaration of Helsinki can be found at http://www.wma.net/en/30publications/10policies/b3/17c.pdf (last accessed on October 12, 2010).

**Individually identifiable information:** Data records or biological materials that contain or are linked to a personal identifier (such as a person's name or a patient number) either directly or through a code, even when the key to the code is held by someone other than the investigator. Records or materials are considered unidentifiable when they lack any personal identifiers (such as samples taken from repositories that do not possess information on the individuals from whom the samples originated, or records that have been "anonymized" by the removal of any information, including any code, that could link them to any particular person).

**International Clinical Trial Register Platform:** A platform set up by WHO (meta-register) that collates information from selected registers of research studies (clinical trials or intervention trials) that prospectively assign human participants or a group of human participants to one or more health-related interventions to evaluate the effects on health outcomes. Website: http://www.who.int/ictrp/en/ [last accessed on October 12, 2010]

**Legally authorized representative:** An individual or a judicial or other body with the authority under applicable law to give permission for participation in research to a person who lacks the capacity to decide whether to consent for him or herself.

**Multi-center study:** Research conducted at multiple sites using a common research protocol.

**Principal Investigator (PI):** The lead scientist for a particularly well-defined social science, biomedical, behavioural or epidemiological research project; responsible and accountable for the appropriate conduct of the research.

**Quorum:** A fixed minimum percentage or number of members of committee who must be present before the members can conduct valid business.

**Regional Director:** An elected chief executive of the WHO Regional Office for the Western Pacific who controls and governs the affairs of that office.

**Research:** Any social science, biomedical, behavioural, or epidemiological activity that entails systematic collection or analysis of data with the intent to generate new generalizable knowledge.

**Research *involving human participants*** (sometimes termed "human subjects") when human beings

i) are exposed to intervention, manipulation, observation or other interaction with investigators, either directly or through alteration of their environment; or

ii) become individually identifiable through investigators' collection, preparation or use of medical or other records or of biological material from human beings.

**Research Team:** The group of qualified personnel that implements a research proposal; it typically includes a principal investigator, additional investigators, a research coordinator and research assistants.

**Research Proposal:** A document written for the purpose of obtaining funding for a research project. In addition to including the research protocol, it also includes information on the investigators (e.g. their CVs and institutional affiliation), approvals from various relevant organizations and persons, budgets, dissemination plans, etc.

**Research Protocol:** A document describing in detail how a research study is to be conducted in practice, including the study design and methodology, data analysis plan, and a budget. A research protocol is part of a research proposal.

**Responsible Regional Office staff member:** A staff member of the Regional Office for the Western Pacific responsible for representing its involvement in the research (e.g. contracting with investigators to implement such a project or who have provided direct technical or logistical support to such investigators) and liaising with external parties on matters involving a specific research proposal.

**Private information:** Individually identifiable data that have been provided by a person, or obtained through observation of or interaction with a person, under circumstances in which the person could reasonably have believed either that the data (such as contained in medical records) would not be made public or shared with others or that the data were not being recorded.

**United Nations Convention on the Elimination of all forms of Discrimination against women**: see http://www.un.org/womenwatch/daw/cedaw/ as accessed on October 21, 2010

**United Nations Convention on the Rights of the Child:** see http://www2.ohchr.org/english/law/crc.htm as accessed on October 21, 2010.

**WHO-funded Research:** Research conducted by the investigator(s) under a contract with WHO, which provides, or serves as a conduit for, direct financial support for research project.

**WHO-supported Research:** Research activities in which WHO staff organize and coordinate the research, participate significantly in the design of the research, or provide significant review of, or technical advice on, the research project as a whole, but not when:

1. WHO staff have provided technical advice only on portions of a research project;

2. the investigators working on the project and seeking advice are neither employed under a contract with WHO to formulate the research proposal or carry out the research;

and

3. the WHO staff have notified those investigators in writing that the project has not been formally reviewed by WHO and the technical advice provided by WHO staff do not constitute endorsement of, or support for, the research project by WHO and should not be construed or portrayed as such.

**WHO's Ethics Review Committee (WHO-ERC):** A 26-member Committee established and appointed by the Director-General to ensure the highest ethical standards in research supported by WHO. It is mandated to review all research projects that involve human participants, and are supported either financially or technically by WHO. Website: http:// www.who.int/rpc/research_ethics/erc/eng

# Annex 1: Recommended format for research proposal for financial support from WPRO/WHO

## I. Summary Sheet And Checklist Of Required Documents

| | | |
|---|---|---|
| 1 | | Principal Investigator Prof/Dr/Mr/Ms.<br>FAMILY NAME (SURNAME):<br><br>FIRST NAME: OTHER NAMES: |
| | 1.1 | Title of post, position or appointment presently held by principal investigator |
| | 1.2 | Complete postal address:<br>Email: |
| 2 | | Institution responsible for the research proposed<br><br>Name and address (including website address, if any) |
| 3 | | Title of health research proposed<br>(should be brief, precise and informative to workers outside your field) |
| | 3.1 | Objectives of research proposed<br>(clearly and concisely list specific objectives of the proposed study) |
| | 3.2 | Duration of research from preparations for field work till analysis and compilation of final research results<br><br>From (date):<br><br>To (date): Total (years): |
| | 3.3 | Funds required (US$) |
| | 3.4 | Any conflict of interest by research institute/PI/funding source declared<br>Yes____ No_____ |

| | | |
|---|---|---|
| 4 | 4.1 | Informed consent documentation included in the proposal<br>Yes____ No_____ |
| | 4.2 | Questionnaires for collection of data included in the proposal<br>Yes____ No_____ |
| | 4.3 | If the study design involves a clinical trial, proof of Registration in a database linked to Search Portal of International Clinical Trial Register Platform of WHO is attached<br>Yes____ No_____ Not a clinical trial____ |
| 5 | 5.1 | Institutional and national ethical clearance<br>Name and contact details of the local ERC/IRB/ERB in the country of research where the proposal has been reviewed/ submitted:<br>Name of local ERC/IRB:<br>Contact details including email address: |
| | 5.2 | Institutional/national ethical clearance enclosed<br><br>Proposal under review by institutional/national ERC<br>Yes____ No_____<br>(proof of submission to local ERC enclosed) |
| 6 | | Approval of national Ministry of Health or national Medical Research Council (or equivalent body)<br>National approval document enclosed<br>Yes____ No_____ |
| 7 | | Institutional endorsement (can be attached as a separate document also)<br><br>Head of Institution Title:_____<br><br>Name: _____ Date: _____<br>(print)<br>Signature: |
| 8 | | Curriculum Vitae of Principal Investigator attached<br>Yes____ No_____ |
| 9 | | Applicant's signature<br>Date: Signature: |

## II. Recommended Format For Research Protocol

_____

Title of research:

_____

1. Statement of the problem
2. Relevance of the problem to national or local health objectives
3. Field(s) of application of the proposed research results
   (a) Potential users of research results
   (b) Plan for dissemination of research results
   (c) Plan for utilization of research results
4. Review of literature and other existing information
5. Statement of research objectives
6. Statement of research hypotheses, if any
7. Research design
   7.1 Key research design (e.g. experimental study, cross-sectional survey, facility survey, etc)
   7.2 Research setting (country, district, province etc) and study population (age groups, women, men, etc)
   7.3 Sampling design, sample size, and use of controls (if applicable)
   7.4 Study instrument(s)
   7.5 Plans for fieldwork for collecting data
   7.6 Data analysis plan including description of key outcome indicators proposed to be measured in the research
8. Ethical considerations
   8.1 Assessment of risk to research participants
   8.2 Information Sheet for Research participants
   8.3 Informed consent certificate
9. Timeline for research implementation
10. Budget (use attached Section III. Budget Sheet)

## III. Recommended Format for presenting Budget

| | | ITEM | Amount (US $) |
|---|---|---|---|
| 1 | PERSONNEL (allowances to be paid) | | |
| | 1.1 | Professional scientific Staff (name and functional title) | |
| | 1.2 | Technical staff (name and functional title) | |
| | 1.3 | Other staff (name and functional title) | |
| | Subtotal | | |
| 2. | MAJOR EQUIPMENT (over US$ 500) | | |
| | (include specifications, shipment and freight insurance costs; comment on local provision for maintenance/service | | |
| | Subtotal | | |
| 3 | SUPPLIES | | |
| | 3.1 | Chemicals | |
| | 3.2 | Glassware | |
| | 3.3 | Minor equipment (less than US$ 500 each) | |
| | 3.4 | Animals | |
| | 3.5 | Other supplies | |
| | 3.6 | Operating cost (specify maintenance of equipment, gasoline, etc) | |
| | Subtotal | | |
| 4. | TRAVEL (specify domestic and international) | | |
| | Subtotal | | |
| 5. | DATA ANALYSIS COST | | |
| | Subtotal | | |
| 6. | COST OF DISSEMINATION OF RESULTS | | |
| | Subtotal | | |
| 7. | MISCELLANEOUS EXPENDITURES | | |
| | Subtotal | | |
| 8. | SUMMARY | | |
| | (1) Personnel | | |
| | (2) Major equipment | | |
| | (3) Supplies | | |
| | (4) Travel | | |
| | (5) Data analysis cost | | |
| | (6) Cost of dissemination of results | | |
| | (7) Miscellaneous expenses | | |
| | TOTAL | | |

# Annex 2: Additional documents (or information) to be included in a research proposal (where applicable), for submission to WPRO-ERC for review

In addition to the items required in Section IV-B for all research proposals involving human participants, the Responsible Regional Office Staff Member shall submit additional information that may be helpful in the review process, such as:

1) An explanation of how the research is relevant to the health needs of the population in which it will be conducted and how it is consistent with the research agenda of the country where it will be conducted, or, in the absence of such relevance or consistency, a justification for why it is appropriate to conduct the research in that country.
2) A copy of any instruments being used to collect data, such as questionnaires that will be administered, including translations into the local language.
3) Detailed information about how biological materials or other data from the research will be collected, preserved, transported and stored, and the conditions under which such items will be released in the future to people outside the present research project. A copy of the information that will be provided to participants about such future use and whether, and if so how, their consent will be sought before such use outside the present project would occur, and whether they will be provided with information derived from such future studies.
4) A description of the plans that have been made and any formal agreements that have been negotiated with representatives of the participant population or officials of the country where the research will occur. The description should include plans to continue to provide any drug, device, vaccine or other product being tested, or any other service, to any participants who are benefiting from such intervention at the conclusion of their participation in the research or a justification for the absence of such plans.
5) A description of the plans that have been made and any formal agreements that have been negotiated with officials of the country where the research will occur (or with any agency providing services to the members of the population from which participants will be drawn or to residents of that country) to make any drug, device, vaccine or other product being tested, or any other service, available at an affordable cost to the population or residents once such drug, device, vaccine or other product has been approved for use by the relevant authorities or a justification for the absence of such plans.
6) Complete information on the regulatory status of any drug, vaccine or device being studied, including an adequate summary of all safety,

pharmacological, pharmaceutical and toxicological data available on the product and of the clinical experience to date.

7) Where the research involves a risk of injury (such as research on an infectious agent or research involving venipuncture), a description of the means that will be used to avoid or minimize risks to the investigator and other persons conducting the research.

8) Where the research involves an infectious agent or a vaccine, a description of any risk to people who are not directly involved in the research but who might be exposed to risk through contact with participants or otherwise.

9) A description of the arrangements that have been put in place to address any needs that will arise should harm occur to the people conducting the research or to other people who might be harmed in the foreseeable future.

10) Details concerning any Data Safety and Monitoring Board (DSMB) or comparable body that will be established to oversee the research, including information on who will appoint the DSMB, to whom it will report (including the circumstances for which it will provide specified information to the Committee), and the decision rules it will use in deciding or recommending that the research should be altered or halted.

# Annex 3: Examples of guidelines and templates of informed consent forms

- World Health Organization. Informed consent form templates. Accessed on 12 October 2010 at http://www.who.int/rpc/research_ethics/informed_consent/en/
- Code of Federal Regulations, Title 45, Public Welfare, Department of Health and Human Services (HHS), U.S. Government. Last visited on September 20, 2010 at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm

**Other templates**

- World Health Organization. WHO-ERC guide for principal investigators. Accessed on October 26, 2010. http://www.who.int/rpc/research_ethics/Guide%20for%20PIs.doc

# Annex 4: WPRO-ERC Protocol Review standards*

## Minimum regulatory requirements for WPRO-ERC review, discussion, documentation in the meeting minutes

| Regulatory Review Requirement | Suggested question for WPRO-ERC discussion |
|---|---|
| 1. The proposed research design is scientifically sound and will not unnecessarily expose human research participants to risk | a) Is the hypothesis or research question clear? Is it clearly stated?<br>b) Is the study design appropriate to prove the hypothesis or answer the research question?<br>c) Will the research contribute to generalizable knowledge and is it worth exposing human research participants to risk? |
| 2. Risks to the participants are reasonable in relation to anticipated benefits, it any, to the participants and the importance of knowledge that may reasonably be expected to result. | a) What does the WPRO-ERC consider the level of risk to be? (See risk assessment guide on back of form).<br>b) What does PI consider the level of risk/discomfort/inconvenience to be?<br>c) Is there prospect of direct benefit to human research participants? (see benefit assessment guide below) |
| 3. Participant selection is equitable | a) Who is to be enrolled? Men? Women? Ethnic Minorities? Children (rationale for inclusion/ exclusion addressed)? Seriously ill patients? Healthy volunteers?<br>b) Are these research participants appropriate for the protocol? |
| 4. Additional safeguards required for subjects likely to be vulnerable to coercion or undue influence. | a) Are appropriate protection in place for vulnerable participants, e.g. pregnant women, socially or economically disadvantaged, decisionally impaired, subjects in special situations e.g. doc-patient relationship making them more vulnerable? |

**adapted from the National Institutes of Health, USA and WHO-ERC review standards*

| Regulatory Review Requirement | Suggested question for WPRO-ERC discussion |
|---|---|
| 5. Informed consent is obtained from research subjects or their legally authorized representative(s). | a) Is the informed consent document include all the required elements?<br>b) Is the consent document understandable to participants?<br>c) Who will obtain the consent (PI, nurse, other?) and in what setting?<br>d) Is WPRO-ERC requested to waive or alter any informed consent requirements? |
| 6. Risks to the subjects are minimised? | a) Does the research design minimize risks to subjects?<br>b) Would use of a data and safety monitoring board or other research oversight process enhance subject safety. |
| 7. Subject privacy and confidentiality are maximized. | a) Will personally-identifiable research data be protected to the extent possible from access or use?<br>b) Are any special privacy and confidentiality issues properly addressed, e.g. use of genetic information? |

**Risk/Benefit Assessment**

**Risk:** Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in the daily life or during the performance of routine physical or psychological examination or tests.

**Check appropriate risk category:**

1._____ The research involves no more than minimal risk to subject.

2._____ The research involves more than minimal risk to subjects.

- o The risk(s) represents a minor increase over minimal risk, OR
- o The risk(s) represents more than a minor increase over minimal risk.

**Benefit:** A research benefit is considered to be something of a health-related, psychosocial, or other value to an individual research subject, or something that will contribute to the acquisition of generalizable knowledge. Money or other compensation for participation in research is not considered to be a benefit, but rather compensation for research-related inconveniences.

**Check appropriate benefit category(ies):**

1._____ no prospect of direct benefit to individual participants, but likely to yield generalizable knowledge about the participants' disorder or condition.

2._____ no prospect of direct benefit to individual participants, but likely to yield generalizable knowledge to further society's understanding or the disorder or condition under study; or

3._____ the research involves the prospect of direct benefit to individual participants

# Annex 5: Format for all WPRO-ERC minutes

(The order in which agenda items are reviewed is at the discretion of WPRO-ERC Chairperson)

Minutes of the WPRO-ERC Meeting Held on (date)

| | | | |
|---|---|---|---|
| Members present: (indicate who is a non-scientist, non-WPRO affiliated etc.) | _____ | (Chairperson) | _____ |
| | _____ | | _____ |
| | _____ | | _____ |
| | _____ | | _____ |
| | _____ | | _____ |
| | _____ | | _____ |
| | _____ | | _____ |
| | _____ | | _____ |
| | _____ | | _____ |
| Members Absent | _____ | | _____ |
| | _____ | | _____ |
| | _____ | | _____ |
| | _____ | | _____ |
| | _____ | | _____ |
| Guests: (include affiliation) | _____ | | _____ |
| | _____ | | _____ |
| | _____ | | _____ |

The meeting convened at --:-- (a.m./p.m.) with a quorum present.

1. MINUTES OF THE MEETING HELD ON (DATE). (The minutes must be voted on and any changes documented.)
2. ANNOUNCEMENTS
3. INITIAL REVIEWS.

A. Principal Investigator:

Protocol Title:

Protocol summary:

(a) Discussion:

General discussion:

Specific discussions: (include the following headings)

- Scientific design (discuss and note that Institute pre-scientific review has been done)
- Risks/benefits (assign a level of risk here or at the time of the WPRO-ERC decision and vote, [(d) below] consistent with page 2, WPRO-ERC Protocol Review Standards form.

- Subject selection (discuss populations to be studied and recruitment plan)
- Additional safeguards for vulnerable subjects
- Minimization of risks to subjects
- Privacy and confidentiality.
- Consent document (document that all required elements are present)
- Additional considerations (e.g. multi-center research; collaborative research; nested study. State if these considerations do not apply)

(b) Stipulations (number the stipulations)

(c) Recommendations (number the recommendations)

(d) IRB Decision and Vote: State whether the vote is unanimous; if not, state how many members voted for, against or abstained. Document in or attach to the minutes the reason(s) for the minority opinion(s).

If the protocol is approved with stipulations and/or recommendations, the minutes must state whether the WPRO-ERC votes that the stipulations and/or recommendations are to be reviewed by the Chairperson, by secretariat, by a subcommittee of the WPRO-ERC, or by the full WPRO-ERC.

B., C., etc. (Follow same format as above for additional new protocols)

4. CONTINUING REVIEWS OR Re-review of proposals submitted earlier either due to proposed AMENDMENTS or otherwise

A. Principal Investigator:

Title and type of expedited action:

Date approved by the Committee Chairperson or designee:

Description of expedited action: (Expedited actions must be listed separately in the minutes. The Chairperson should provide a brief explanation of any expedited actions. A vote is not required but the WPRO-ERC has the prerogative to discuss, rescind or amend expedited actions.)

B., C. etc. (List additional expedited actions following the above format

5. CONTINUING REVIEWS (it is useful for the primary or secondary reviewer or the WPRO-ERC secretariat to have the entire protocol file available for reference at the meeting)

A. Principal Investigator:

Protocol Title:

Protocol Number:

Expiration Date:

Protocol Summary (if not provided in discussion at (a) below):

(a) Discussion:

(b) Stipulations (number the stipulations)

(c) Recommendations (number the recommendations)

(d) WPRO-ERC Decision and Vote (Include WPRO-ERC reaffirmation of the level of risk or establishment of a new risk level consistent with the Protocol Review Standards form, page 2)

B., C. etc. (Follow the same format as above for additional continuing reviews)

6. AMENDMENTS to a research proposal approved earlier

A. Principal Investigator:

Protocol Title:

Protocol Number:

Expiration Date:

Description of the amendment:

(a) Discussion:

(b) Stipulations (number the stipulations)

(c) Recommendations (number the recommendations)

(d) WPRO-ERC Decision and Vote (include a statement indicating whether or not the protocol's level of risk is altered by the amendment)

B., C. etc. (Follow the same format as above for additional amendments)

7. REPORT OF ADVERSE EVENT(S)

Principal Investigator:

Protocol Title:

Protocol Number:

Date of Adverse Event(s):

Description of the adverse event(s):

Document WPRO-ERC's acknowledgement of receipt of the adverse event report(s) and discussion. Discussion of serious adverse events occurring on an protocol should include immediate actions taken as a result of the event by the PI; recommendations for further actions, if any, by the WPRO-ERC (e.g., suspension of subject accrual, etc.), and any necessary recommendations for further reporting (RD, WR, etc)

If the adverse events are reported from non-WPRO sites for the WPRO-ERC's information only, and no action is required on the WPRO-ERC's part, acknowledgement of the report(s) should be documented.

8. INFORMATION ITEMS

(a)

(b)

9. ADJOURNMENT The meeting adjourned at --:-- (a.m./p.m.).

# Annex 6: Declaration of Helsinki (2008)

**WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI**

**Ethical Principles for Medical Research Involving Human Subjects**

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)

55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)

59th WMA General Assembly, Seoul, October 2008

**A. INTRODUCTION**

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented

in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

**B. PRINCIPLES FOR ALL MEDICAL RESEARCH**

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-

study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the

legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

**C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE**

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it

offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

# Annex 7: International Ethical Guidelines for biomedical research involving human subjects (CIOMS, 2002)**

**Guideline 1: Ethical justification and scientific validity of biomedical research involving human beings**

The ethical justification of biomedical research involving human subjects is the prospect of discovering new ways of benefiting people's health. Such research can be ethically justifiable only if it is carried out in ways that respect and protect, and are fair to, the subjects of that research and are morally acceptable within the communities in which the research is carried out. Moreover, because scientifically invalid research is unethical in that it exposes research subjects to risks without possible benefit, investigators and sponsors must ensure that proposed studies involving human subjects conform to generally accepted scientific principles and are based on adequate knowledge of the pertinent scientific literature.

**Guideline 2: Ethical review committees**

All proposals to conduct research involving human subjects must be submitted for review of their scientific merit and ethical acceptability to one or more scientific review and ethical review committees. The review committees must be independent of the research team, and any direct financial or other material benefit they may derive from the research should not be contingent on the outcome of their review. The investigator must obtain their approval or clearance before undertaking the research. The ethical review committee should conduct further reviews as necessary in the course of the research, including monitoring of the progress of the study.

**Guideline 3: Ethical review of externally sponsored research**

An external sponsoring organization and individual investigators should submit the research protocol for ethical and scientific review in the country of the sponsoring organization, and the ethical standards applied should be no less stringent than they would be for research carried out in that country. The health authorities of the host country, as well as a national or local ethical review committee, should ensure that the proposed research is responsive to the health needs and priorities of the host country and meets the requisite ethical standards.

**Guideline 4: Individual informed consent**

For all biomedical research involving humans the investigator must obtain the voluntary informed consent of the prospective subject or, in the case of an individual who is not capable of giving informed consent, the permission of

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a legally authorized representative in accordance with applicable law. Waiver of informed consent is to be regarded as uncommon and exceptional, and must in all cases be approved by an ethical review committee.

**Guideline 5: Obtaining informed consent: Essential information for prospective research subjects**

Before requesting an individual's consent to participate in research, the investigator must provide the following information, in language or another form of communication that the individual can understand:

1. that the individual is invited to participate in research, the reasons for considering the individual suitable for the research, and that participation is voluntary;
2. that the individual is free to refuse to participate and will be free to withdraw from the research at any time without penalty or loss of benefits to which he or she would otherwise be entitled;
3. the purpose of the research, the procedures to be carried out by the investigator and the subject, and an explanation of how the research differs from routine medical care;
4. for controlled trials, an explanation of features of the research design (e.g., randomization, double-blinding), and that the subject will not be told of the assigned treatment until the study has been completed and the blind has been broken;
5. the expected duration of the individual's participation (including number and duration of visits to the research centre and the total time involved) and the possibility of early termination of the trial or of the individual's participation in it;
6. whether money or other forms of material goods will be provided in return for the individual's participation and, if so, the kind and amount;
7. that, after the completion of the study, subjects will be informed of the findings of the research in general, and individual subjects will be informed of any finding that relates to their particular health status;
8. that subjects have the right of access to their data on demand, even if these data lack immediate clinical utility (unless the ethical review committee has approved temporary or permanent non-disclosure of data, in which case the subject should be informed of, and given, the reasons for such nondisclosure);
9. any foreseeable risks, pain or discomfort, or inconvenience to the individual (or others) associated with participation in the research, including risks to the health or well-being of a subject s spouse or partner;
10. the direct benefits, if any, expected to result to subjects from participating in the research
11. the research proposal approved earlier;
12. whether, when and how any products or interventions proven by the research to be safe and effective will be made available to subjects after

they have completed their participation in the research, and whether they will be expected to pay for them;

13. any currently available alternative interventions or courses of treatment;
14. the provisions that will be made to ensure respect for the privacy of subjects and for the confidentiality of records in which subjects are identified;
15. the limits, legal or other, to the investigators' ability to safeguard confidentiality, and the possible consequences of breaches of confidentiality;
16. policy with regard to the use of results of genetic tests and familial genetic information, and the precautions in place to prevent disclosure of the results of a subject's genetic tests;
17. to immediate family relatives or to others (e.g., insurance companies or employers) without the consent of the subject;
18. the sponsors of the research, the institutional affiliation of the investigators, and the nature and sources of funding for the research;
19. the possible research uses, direct or secondary, of the subject's medical records and of biological specimens taken in the course of clinical care (See also Guidelines 4 and 18 Commentaries);
20. whether it is planned that biological specimens collected in the research will be destroyed at its conclusion, and, if not, details about their storage (where, how, for how long, and final disposition) and possible future use, and that subjects have the right to decide about such future use, to refuse storage, and to have the material destroyed (See Guideline 4 Commentary);
21. whether commercial products may be developed from biological specimens, and whether the participant will receive monetary or other benefits from the development of such products;
22. whether the investigator is serving only as an investigator or as both investigator and the subject's physician;
23. the extent of the investigator's responsibility to provide medical services to the participant;
24. that treatment will be provided free of charge for specified types of research related injury or for complications associated with the research, the nature and duration of such care, the name of the organization or individual that will provide the treatment, and whether there is any uncertainty regarding funding of such treatment.
25. in what way, and by what organization, the subject or the subject's family or dependants will be compensated for disability or death resulting from such injury (or, when indicated, that there are no plans to provide such compensation);
26. whether or not, in the country in which the prospective subject is invited to participate in research, the right to compensation is legally guaranteed;
27. that an ethical review committee has approved or cleared the research protocol.

**Guideline 6: Obtaining informed consent: Obligations of sponsors and investigators**

Sponsors and investigators have a duty to:

- refrain from unjustified deception, undue influence, or intimidation;
- seek consent only after ascertaining that the prospective subject has adequate understanding of the relevant facts and of the consequences of participation and has had sufficient opportunity to consider whether to participate;
- as a general rule, obtain from each prospective subject a signed form as evidence of informed consent — investigators should justify any exceptions to this general rule and obtain the approval of the ethical review committee (See Guideline 4 Commentary, Documentation of consent);
- renew the informed consent of each subject if there are significant changes in the conditions or procedures of the research or if new information becomes available that could affect the willingness of subjects to continue to participate; and,
- renew the informed consent of each subject in long-term studies at predetermined intervals, even if there are no changes in the design or objectives of the research.

**Guideline 7: Inducement to participate**

Subjects may be reimbursed for lost earnings, travel costs and other expenses incurred in taking part in a study; they may also receive free medical services. Subjects, particularly those who receive no direct benefit from research, may also be paid or otherwise compensated for inconvenience and time spent. The payments should not be so large, however, or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgment ("undue inducement"). All payments, reimbursements and medical services provided to research subjects must have been approved by an ethical review committee.

**Guideline 8: Benefits and risks of study participation**

For all biomedical research involving human subjects, the investigator must ensure that potential benefits and risks are reasonably balanced and risks are minimized.

- Interventions or procedures that hold out the prospect of direct diagnostic, therapeutic or preventive benefit for the individual subject must be justified by the expectation that they will be at least as advantageous to the individual subject, in the light of foreseeable risks and benefits, as any available alternative. Risks of such 'beneficial' interventions or procedures must be justified in relation to expected benefits to the individual subject.
- Risks of interventions that do not hold out the prospect of direct diagnostic, therapeutic or preventive benefit for the individual must

be justified in relation to the expected benefits to society (generalizable knowledge). The risks presented by such interventions must be reasonable in relation to the importance of the knowledge to be gained.

**Guideline 9: Special limitations on risk when research involves individuals who are not capable of giving informed consent**

When there is ethical and scientific justification to conduct research with individuals incapable of giving informed consent, the risk from research interventions that do not hold out the prospect of direct benefit for the individual subject should be no more likely and not greater than the risk attached to routine medical or psychological examination of such persons. Slight or minor increases above such risk may be permitted when there is an overriding scientific or medical rationale for such increases and when an ethical review committee has approved them.

**Guideline 10: Research in populations and communities with limited resources**

Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that:

- the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and
- any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.

**Guideline 11: Choice of control in clinical trials**

As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or "no treatment".

Placebo may be used:

- when there is no established effective intervention;
- when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms;
- when use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects.

**Guideline 12: Equitable distribution of burdens and benefits in the selection of groups of subjects in research**

Groups or communities to be invited to be subjects of research should be selected in such a way that the burdens and benefits of the research will be equitably distributed. The exclusion of groups or communities that might benefit from study participation must be justified.

**Guideline 13: Research involving vulnerable persons**

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.

**Guideline 14: Research involving children**

Before undertaking research involving children, the investigator must ensure that:

- the research might not equally well be carried out with adults;
- the purpose of the research is to obtain knowledge relevant to the health needs of children;
- a parent or legal representative of each child has given permission;
- the agreement (assent) of each child has been obtained to the extent of the child's capabilities; and,
- a child's refusal to participate or continue in the research will be respected.

**Guideline 15: Research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent**

Before undertaking research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent, the investigator must ensure that:

- such persons will not be subjects of research that might equally well be carried out on persons whose capacity to give adequately informed consent is not impaired;
- the purpose of the research is to obtain knowledge relevant to the particular health needs of persons with mental or behavioural disorders;
- the consent of each subject has been obtained to the extent of that person's capabilities, and a prospective subject's refusal to participate in research is always respected, unless, in exceptional circumstances, there is no reasonable medical alternative and local law permits overriding the objection; and,
- in cases where prospective subjects lack capacity to consent, permission is obtained from a responsible family member or a legally authorized representative in accordance with applicable law.

**Guideline 16: Women as research subjects**

Investigators, sponsors or ethical review committees should not exclude women of reproductive age from biomedical research. The potential for becoming pregnant during a study should not, in itself, be used as a reason for precluding or limiting participation. However, a thorough discussion of risks to the pregnant woman and to her fetus is a prerequisite for the woman s ability to make a rational decision to enrol in a clinical study. In this discussion, if participation in the research might be hazardous to a fetus or a

woman if she becomes pregnant, the sponsors/investigators should guarantee the prospective subject a pregnancy test and access to effective contraceptive methods before the research commences. Where such access is not possible, for legal or religious reasons, investigators should not recruit for such possibly hazardous research women who might become pregnant.

**Guideline 17: Pregnant women as research participants**

Pregnant women should be presumed to be eligible for participation in biomedical research. Investigators and ethical review committees should ensure that prospective subjects who are pregnant are adequately informed about the risks and benefits to themselves, their pregnancies, the fetus and their subsequent offspring, and to their fertility.

Research in this population should be performed only if it is relevant to the particular health needs of a pregnant woman or her fetus, or to the health needs of pregnant women in general, and, when appropriate, if it is supported by reliable evidence from animal experiments, particularly as to risks of teratogenicity and mutagenicity .

**Guideline 18: Safeguarding confidentiality**

The investigator must establish secure safeguards of the confidentiality of subjects research data. Subjects should be told the limits, legal or other, to the investigators' ability to safeguard confidentiality and the possible consequences of breaches of confidentiality.

**Guideline 19: Right of injured subjects to treatment and compensation**

Investigators should ensure that research subjects who suffer injury as a result of their participation are entitled to free medical treatment for such injury and to such financial or other assistance as would compensate them equitably for any resultant impairment, disability or handicap. In the case of death as a result of their participation, their dependants are entitled to compensation. Subjects must not be asked to waive the right to compensation.

**Guideline 20: Strengthening capacity for ethical and scientific review and biomedical research**

Many countries lack the capacity to assess or ensure the scientific quality or ethical acceptability of biomedical research proposed or carried out in their jurisdictions. In externally sponsored collaborative research, sponsors and investigators have an ethical obligation to ensure that biomedical research projects for which they are responsible in such countries contribute effectively to national or local capacity to design and conduct biomedical research, and to provide scientific and ethical review and monitoring of such research.

Capacity-building may include, but is not limited to, the following activities:

- establishing and strengthening independent and competent ethical review processes/ committees

- strengthening research capacity
- developing technologies appropriate to health-care and biomedical research
- training of research and health-care staff
- educating the community from which research subjects will be drawn

**Guideline 21: Ethical obligation of external sponsors to provide health-care services**

External sponsors are ethically obliged to ensure the availability of:

- health-care services that are essential to the safe conduct of the research;
- treatment for subjects who suffer injury as a consequence of research interventions; and,
- services that are a necessary part of the commitment of a sponsor to make a beneficial intervention or product developed as a result of the research reasonably available to the population or community concerned.

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