

The Research Ethics Review Committee of WHO Regional Office for South-East Asia (SEARO-ERC)

Standard operating procedures

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ISBN: 978-92-9022-927-8

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Foreword



WHO is committed to investing in high-quality health research in the South-East Asia Region, in line with its constitutional mandate and the Regional Strategy on Research for Health 2018–2022.

To streamline the research approval process, I am pleased to establish a Regional Ethics Review Committee, in accordance with provisions outlined in the WHO eManual chapters XV.1 and XV.2 and XV.3.1.20.

The Standard Operating Procedures (SOPs) contained herein delineate the structure, functions and processes to be followed by the Committee, ensuring that research in the Region supported by WHO meets the highest ethical and technical standards. An online portal will soon be developed to manage the review process and provide access to research outputs.

The Regional Office will continue to review the Committee's SOPs and its overall performance, with the understanding that this document will be a living document and will be amended as required.

I look forward to the Committee's ongoing contributions to excellence in research across our Region.

A handwritten signature in black ink, reading "P. Khetrpal".

Dr Poonam Khetrpal Singh
Regional Director
WHO South-East Asia

List of acronyms

| | |
|-----------|---|
| CIOMS | Council for International Organization of Medical Sciences |
| ERB | Ethics Review Board |
| ERC | Ethics Review Committee |
| ID | Identifier |
| R&I | Research and Innovation |
| IRB | Institutional Review Board |
| SOP | standard operating procedures |
| UNESCO | United Nations Educational Scientific and Cultural Organization |
| WHO | World Health Organization |
| WMA | World Medical Assembly |
| SEARO | WHO Regional Office for South-East Asia |
| SEARO-ERC | Research Ethics Review Committee of the South-East Asia Regional Office of WHO |
| WCO | WHO Country Offices |
| WHO ERC | Research Ethics Review Committee of WHO HQ |

I.

Overview of the Research Ethics Review Committee

These standard operating Procedures (“SOP”) delineate the structure, functions and process (including the review criteria) to be followed by the Research Ethics Review Committee of the WHO Regional Office for South-East Asia (SEARO) (the “Committee” or “SEARO-ERC”) for ethical review of research supported by SEARO or by any of its 11 country offices (WCOs). The SOP will override any other administrative rules or procedures¹ specified elsewhere before March 2022. A new information circular will be issued to all the staff to inform them about these SOPs and other procedural issues.

A. Purpose of SEARO-ERC

The main functions of SEARO-ERC will include:

- (1) Ensuring that any research involving human participants in which the WHO Regional Office for South-East Asia is involved either as a funder, manager, technical assistance partner, or collaborator meets ethical standards following three basic ethical principles: respect for persons, 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

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

¹ This overrides the information circulars IC-2017-06 and IC-2019-25 (“Review process of health research proposals at Regional office of SEA Asia” dated October 8, 2019)

II.

SEARO-ERC structure

A. Members

The Committee shall consist of 15 members excluding the Regional Advisor (Research and Innovation), who serves as an ex-officio member and Secretary to SEARO-ERC. The Regional Director will appoint two of these members to serve as Chairperson and Vice-Chairperson of the Committee.

- (1) The Committee shall present 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 the law.
- (2) At least one of the appointed members will be from a non- public health or non-medical background.
- (3) Most of the members will be appointed from Regional office and its country offices. 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 members of the Committee to any other technical staff in their unit/team or programme.
- (4) There shall be at least one Committee member not employed by WHO. These members shall be known as “nonaffiliated members”. These members also will serve in an individual capacity and not as official representatives of their organization.

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

B. Appointment of members

Members shall be appointed by the Regional Director for a three-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, human rights, finance or another field, as appropriate.
 - (c) their willingness to acquire knowledge of research ethics through appropriate training and education within three months of beginning service on the Committee.
- (2) Notwithstanding their term of appointment, the service of Regional Office or Country Office staff on the Committee shall end when their employment terminates. For Regional Office or Country office staff members on short-term contracts, breaks between contracts of up to one month shall not constitute termination of appointment under these rules. However, during such break periods, they shall not perform any function for the Committee.
- (3) Members unable to fulfil 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 in a year.
- (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 may only 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 a primary reviewer of assigned research proposals.
 - (d) flagrant departure from the terms of the Committee's 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 of the Department that houses the secretariat of SEARO-ERC.
- (b) Appointment as Chair and Vice-Chair shall be for a maximum of two renewable terms of three years each or for the duration of the membership, whichever is shorter.

(2) Responsibilities

The Chairman or, when the Chairman is absent or unable discharge 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 and general policy related to the ethics of research involving human participants or other domains of bioethics² 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, endeavouring to ensure an appropriate balance of expertise, gender, geography, and cross-division involvement.

2 This may include medical ethics, public health ethics, health policy ethics, etc.

- (3) The Chairperson will hand over the Office's responsibility to the Vice-Chairperson whenever proposals from the Chair'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.) If 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 the officer who is discharging the role of the Chair.

D. Secretary

- (1) The Secretary of the Committee shall be the Regional Advisor (Research and Innovation) in the technical unit of Research and Innovation (R&I) in the Department of Healthier Populations and Noncommunicable Diseases in the Regional Office for South-East Asia. 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 Research and Innovation team. However, neither the Secretary nor the delegated people will count towards the 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 the organization, which proposals the Committee has duly approved 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 South-East Asia.

- (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 the SEARO-ERC.
 - (ii) ensuring 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 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 otherwise directed by the Committee to ensure prompt reviews of new and pending research proposals.
 - (vi) informing the Responsible Technical 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 the Committee;
 - (viii) work with the Chair 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 thereof;
 - (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) Regional Office Research Registry data³ 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.
- (3) All project-related documentation shall be retained for 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 Archives Department of WHO.

E. Ad hoc committee members

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

³ Only the title and abstract of the proposal will be in public domain, the other deliberations and full proposal will be kept confidential accessible only to appropriate stakeholders.

III.

Committee meetings

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) Not to cause undue delay in the conduct of research, the Secretariat will ensure that a Committee meeting will be held within three weeks of receiving the proposal by the Secretariat.
- (3) To give sufficient time to the Committee Members to review the proposal, the Secretariat shall provide them with at least one week's notice of all meetings, together with a copy of the proposed agenda and necessary meeting materials.

B. Attendance

- (1) Committee meetings may only be attended by members, the Secretary and the Secretariat staff and such additional persons permitted under these rules to be present in 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. The Secretariat shall maintain records of the service of each member and distribute assignments accordingly.
- (4) At the invitation of the Chairperson, the WHO staff member (either from the Regional Office or from the Country Office) responsible for a submitted proposal (or in their 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. This is to ensure faster decisions on the research proposals by on-the-spot clarification on any issues raised. However, Responsible Staff Members may not participate or influence the final decision-making process on the proposal.

- (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 such 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/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 participate in discussions unless explicitly invited by the Chairperson to do so. The Chairperson, at his/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 maintaining confidentiality regarding the Committee's work at 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. (see Annex 5 for the 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 functions.

D. Quorum

At least five members, including the Chairperson, must be present to constitute a quorum. A meeting can only commence once a quorum is secured. If at any time during the meeting the quorum is not met, the meeting must be concluded. Members of the Secretariat and other experts or observers do not constitute part of 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 must be submitted online at <http://researchportal.searo.who.int> by the responsible WHO staff member either in the Regional Office or in the country office, who holds overall responsibility for the conduct of research on behalf of WHO and associated with the research in any capacity — either as principal investigator, co-investigator, manager of the research at the Regional Office or country office, or providing technical assistance to the principal investigator. The responsible Technical Staff Member should ensure that the required documentation, as outlined in Subsection B of this section, for each proposal is complete. They 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. They will serve as 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, 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.

SEARO-ERC review can take place in before, in parallel, or after the review the local ERC. If the review takes place before or in parallel, SEARO-ERC

with share its outcome with the local ERC and if it is after local ERC review, it will take into consideration the review feedback of the local ERC. Notwithstanding the sequence of review by local ERC/IRB and by SEARO-ERC, the research can be commenced only after receiving both the local and SEARO ERC approval.

- (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 the research proposal and summary sheet):
 - (a) a brief background and justification;
 - (b) objective/purpose of the 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 the 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 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 analyzed 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, 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

The SEARO ERC will not accept proposals directly from the investigators. All research proposals must be submitted online by the Responsible Technical Staff Member either from the technical departments of Regional Office or of the country office at the SEARO-ERC portal <http://searo.researchportal.who.int/SEARO>. In cases where proposals are developed by PIs and submitted to WHO for funding, the PIs submit the research protocol, study instruments, informed consents form and other associated documents to the WHO responsible officer, who then submits all these documents for the SEARO-ERC review. Once a proposal has been submitted⁴, the Committee secretariat will inform the Responsible Technical Member whether the documentation is complete or incomplete within two working days of submission of the proposal. Incomplete submissions will not be reviewed.

If the research is based on two or more research sites located across different WHO Regions including SEARO, then the research proposal will be submitted directly to WHO HQ Research Ethics Review Committee rather than to this Committee.

⁴ **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 the online submission, and an automated confirmation for successful submission along with a unique ID will be sent to the responsible technical 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 Technical 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 its 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 behaviour *with no specific intervention targeted at specific individual and no collection of individual data (e.g. trends in OPD consultations)*;
- (5) intervention is limited to public health surveillance⁵ involving routine data collection at health facilities or routine evaluation of health programmes carried out pursuant to the statutory or regulatory authority; and
- (6) proposals when the study has been reviewed and approved by WHO HQ's Research Ethics Review Committee (WHO-ERC). WHO-ERC approval needs to be uploaded in the Regional Office's research portal.

D. Which research proposals may be reviewed on an expedited basis?

The following types of proposals may be reviewed on an expedited basis:

- (1) The research proposal is based on a standardized protocol (e.g., protocol for periodic population-based or school-based or facility-based surveys repeated periodically) that has been approved previously by WHO HQ or SEARO-ERC on a full review. There is none or minimal deviation from that approved protocol in the current proposal.

⁵ Research should not be confused with routine disease surveillance which does not involve a decision to select few among equals based on a strategy, does not require participants to do something more beyond their routine care, does not put additional burden on few participants in terms of additional clinic visits, provision of extra samples, or taking additional/special drugs, and part of statutory requirements(e.g. outbreak investigation)

- (2) Previously approved research proposals submitted for continuing review after a year.
- (3) Proposal for an additional research site for an already approved protocol for a multisite research.
- (4) The research proposals determined to have less than minimal or no risk to human participants on initial screening.

E. Authority to decide on exemption of review or on an expedited review

- (1) The Secretariat, in consultation with the Chair, will decide after reviewing the proposal whether the proposal is exempt from review or will be reviewed on an expedited basis 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 technical staff member by the Secretariat, and an appropriate notation will be documented and reflected in the Regional Office’s online research portal. 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 Chair cannot agree on whether a research proposal qualifies as exempt from review, or for expedited review, then the proposal will be submitted for review to the Committee. The Chair may also decide to ask the responsible technical 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 they have been informed of the outcome.

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

F. Committee review: basic procedures

- (1) Procedure for expedited review: Proposals considered eligible for expedited review based on criteria specified in Section V(D), will be sent to two ERC members who are required to provide feedback to Secretariat within 7 working days. As appropriate, the proposal is then either approved or returned to technical officer for further action.
- (2) All proposals for research involving human participants funded or otherwise supported by the Regional Office that are not determined to be exempt by the Secretariat or considered eligible for expedited review in consultation with Chairperson (see Section V-D) will be subject to 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 technical staff member at the Committee meeting would be desirable, they should promptly notify the Secretariat, who shall then attempt to obtain the needed information.
- (3) 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.
- (4) A Committee decision on research proposals shall be made by consensus. When consensus cannot be reached, the Chairperson can at their discretion exercise the following two options:
 - (a) They may ask the Committee to vote. Committee action shall require a two-thirds majority.

- (b) They 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.

G. Committee review: criteria for review

The evaluation of research proposals by the Committee shall be guided by the Declaration of Helsinki (WMA 2013) (See Annex 6), the International Guidelines for Biomedical Research Involving Human Subjects (CIOMS, 2016) (See Annex 7). 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 the 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) The 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 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.

H. 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 local ERB or IRB or ERC or proof of clinical trial registration in the international trial registry when appropriate.
- (2) **Conditionally approved (or revise and resubmit):** 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 review by the full Committee after addressing all those concerns.

I. Reporting the outcome of a review

The outcome of a review shall be communicated by the Secretariat to the responsible technical 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 technical 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).

J. 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. *The PI will ensure timely review to avoid any interruption in data collection.* 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 technical 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 technical 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.

K. 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 South-East Asia 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 South-East Asia Regional Office is the lead agency funding or organizing the research, an expedited review by the Secretariat in consultation with the 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 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 an 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 persons under contract to Regional Office for the South-East Asia 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 the 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 technical 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 outlined in these rules. However, the Responsible Technical 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 primary research before approving the nested study.

L. 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 technical staff member and for the Committee beyond the obligation to perform continuing reviews.

- (1) The responsible technical 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 technical 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 technical 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 endeavour 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 technical staff member and 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 technical 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 technical staff member.
 - (d) It shall remain the obligation of the responsible technical 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 a research project:
- (a) The Principal Investigator is requested to submit a final report and a financial report (if financially supported by South-East Asia Regional Office or its country offices) upon completion of the research project, if it had been reviewed by the Committee earlier, to the responsible technical 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 technical 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 online system accordingly.
 - (c) The responsible technical 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 online ERC research portal.

VI.

Special considerations for vulnerable persons or groups

A. Definition of vulnerable populations

- (1) Vulnerable populations are those that are relatively (or absolutely) incapable of protecting their interests, either due to insufficient power, intelligence, education, resources, strength or other needed attributes to protect their own interests (CIOMS, 2016). 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.
 - (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 persons 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 19-20 and Articles 26-30 of the Helsinki Declaration and Guideline 15 “Research Involving Vulnerable Persons and Groups” (CIOMS, 2016) in reviewing proposals involving vulnerable populations. Article 20 of Helsinki Declaration clearly states that “*Medical research with a vulnerable group*

is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from 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 using additional forms and signatures, including those adequately informing their parents or other legally authorized representatives or guardians. The Committee will be guided by Guideline 17, “Research involving children and adolescents”, of the International Guidelines for Biomedical Research (CIOMS, 2016) 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 18, “Women as research participants” and Guideline 19, “Pregnant and breast feeding women as research participants” of the international Guidelines for Biomedical Research (CIOMS, 2016) 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 13, “reimbursement and compensation for research participants”, and Guideline 2 “research conducted in low research settings” of the International Guidelines for Biomedical Research (CIOMS, 2016) in reviewing proposals involving research in populations and communities with limited resources.

VII.

Conflicts of interest

The avoidance of conflicts of interest or the appearance thereof is essential to ensure both the quality and credibility of research ethics reviews. The Committee will therefore take necessary steps to avoid conflicts of interest and the appearance of conflicts of interest for investigators, responsible WHO 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 on 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) WHO 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) Non-affiliated 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 members: role conflicts

A Committee member who is also a responsible WHO 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. Such members will not participate in the review of these proposals.

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, and 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 / 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 their responsibility to the Vice-Chairperson whenever he/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.

VIII.

Evaluation and improvement

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 the 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 research ethics review committees, provided such evaluators are not members of the Committee, and they 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 responsible technical staff members and Principal Investigators whose research proposals have been reviewed by the Committee during the period under review.

- (3) The evaluator(s) should endeavour 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 SOP

A. Adoption of SOP

The SOP will be approved by the Regional Director, South-East Asia Region, for adoption by the Committee. These will be available publicly on the external website of Regional Office for South-East Asia. These SOP will supersede any other publications in this regard, including the specific procedures announced by the Regional Office for South-East Asia in its last information circular (IC-2019-25) related to the research review process.

B. Amendment of SOP

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.

X.

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 analyzes 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, non-governmental, 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 the 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 several times since then with the latest revision in 2016, 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 2016 and consists of a preamble and 25 guidelines that 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 Eighteenth World Medical Assembly (WMA) 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 several times since then, with the latest revision in 2013 by the Sixteenth 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 <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/> (last accessed on Feb 23, 2022).

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 Trials 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 February 23, 2022)

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-centre 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 for South-East Asia Region who controls and governs the affairs of the WHO South-East Asia Region.

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:

- (1) are exposed to intervention, manipulation, observation, or other interaction with investigators, either directly or through alteration of their environment; or
- (2) become individually identifiable through investigators’ collection, preparation or use of 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 technical staff member: A staff member of the Regional Office or Country office 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 January 14, 2022.

United Nations Convention on the Rights of the Child: See <https://www.ohchr.org/en/professionalinterest/pages/crc.aspx> as accessed on February 23, 2022

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 the 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 a 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 an endorsement of, or support for, the research project by WHO and should not be construed or portrayed as such.

WHO's Research Ethics Review Committee (WHOERC): A 27-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 as accessed on February 23, 2022: <https://www.who.int/groups/research-ethics-review-committee/>

Annex 1

Recommended format for research proposal (checklist, proposal format and budget template) for financial and or technical support from WHO Regional Office for South-East Asia

I. SUMMARY SHEET AND CHECKLIST OF REQUIRED DOCUMENTS FOR SEARO-ERC SUBMISSION

| | | |
|---|-----|--|
| 1 | | <u>Principal Investigator</u> Professor/Dr/Mr/Ms _____ FAMILY NAME (SURNAME): _____ FIRST NAME: _____ OTHER NAMES: _____ |
| | 1.1 | <u>Title of post, position or appointment presently held by principal investigator</u> |
| | 1.2 | Complete postal address: _____ _____ Email: _____ |
| 2 | | Institution responsible for the research proposed Name and address (including website address, if any) |

| | | |
|---|-----|---|
| 3 | | Title of health research proposed: (should be brief, precise and informative to workers outside your field) |
| | 3.1 | <u>Objectives of research have been clearly listed.</u> Yes <input type="checkbox"/> No <input type="checkbox"/> |
| | 3.2 | <u>Duration of research from preparations for field work till analysis and compilation of final research results</u> From (date): _____ To(date): _____ Total (years): _____ |
| | 3.3 | <u>Total budget of research (US\$)</u> |
| | 3.4 | Any conflict of interest by research institute/PI/funding source declared Yes <input type="checkbox"/> No <input type="checkbox"/> |
| 4 | 4.1 | Informed consent documentation (Participant Information Sheet and Informed Consent Form) included in the proposal Yes <input type="checkbox"/> No <input type="checkbox"/> |
| | 4.2 | Questionnaires for collection of data included in the proposal Yes <input type="checkbox"/> No <input type="checkbox"/> |
| | 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 Yes <input type="checkbox"/> No <input type="checkbox"/> Not a clinical trial <input type="checkbox"/> |

| | | |
|---|-----|--|
| 5 | 5.1 | <u>Institutional and national ethical clearance</u> Name and contact details of the local ERC/IRB/ERB in the country of research where the proposal has been reviewed/submitted: _____ _____ Name of local ERC/IRB: _____ Contact details including email address: _____ _____ |
| | 5.2 | Institutional/national ethical clearance enclosed Proposal under review by institutional/national ERC Yes <input type="checkbox"/> No <input type="checkbox"/> (proof of submission to local ERC enclosed) |
| 6 | | <u>Approval of national Ministry of Health or national Medical Research Council (or equivalent body)</u> National approval document enclosed Yes <input type="checkbox"/> No <input type="checkbox"/> |
| 7 | | <u>Institutional endorsement (can be attached as a separate document also)</u> Head of Institution Title: _____ Name: _____ Date: _____ (print) Signature: _____ |
| 8 | | Curriculum Vitae of Principal Investigator attached Yes <input type="checkbox"/> No <input type="checkbox"/> |
| 9 | | Applicant's signature Date: _____ Signature: _____ |

II. Recommended format for research protocol

The recommended format is aligned with what is recommended by WHO HQ at (as accessed on Feb 23, 2022). <https://www.who.int/groups/research-ethics-review-committee/recommended-format-for-a-research-protocol>

Research Protocol: Part 1

- (1) **Project Summary:** should be no more than 300 words
- (2) **General information** (protocol title, version, date, name & address of sponsor/funder, name and titles of investigators; address and telephone number of research sites; name and address of clinical laboratories and other institutions involved in research.
- (3) **Rationale for conducting the research** (or problem statement) **and background information** (literature review of what we already know about the issue at hand).
- (4) **Study goals and objectives or study hypothesis.**
- (5) **Study design and methodology:** Key research design (e.g. experimental study, cross-sectional survey, facility survey, etc.); Research setting (country, district, province, etc.) and study population (age groups, women, men, etc.); Sampling design, sample size and use of controls (if applicable); Study instruments
- (6) **Ethical and safety considerations:** safety considerations (for research participants, communities and researcher themselves), follow-up provided to research participants, if any. Documentation of issues that are likely to raise ethical concerns (risk assessment for different stakeholders), how informed consent will be obtained from research participants. Inclusion of informed consent forms and information sheet for research participants as part of the proposal.
- (7) **Data collection and analysis:** Plans for fieldwork for collecting data; Data analysis plan, including a description of key outcome indicators proposed to be measured in the research.
- (8) **Time line for research implementation**

Research Protocol: Part 2

- (1) Budget (please see the template at annex 3), please highlight any compensation/reimbursements made to research participants and the justification for that. Also highlight the salaries paid to PIs who are staff members of the contracting Institution.
- (2) Other support for the project funding received or anticipated for this project from other funding organization)
- (3) Collaboration with other scientists or research institutions
- (4) Links to other projects
- (5) Curriculum Vitae of Investigators (In general CVs should not be more than 1 page, unless a complete CV is specifically requested for).
- (6) Other research activities of the investigators (PI should list all ongoing research projects that they are involved in, the source of funding of those projects, the duration of those projects and the percentage of time spent on each.
- (7) Financing and insurance—where relevant.

III. Recommended format for presenting budget

| ITEM | | Amount (local currency) | Amount (US \$) |
|------|---|-------------------------------|-------------------|
| 1 | PERSONNEL^a (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^a (over US\$ 500) (include specifications, shipment and freight insurance costs; comment on local provision for maintenance and service | | |
| | Subtotal | | |

| ITEM | | Amount (local currency) | Amount (US \$) | |
|------|---|--|-------------------|--|
| 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 | | | |
| | TRAVEL^a (specify domestic and international) | | | |
| | Subtotal | | | |
| 5. | DATA ANALYSIS COST^a | | | |
| | Subtotal | | | |
| 6. | COST OF DISSEMINATION OF RESULTS* (including that of publication in any peer reviewed journal for making it open access^b) | | | |
| | Subtotal | | | |
| 7. | MISCELLANEOUS EXPENDITURES^a | | | |
| | 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 | | | |

^aplease provide detailed budget providing sufficient break-up of costs included under each budget item to facilitate expedited approval.

^bThe condition 7.2 provides the publication will in accordance with WHO policy on open access (<https://www.who.int/about/policies/publishing/open-access>) and from Jan 1, 2021, all WHO authored and WHO funded articles that are submitted for publication in peer-review journals must be published in an open access journal or an open access platform. It further states that where applicable, reasonable article processing charges (APCs) will be covered by WHO for articles published in open-access journals or on open-access platforms that are compatible with the requirements mentioned in its open access policy.

IV Recommended format for Curriculum Vitae for Investigators

Name and Contact information

Name : _____

Designation : _____

Institute : _____

Address : _____

Email : _____

Cell phone No. : _____

ORCID ID : _____

Educational Background (Bachelor and above, maximum three):

| Name of Degree/ Diploma | Institute, University, City, Country | Year of passing |
|----------------------------|--------------------------------------|--------------------|
| | | |
| | | |
| | | |

Training on research methods/ethics (title, organization, duration):

- 1.
- 2.
- 3.

Past three position(s) held (with dates: From – To):

- 1.
- 2.
- 3.

Last five years publication in peer reviewed journals (Use Vancouver style; Do not include abstract supplements/proceedings):

- 1.
- 2.
- 3.

Annex 2

Additional documents (or information) to be included in a research proposal

(where applicable) for submission to the Committee for review

In addition to the items required in Section IV-B for all research proposals involving human participants, the responsible technical 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 February 23, 2022 at <https://www.who.int/groups/research-ethics-review-committee/guidelines-on-submitting-research-proposals-for-ethics-review/templates-for-informed-consent-forms>
- ⦿ Code of Federal Regulations, Title 45, Public Welfare, Department of Health and Human Services (HHS), U.S. Government. Last visited on February 23, 2022 at <https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html>

Other templates

World Health Organization. WHO-ERC guide for principal investigators. Accessed on February 23, 2022. https://cdn.who.int/media/docs/default-source/documents/ethics/guide-for-practical-investigation.pdf?sfvrsn=826ad3be_0

Annex 4

Committee protocol review standards

[adapted from the National Institutes of Health, United States of America and WHO-ERC review standards]

Minimum regulatory requirements for Committee review, discussion, documentation in the meeting minutes

| Regulatory Review Requirement | Suggested question for SEARO-ERC discussion |
|---|---|
| 1. The proposed research design is scientifically sound and will not unnecessarily expose human research participants to risk | <p>(a) Is the hypothesis or research question clear? Is it clearly stated?</p> <p>(b) Is the study design appropriate to prove the hypothesis or answer the research question?</p> <p>(c) Will the research contribute to generalizable knowledge, and is it worth exposing human research participants to risk?</p> |
| 2. Risks to the participants are reasonable in relation to anticipated benefits, if any, to the participants and the importance of the knowledge that may reasonably be expected to result. | <p>(a) What does the Committee consider the level of risk to be? (See risk assessment guide on the back of form).</p> <p>(b) What does PI consider the level of risk/discomfort/inconvenience to be?</p> <p>(c) Is there a prospect of direct benefit to human research participants (see benefit assessment guide below)</p> |
| 3. Participant selection is equitable | <p>(a) Who is to be enrolled? Men? Women? Ethnic minorities? Children (rationale for inclusion/exclusion addressed)? Seriously ill patients? Healthy volunteers?</p> <p>(b) Are these research participants appropriate for the protocol?</p> |

| Regulatory Review Requirement | Suggested question for SEARO-ERC discussion |
|--|---|
| 4. Additional safeguards required for subjects likely to be vulnerable to coercion or undue influence. | (a) Is appropriate protection in place for vulnerable participants, e.g. pregnant women, socially or economically disadvantaged, cognitively impaired, subjects in special situations, e.g. doctor-patient relationship making them more vulnerable? |
| 5. Informed consent is obtained from research participants or their legally authorized representative (s). | (a) Does the informed consent document include all the required elements? (b) Is the consent document understandable to participants? (c) Who will obtain the consent (PI, nurse, other?) and in what setting? (d) Is the Committee asked to waive or alter any informed consent requirements? |
| 6. Risks to the participants are minimised? | (a) Does the research design minimize risks to participants? (b) Would using data and safety monitoring board or other research oversight process enhance participant safety? |
| 7. Subject privacy and confidentiality are maximized. | (a) Will personally identifiable research data be protected to the extent possible from access or use? (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 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 the participant.
2. _____ The research involves more than minimal risk to participants.
 - Ⓐ The risk(s) represents a minor increase over minimal risk, OR
 - Ⓑ The risk(s) represents more than a minor increase over minimal risk.

Benefit: A research benefit is considered to be something of 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 participant's disorder or condition.
2. _____ No prospect of direct benefit to individual participants, but likely to yield generalizable knowledge to further society's understanding of the disorder or condition under study.
3. _____ The research involves the prospect of direct benefit to individual participants.

Annex 5

Format for all SEARO-ERC minutes

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

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

Members Present: _____ (Chairperson) _____

(indicate who is _____
a non-scientist, _____
non-Regional office _____
affiliated, etc.) _____

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:

Responsible Regional Office Technical Officer:

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 decision and vote, [(d) below] consistent with page 2, SEARO-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 (a document that all required elements are present)
 - ⦿ Status of approval from ERC of the country where research is proposed to be carried out
 - ⦿ Additional considerations (e.g. multi-centre 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 it and 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 Committee votes that the stipulations and/or recommendations are to be reviewed by the Chairperson, by the Secretariat, by a subcommittee of the SEARO-ERC, or by the full SEARO-ERC.

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

(4) CONTINUING REVIEWS OR a second review of proposals submitted earlier either due to proposed AMENDMENTS or otherwise.

A. Principal Investigator:

Title and type of expedited action:

Date approved by SEARO-ERC 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 Committee 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 Committee 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) SEARO-ERC Decision and Vote (Include Committee 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) Committee Decision and Vote (include a statement indicating whether 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 the Committee's acknowledgement of receipt of the adverse event report(s) and discussion. Discussion of serious adverse events occurring on a protocol should include immediate actions taken as a result of the event by the PI; recommendations for further actions, if any, by the Committee (e.g. suspension of subject accrual, etc.), and any necessary recommendations for further reporting.

If the adverse events are reported from non-Regional office sites for the Committee's information only, and no action is required by the Committee, 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 (2013)

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

64th WMA General Assembly, Fortaleza, Brazil, October 2013

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) Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

- (3) 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."

- (4) 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.
- (5) Medical progress is based on research that ultimately must include studies involving human subjects.
- (6) 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 proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
- (7) Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
- (8) While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
- (9) It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
- (10) Physicians must 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.
- (11) Medical research should be conducted in a manner that minimises possible harm to the environment.
- (12) Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

- (13) Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
- (14) Physicians who combine medical research with medical care should involve their patients in research only to the extent that this 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.
- (15) Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

- (16) In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

- (17) All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

- (18) Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

- (19) Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

- (20) Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research

cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

- (21) 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.
- (22) The design and performance of each research study involving human subjects must be clearly described and justified 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, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions

Research Ethics Committees

- (23) The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. 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 amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

- (24) Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

- (25) Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
- (26) In medical research involving human subjects capable of giving informed consent, 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, post-study provisions 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.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

- (27) When seeking informed consent for participation in a research study the physician must 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 must be sought by an appropriately qualified individual who is completely independent of this relationship.
- (28) For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised 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 group represented by the potential subject, the research

cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

- (29) When a potential research subject who is deemed incapable of giving informed consent 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 authorised representative. The potential subject's dissent should be respected.
- (30) 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 group. In such circumstances the physician must seek informed consent from the legally authorised 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 must be obtained as soon as possible from the subject or a legally authorised representative.
- (31) The physician must fully inform the patient which aspects of their 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 adversely affect the patient-physician relationship.
- (32) For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

- (33) The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

- (34) Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
- (35) Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers 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. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

- (36) In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Annex 7

International guidelines for biomedical research involving human subjects (CIOMS, 2016)

[** for the detailed commentary under each guideline, please refer to the complete document at CIOMS website at <http://www.cioms.ch/>]

Guideline 1: Scientific and Social Value and Respect of Rights

The ethical justification for undertaking health-related research involving humans is its scientific and social value: the prospect of generating the knowledge and the means necessary to protect and promote people's health. Patients, health professionals, researchers, policy-makers, public health officials, pharmaceutical companies and others rely on the results of research for activities and decisions that impact individual and public health, welfare, and the use of limited resources. Therefore, researchers, sponsors, research ethics committees, and health authorities, must ensure that proposed studies are scientifically sound, build on an adequate prior knowledge base, and are likely to generate valuable information.

Although scientific and social value are the fundamental justification for undertaking research, researchers, sponsors, research ethics committees and health authorities have a moral obligation to ensure that all research is carried out in ways that uphold human rights, and respect, protect, and are fair to study participants and the communities in which the research is conducted. Scientific and social value cannot legitimate subjecting study participants or host communities to mistreatment, or injustice.

Guideline 2: Research conducted in low-resource settings

Before instituting a plan to undertake research in a population or community in low-resource settings, the sponsor, researchers, and relevant public health authority must ensure that the research is responsive to the health needs or priorities of the communities or populations where the research will be conducted.

As part of their obligation, sponsors, and researchers must also:

- make every effort, in cooperation with government and other relevant stakeholders, to make available as soon as possible any intervention or product developed, and knowledge generated, for the population or

community in which the research is carried out, and to assist in building local research capacity. In some cases, in order to ensure an overall fair distribution of the benefits and burdens of the research, additional benefits such as investments in the local health infrastructure should be provided to the population or community; and

- consult with and engage communities in making plans for any intervention or product developed available, including the responsibilities of all relevant stakeholders.

Guideline 3: Equitable Distribution of Benefits and Burdens in the Selection of Individuals and Groups of Participants in Research

Sponsors, researchers, governmental authorities, research ethics committees and other stakeholders must ensure that the benefits and burdens of research are equitably distributed. Groups, communities and individuals invited to participate in research must be selected for scientific reasons and not because they are easy to recruit because of their compromised social or economic position or their ease of manipulation. Because categorical exclusion from research can result in or exacerbate health disparities, the exclusion of groups in need of special protection must be justified. Groups that are unlikely to benefit from any knowledge gained from the research should not bear a disproportionate share of the risks and burdens of research participation. Groups that are under-represented in medical research should be provided appropriate access to participate.

Guideline 4: Potential Individual Benefits and Risks of Research

To justify imposing any research risks on participants in health research, the research must have social and scientific value. Before inviting potential participants to join a study, the researcher, sponsor and the research ethics committee must ensure that risks to participants are minimized and appropriately balanced in relation to the prospect of potential individual benefit and the social and scientific value of the research. The potential individual benefits and risks of research must be evaluated in a two-step process. First, the potential individual benefits and risks of each individual research intervention or procedure in the study must be evaluated.

- For research interventions or procedures that have the potential to benefit participants, risks are acceptable if they are minimized and outweighed by the prospect of potential individual benefit and the available evidence suggests that the intervention will be at least as advantageous, in the light of foreseeable risks and benefits, as any established effective alternative. Therefore, as a general rule, participants in the control group of a trial must

receive an established effective intervention. The conditions under which a placebo may be used are spelled out in Guideline 5 – Choice of control in clinical trials.

- ⦿ For research interventions or procedures that offer no potential individual benefits to participants, the risks must be minimized and appropriate in relation to the social and scientific value of the knowledge to be gained (expected benefits to society from the generalizable knowledge).
- ⦿ In general, when it is not possible or feasible to obtain the informed consent of participants, research interventions or procedures that offer no potential individual benefits must pose no more than minimal risks. However, a research ethics committee may permit a minor increase above minimal risk when it is not possible to gather the necessary data in another population or in a less risky or burdensome manner, and the social and scientific value of the research is compelling (see Guideline 16 – Research involving adults incapable of giving informed consent, and Guideline 17 – Research involving children and adolescents).

In a second step, the aggregate risks and potential individual benefits of the entire study must be assessed and must be considered appropriate.

- ⦿ The aggregate risks of all research interventions or procedures in a study must be considered appropriate in light of the potential individual benefits to participants and the scientific social value of the research.
 - ⦿ The researcher, sponsor and research ethics committee must also consider risks to groups and populations, including strategies to minimize these risks.
- Guideline 4: Potential individual benefits and risks of research

Guideline 5: Choice of Controls in Clinical Trials

As a general rule, the research ethics committee must ensure that research participants in the control group of a trial of a diagnostic, therapeutic, or preventive intervention receive an established effective intervention.

Placebo may be used as a comparator when there is no established effective intervention for the condition under study, or when placebo is added on to an established effective intervention.

When there is an established effective intervention, placebo may be used as a comparator without providing the established effective intervention to participants only if:

- ⦿ there are compelling scientific reasons for using placebo; and
- ⦿ delaying or withholding the established effective intervention will result in no more than a minor increase above minimal risk to the participant and risks are minimized, including through the use of effective mitigation procedures.

Risks and benefits of other study interventions and procedures should be evaluated according to the criteria set out in Guideline 4 – Potential individual benefits and risks of research.

Guideline 6: Caring for Participants' Health Needs

Especially in the context of clinical trials, researchers and sponsors must make adequate provisions for addressing participants' health needs during research and, if necessary, for the transition of participants to care when the research is concluded. The obligation to care for participants' health needs is influenced, among other things, by the extent to which participants need assistance and established effective care is available locally.

When participants' health needs during and after research cannot be met by the local health infrastructure or the participant's pre-existing health insurance, the researcher and sponsor must make prior arrangements for adequate care for participants with local health authorities, members of the communities from which persons are drawn, or nongovernmental organizations such as health advocacy groups.

Addressing participants' health needs requires at least that researchers and sponsors make plans for:

- ⦿ how care will be adequately provided for the condition under study;
- ⦿ how care will be provided during the research when researchers discover conditions other than those under study (“ancillary care”);
- ⦿ transitioning participants who continue to need care or preventive measures after the research to appropriate health services;
- ⦿ providing continued access to study interventions that have demonstrated significant benefit; and
- ⦿ consulting with other relevant stakeholders, if any, to determine everyone's responsibilities and the conditions under which participants will receive continued access to a study intervention, such as an investigational drug, that has demonstrated significant benefit in the study.

When access is provided after the research to investigational interventions that have demonstrated significant benefit, the provision may end as soon as the study intervention is made available through the local public health-care system or after a predetermined period of time that the sponsors, researchers and community members have agreed before the start of a trial.

Information on care for participants' health needs during and after the research must be included in the informed consent process.

Guideline 7: Community Engagement

Researchers, sponsors, health authorities and relevant institutions should engage potential participants and communities in a meaningful participatory process that involves them in an early and sustained manner in the design, development, implementation, design of the informed consent process and monitoring of research, and in the dissemination of its results.

Guideline 8: Collaborative partnerships and capacity-building for research and research review

It is the responsibility of governmental authorities in charge of health-related research involving human participants to ensure that such research is reviewed ethically and scientifically by competent and independent research ethics committees and is conducted by competent research teams. Independent scientific and ethical review is critical to engender community trust for research (see Guideline 23 – Requirements for establishing research ethics committees and for their review of protocols). Health-related research often requires international collaboration and some communities lack the capacity to assess or ensure the scientific quality or ethical acceptability of health-related research proposed or carried out in their jurisdictions. Researchers and sponsors who plan to conduct research in these communities should contribute to capacity-building for research and review.

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

- ⦿ research infrastructure building and strengthening research capacity;
- ⦿ strengthening research ethics review and oversight capacity in host communities (see Guideline 23 – Requirements for establishing research ethics committees and for their review of protocols);
- ⦿ developing technologies appropriate to health care and health-related research;

- ⦿ educating research and health-care personnel and making arrangements to avoid undue displacement of health care personnel;
- ⦿ engaging with the community from which research participants will be drawn (see Guideline 7 – Community engagement);
- ⦿ arranging for joint publication consistent with recognized authorship requirements and data sharing (see Guideline 24 – Public accountability for health-related research); and
- ⦿ preparing a benefit-sharing agreement to distribute eventual economic gains from the research.

Guideline 9: Individuals capable of giving informed consent

Researchers have a duty to provide potential research participants with the information and the opportunity to give their free and informed consent to participate in research, or to decline to do so, unless a research ethics committee has approved a waiver or modification of informed consent (see Guideline 10 – Modifications and waivers of informed consent). Informed consent should be understood as a process, and participants have a right to withdraw at any point in the study without retribution.

Researchers have a duty to:

- ⦿ seek and obtain consent, but only after providing relevant information about the research and ascertaining that the potential participant has adequate understanding of the material facts;
- ⦿ refrain from unjustified deception or withholding of relevant information, undue influence, or coercion (see Guideline 10 – Modifications and waivers of informed consent);
- ⦿ ensure that the potential participant has been given sufficient opportunity and time to consider whether to participate; and
- ⦿ as a general rule, obtain from each potential participant a signed form as evidence of informed consent. Researchers must justify any exceptions to this general rule and seek the approval of the research ethics committee.

With the approval of the research ethics committee, researchers must renew the informed consent of each participant if there is a substantive change in the conditions or procedures of the research, or if new information becomes available that could affect the willingness of participants to continue. In long-term studies, researchers should ensure at pre-determined intervals that each participant is willing to stay in the study, even if there are no changes in the design or objectives of the research.

It is the principal investigator's responsibility to ensure that all personnel obtaining informed consent for a study comply with this Guideline

Guideline 10: Modifications and waivers of informed consent

Researchers must not initiate research involving humans without obtaining each participant's individual informed consent or that of a legally authorized representative, unless researchers have received explicit approval to do so from a research ethics committee. Before a waiver of informed consent is granted, researchers and research ethics committees should first seek to establish whether informed consent could be modified in a way that would preserve the participant's ability to understand the general nature of the investigation and to decide whether to participate.

A research ethics committee may approve a modification or waiver of informed consent to research if:

- ⦿ the research would not be feasible or practicable to carry out without the waiver or modification;
- ⦿ the research has important social value; and
- ⦿ the research poses no more than minimal risks to participants.

Additional provisions may apply when waivers or modifications of informed consent are approved in specific research contexts.

Guideline 11: Collection, Storage and use of biological materials and related data

When biological materials and related data, such as health or employment records, are collected and stored, institutions must have a governance system to obtain authorization for future use of these materials in research. Researchers must not adversely affect the rights and welfare of individuals from whom the materials were collected.

When specimens are collected for research purposes, either specific informed consent for a particular use or broad informed consent for unspecified future use must be obtained from the person from whom the material originally is obtained. The ethical acceptability of broad informed consent relies on proper governance. This type of consent must be obtained in the same way as described in Guideline 9 – Individuals capable of giving informed consent.

When human biological materials are left over after clinical diagnosis or treatment (so-called "residual tissue") and are stored for future research, a specific or broad informed

consent may be used or may be substituted by an informed opt-out procedure. This means that the material is stored and used for research unless the person from whom it originates explicitly objects. The informed opt-out procedure must fulfil the following conditions: 1) patients need to be aware of its existence; 2) sufficient information needs to be provided; 3) patients need to be told that they can withdraw their data; and 4) a genuine possibility to object has to be offered.

When researchers seek to use stored materials collected for past research, clinical or other purposes without having obtained informed consent for their future use for research, the research ethics committee may waive the requirement of individual informed consent if: 1) the research would not be feasible or practicable to carry out without the waiver; 2) the research has important social value; and 3) the research poses no more than minimal risks to participants or to the group to which the participant belongs.

Custodians of biological materials must arrange to protect the confidentiality of the information linked to the material, by sharing only anonymized or coded data with researchers, and limiting access to the material of third parties. The key to the code must remain with the custodian of the biological material.

The transfer of biological materials must be covered by a Material Transfer Agreement (MTA).

Biological materials and related data should only be collected and stored in collaboration with local health authorities. The governance structure of such collection should have representation of the original setting. If the specimen and data are stored outside the original setting, there should be provisions to return all materials to that setting and share possible results and benefits (see Guideline 3 – Equitable distribution of benefits and burdens in the selection of individuals and groups of participants in research, Guideline 7 – Community engagement, and Guideline 8 – Collaborative partnership and capacity building for research and review).

Guideline 12: Collection, storage and use of data in health-related research

When data are stored, institutions must have a governance system to obtain authorization for future use of these data in research. Researchers must not adversely affect the rights and welfare of individuals from whom the data were collected.

When data are collected and stored for research purposes, either specific informed consent for a particular use or broad informed consent for unspecified future use must be obtained from the person from whom the data were originally obtained. The ethical acceptability of broad informed consent relies on proper governance. This type

of informed consent must be obtained in the same way as described in Guideline 9 – Individuals capable of giving informed consent.

When data are used that were collected in the context of routine clinical care, an informed opt-out procedure must be used. This means that the data may be stored and used for research unless a person explicitly objects. However, a person's objection is not applicable when it is mandatory to include data in population-based registries. The informed opt-out procedure must fulfil the following conditions: 1) patients need to be aware of its existence; 2) sufficient information needs to be provided; 3) patients need to be informed that they can withdraw their data; and 4) a genuine possibility to object has to be offered.

When researchers seek to use stored data collected for past research, clinical or other purposes without having obtained informed consent for their future use for research, the research ethics committee may consider to waive the requirement of individual informed consent if: 1) the research would not be feasible or practicable to carry out without the waiver; and 2) the research has important social value; and 3) the research poses no more than minimal risks to participants or to the group to which the participant belongs. Custodians of the data must arrange to protect the confidentiality of the information linked to the data, by sharing only anonymised or coded data with researchers, and limiting access to the material of third parties. The key to the code must remain with the custodian of the data.

Data from low-resource settings should only be collected and stored in collaboration with local health authorities. The governance structure of such a databank must have representation of the original setting. If the collection is stored outside the original setting there should be provisions to return all data to that setting and share possible results and benefits (see Guideline 3 – Equitable distribution of benefits and burdens in the selection of individuals and groups of participants in research, Guideline 7 – Community engagement, and Guideline 8 – Collaborative partnership and capacity building for research and review).

Guideline 13: Reimbursement and compensation for research participants

Research participants should be reasonably reimbursed for costs directly incurred during the research, such as travel costs, and compensated reasonably for their inconvenience and time spent. Compensation can be monetary or non-monetary. The latter might include free health services unrelated to the research, medical insurance, educational materials, or other benefits.

Compensation must not be so large as to induce potential participants to consent to participate in the research against their better judgment (“undue inducement”). A local research ethics committee must approve reimbursement and compensation for research participants.

Guideline 14: Treatment and compensation for research-related harms

Sponsors and researchers must ensure that research participants who suffer physical, psychological or social harm as a result of participating in health-related research receive free treatment and rehabilitation for such harms, as well as compensation for lost wages, as appropriate. Such treatment and compensation are owed to research participants who are harmed physically, psychologically or socially, as a consequence of interventions performed solely to accomplish the purposes of research, regardless of fault. In the case of death resulting from research participation, the participant’s dependents are entitled to compensation. Participants must not be asked to waive the right to free treatment and compensation for research-related harms.

Research ethics committees must determine whether there is an adequate arrangement for treatment and compensation for research-related injuries.

Guideline 15: Research involving vulnerable persons and groups

When vulnerable individuals and groups are considered for recruitment in research, researchers and research ethics committees must ensure that specific protections are in place to safeguard the rights and welfare of these individuals and groups in the conduct of the research.

Guideline 16: Research involving adults incapable of giving informed consent

Adults who are not capable of giving informed consent must be included in health-related research unless a good scientific reason justifies their exclusion. As adults who are not capable of giving informed consent have distinctive physiologies and health needs, they merit special consideration by researchers and research ethics committees. At the same time, they may not be able to protect their own interests due to their lack of capacity to provide informed consent. Specific protections to safeguard the rights and welfare of these persons in research are therefore necessary.

Before undertaking research with adults who are not capable of giving informed consent, the researcher and the research ethics committee must ensure that:

- ⦿ a legally authorized representative of the person who is incapable of giving informed consent has given permission and this permission takes account of the participant's previously formed preferences and values (if any); and
- ⦿ the assent of the subject has been obtained to the extent of that person's capacity, after having been provided with adequate information about the research at the level of the subject's capacity for understanding this information.

If participants become capable of giving informed consent during the research, their consent to continued participation must be obtained.

In general, a potential participant's refusal to enrol in the research must be respected, unless, in exceptional circumstances, research participation is considered the best available medical option for an individual who is incapable of giving informed consent. If participants have made advance directives for participation in research while fully capable of giving informed consent, the directives should be respected.

For research interventions or procedures that have the potential to benefit adults who are incapable of giving informed consent, the risks must be minimized and outweighed by the prospect of potential individual benefit. For research interventions or procedures that have no potential individual benefits for participants, two conditions apply:

- ⦿ the interventions and procedures should be studied first in persons who can give consent when these interventions and procedures target conditions that affect persons who are not capable of giving informed consent as well as those who are capable, unless the necessary data cannot be obtained without participation of persons who are incapable of giving informed consent; and
- ⦿ the risks must be minimized and no more than minimal.

When the social value of the studies with such research interventions and procedures is compelling, and these studies cannot be conducted in persons who can give informed consent, a research ethics committee may permit a minor increase above minimal risk.

Guideline 17: Research involving children and adolescents

Children and adolescents must be included in health-related research unless a good scientific reason justifies their exclusion. As children and adolescents have distinctive physiologies and health needs, they merit special consideration by researchers and research ethics committees. However, their distinctive physiologies and emotional

development may also place children and adolescents at increased risk of being harmed in the conduct of research. Moreover, without appropriate support, they may not be able to protect their own interests due to their evolving capacity to give informed consent. Specific protections to safeguard children's rights and welfare in the research are therefore necessary. Before undertaking research involving children and adolescents, the researcher and the research ethics committee must ensure that:

- ⦿ a parent or a legally authorized representative of the child or adolescent has given permission; and
- ⦿ the agreement (assent) of the child or adolescent has been obtained in keeping with the child's or adolescent's capacity, after having been provided with adequate information about the research tailored to the child's or adolescent's level of maturity.

If children reach the legal age of maturity during the research, their consent to continued participation should be obtained.

In general, the refusal of a child or adolescent to participate or continue in the research must be respected, unless, in exceptional circumstances, research participation is considered the best medical option for a child or adolescent.

For research interventions or procedures that have the potential to benefit children or adolescents, the risks must be minimized and outweighed by the prospect of potential individual benefit.

For research interventions or procedures that have no potential individual benefits for participants, two conditions apply:

- ⦿ the interventions and procedures should be studied in adults first, when these interventions and procedures target conditions that affect adults as well as children and adolescents, unless the necessary data cannot be obtained without participation of children or adolescents; and
- ⦿ the risks must be minimized and no more than minimal.

When the social value of the studies with such research interventions and procedures is compelling, and these studies cannot be conducted in adults, a research ethics committee may permit a minor increase above minimal risk.

Guideline 18: Women as research participants

Women must be included in health-related research unless a good scientific reason justifies their exclusion. Women have been excluded from much health-related research because of their child-bearing potential. As women have distinctive physiologies and

health needs, they merit special consideration by researchers and research ethics committees. Only the informed consent of the woman herself should be required for her research participation.

Since some societies lack respect for women's autonomy, in no case must the permission of another person replace the requirement of individual informed consent by the woman. Women of child-bearing potential must be informed in advance of the possibility of risks to the fetus should they become pregnant during their research participation. When participation in research might be hazardous to a fetus or a woman if she becomes pregnant, sponsors and researchers must guarantee access to pregnancy tests, effective contraceptive methods before and during the research and to safe, legal abortion.

Guideline 19: Pregnant and breastfeeding women as research participants

Pregnant and breastfeeding women have distinctive physiologies and health needs. Research designed to obtain knowledge relevant to the health needs of the pregnant and breastfeeding woman must be promoted. Research in pregnant women must be initiated only after careful consideration of the best available relevant data.

In no case must the permission of another person replace the requirement of individual informed consent by the pregnant or breastfeeding woman.

For research interventions or procedures that have the potential to benefit either pregnant or breastfeeding women or their fetus or infant, risks must be minimized and outweighed by the prospect of potential individual benefit.

For research interventions or procedures that have no potential individual benefits for pregnant and breastfeeding women:

- ⦿ the risks must be minimized and no more than minimal; and
- ⦿ the purpose of the research must be to obtain knowledge relevant to the particular health needs of pregnant or breastfeeding women or their fetuses or infants.

When the social value of the research for pregnant or breastfeeding women or their fetus or infant is compelling, and the research cannot be conducted in non-pregnant or nonbreastfeeding women, a research ethics committee may permit a minor increase above minimal risk.

Short-term and long-term follow-up of the fetus and the child may be required in research involving pregnant and breastfeeding women depending upon the study intervention and its potential risks.

As a general rule, health-related research involving pregnant women that has the potential for harm to the fetus should be conducted only in settings where women can be guaranteed access to a safe, timely and legal abortion in the event that participation in the research makes the pregnancy unwanted.

Guideline 20: Research in Disasters and disease outbreaks

Disasters arising from events such as earthquakes, tsunamis or military conflicts, and disease outbreaks, can have a sudden and devastating impact on the health of large affected populations. In order to identify effective ways of mitigating the health impact of disasters and disease outbreaks, health-related research should form an integral part of disaster response. However, the conduct of research must not unduly impact the response to the victims of a disaster.

In the conduct of research in disasters and disease outbreaks, it is essential to uphold the ethical principles embodied in these Guidelines. Conducting research in these situations raises important challenges such as the need to generate knowledge quickly, maintain public trust, and overcome practical obstacles to implementing research. These challenges need to be carefully balanced with the need to ensure the scientific validity of the research and uphold ethical principles in its conduct.

Researchers, sponsors, international organizations, research ethics committees and other relevant stakeholders should ensure that:

- ⦿ Studies are designed so as to yield scientifically valid results under the challenging and often rapidly evolving conditions of disasters and disease outbreaks (see Guideline 1 – Scientific and social value and respect for rights);
- ⦿ the research is responsive to the health needs or priorities of the disaster victims and affected communities and cannot be conducted outside a disaster situation (see Guideline 2 – Research conducted in low-resource settings);
- ⦿ participants are selected fairly and adequate justification is given when particular populations are targeted or excluded, for example health workers (see Guideline 3 – Equitable distribution of benefits and burdens in the selection of individuals and groups of participants in research);

- ⦿ the potential burdens and benefits of research participation and the possible benefits of the research are equitably distributed (see Guideline 3 – Equitable distribution of benefits and burdens in the selection of individuals and groups of participants in research);
- ⦿ the risks and potential individual benefits of experimental interventions are assessed realistically, especially when they are in the early phases of development (see Guideline 4 – Potential individual benefits and risks of research);
- ⦿ communities are actively engaged in study planning in order to ensure cultural sensitivity, while recognizing and addressing the associated practical challenges (see Guideline 7 – Community engagement);
- ⦿ the individual informed consent of participants is obtained even in a situation of duress, unless the conditions for a waiver of informed consent are met (see Guideline 9 – Individuals capable of giving informed consent, and Guideline 10 – Modifications and waivers of informed consent); and
- ⦿ research results are disseminated, data are shared, and any effective interventions developed or knowledge generated are made available to the affected communities (see Guideline 2 – Research conducted in low-resource settings, and Guideline 23 – Requirements for establishing research ethics committees and for their review of protocols).

Research in disasters and disease outbreaks should ideally be planned ahead. Health officials and research ethics committees should develop procedures to ensure appropriate, expedient and flexible mechanisms and procedures for ethical review and oversight. For example, research ethics committees could pre-screen study protocols in order to facilitate and expedite ethical review in a situation of crisis. Similarly, researchers and sponsors could make pre-arrangements on data- and sample-sharing that research ethics committees review in advance.

Sponsors and research ethics committees should evaluate and seek to minimize the risks to researchers and health professionals conducting research in a disaster context. Sponsors should include in the protocol a plan for mitigating adverse events. Furthermore, appropriate resources for mitigation measures should be included in the protocol budget.

Guideline 21: Cluster randomized trials

In advance of initiating a cluster randomized trial, researchers, sponsors, relevant authorities, and research ethics committees should:

- ⦿ determine who are the research participants and what other individuals or groups are affected, even though they are not directly targeted;
- ⦿ determine whether it is required or feasible to obtain informed consent from patients, health care workers, or community members in certain studies;
- ⦿ determine whether requiring informed consent and allowing refusal to consent may invalidate or compromise the research results;
- ⦿ determine whether a no-intervention group is ethically acceptable as a comparator in a particular cluster randomized trial; and
- ⦿ decide whether permission must be obtained from a gatekeeper

Guideline 22: Use of data obtained from the online environment and digital tools in health-related research

When researchers use the online environment and digital tools to obtain data for health related research they should use privacy-protective measures to protect individuals from the possibility that their personal information is directly revealed or otherwise inferred when datasets are published, shared, combined or linked. Researchers should assess the privacy risks of their research, mitigate these risks as much as possible and describe the remaining risks in the research protocol. They should anticipate, control, monitor and review interactions with their data across all stages of the research.

Researchers should inform persons whose data may be used in the context of research in the online environment of:

- ⦿ the purpose and context of intended uses of data and information;
- ⦿ the privacy and security measures used to protect their data, and any related privacy risks; and
- ⦿ the limitations of the measures used and the privacy risks that may remain despite the safeguards put in place.

In case of a refusal by the person approached, researchers should refrain from using the data of this individual. This informed opt-out procedure must fulfil the following conditions: 1) persons need to be aware of its existence; 2) sufficient information

needs to be provided; 3) persons need to be told that they can withdraw their data; and 4) a genuine possibility to object has to be offered.

Researchers collecting data on individuals and groups through publicly accessible websites without direct interaction with persons should, at a minimum, obtain permission from website owners, post a notice of research intent, and ensure compliance with published terms of website use.

Researchers must describe in the protocol how data obtained from online environments and digital tools will be treated, along with the potential risks of the research and how the potential risks are mitigated.

Guideline 23: Requirements for establishing research ethics committees and for their review protocols

All proposals to conduct health-related research involving humans must be submitted to a research ethics committee to determine whether they qualify for ethical review and to assess their ethical acceptability, unless they qualify for an exemption from ethical review (which may depend upon the nature of the research and upon applicable law or regulations). The researcher must obtain approval or clearance by such a committee before beginning the research. The research ethics committee should conduct further reviews as necessary, for example, when there are significant changes in the protocol. Research ethics committees must review research protocols according to the principles set out in these Guidelines.

Research ethics committees must be formally established and given adequate mandate and support to ensure timely and competent review according to clear and transparent procedures. Committees must include multidisciplinary membership in order to competently review the proposed research. Committee members must be duly qualified and regularly update their knowledge of ethical aspects of health-related research. Research ethics committees must have mechanisms to ensure independence of their operations. Research ethics committees from different institutions or countries should establish efficient communication in cases of externally sponsored and multi-centre research. In externally sponsored research, ethical review must take place in both the host and the sponsoring institution.

Research ethics committees should have a clear procedure for researchers or sponsors to make legitimate appeals against the decisions of research ethics committees.

Guideline 24: Public accountability for health related research

Public accountability is necessary for realizing the social and scientific value of healthrelated research. Therefore, researchers, sponsors, research ethics committees,

funders, editors and publishers have an obligation to comply with recognized publication ethics for research and its results.

Researchers should prospectively register their studies, publish the results and share the data on which these results are based in a timely manner. Negative and inconclusive as well as positive results of all studies should be published or otherwise be made publicly available. Any publication or report resulting from a research study should indicate which research ethics committee has authorized the study.

Researchers and sponsors should also share information about and data from past research.

Guideline 25: Conflicts of Interest

The primary goal of health-related research is to generate, in ethically appropriate ways, the knowledge necessary to promote people's health. However, researchers, research institutions, sponsors, research ethics committees, and policy-makers have other interests (for example, scientific recognition or financial gain) that can conflict with the ethical conduct of research. Such conflicts between the primary goal of health-related research and secondary interests are defined as conflicts of interest.

Conflicts of interest can influence the choice of research questions and methods, recruitment and retention of participants, interpretation and publication of data, and the ethical review of research. It is therefore necessary to develop and implement policies and procedures to identify, mitigate, eliminate, or otherwise manage such conflicts of interest.

Research institutions, researchers and research ethics committees should take the following steps:

- Research institutions should develop and implement policies and procedures to mitigate conflicts of interest and educate their staff about such conflicts;
- Researchers should ensure that the materials submitted to a research ethics committee include a disclosure of interests that may affect the research;
- Research ethics committees should evaluate each study in light of any disclosed interests and ensure that appropriate means of mitigation are taken in case of a conflict of interest; and
- Research ethics committees should require their members to disclose their own interests to the committee and take appropriate means of mitigation in case of a conflict of interest (see Guideline 23 – Requirements for establishing research ethics committees and for their review of protocols).

