IARC Ethics Committee (IEC)
Standard Operating Procedures (SOPs)

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Introduction

Remit of the IARC Ethics Committee

The IARC Ethics Committee (IEC) is responsible for the ethical review of all applications submitted to it by IARC staff and through its international composition ensures, to the extent that is possible, that international consistency and completeness in ethical approval is achieved.

These Standard Operating Procedures (SOPs) provide a framework and guidance for the IEC and the Secretariat provided by the Director’s Office.
Section 1

IARC Ethics Committee

IEC Meetings

1.1 IEC meetings are arranged by the Director’s Office, which is responsible to the Director for all administrative aspects of the ethics review process. The Secretariat of the IEC is provided by the Director’s Office. Neither the responsible individual in the Director’s Office nor the Secretary of the IEC participates in the decision-making process of the IEC.

IEC review of proposals (new submissions)

1.2 The IEC will only approve completed applications for ethical review (see 1.3 below). Before applications are submitted to the IEC, they will be reviewed by the Secretary; any incomplete application will be returned to the Principal Investigator (PI) for completion before submission to the IEC.

1.3 The following are to be included with each application, depending on the type of study:

- Completed IARC questionnaire
- Study protocol
- Participant information sheets, if any
- Informed consent forms, if any
- National and local ethics committees’ approvals or evidence of submission
- Any further relevant documentation

Meeting schedules

1.4 Meetings to review applications are held 4-5 times per year. This can be completed by teleconference if the majority of members are unavailable to attend in person.

1.5 The closing date for applications is no later than 14 working days prior to each IEC meeting.

Agenda

1.6 The Secretary prepares a draft agenda for each IEC meeting for consideration and approval by the IEC. The agenda for each meeting will include:

- The date, time and venue of the meeting
- Minutes of the previous IEC meeting
- Matters arising at the previous meeting(s) that the IEC specifically asked to be considered again
- Declarations of interest relating to items on the agenda
Applications for ethical review to be considered at the meeting, including the names of the lead reviewers
Any other business

1.7 The agenda may also include the following when appropriate:

- Items of importance arising from new guidelines or recent publications
- Matters relating to the establishment or membership of the IEC
- Matters relating to IEC decisions on policy
- Actions by the Chair relevant to previous applications
- Training issues

Lead Reviewer

1.8 The discussion of each application is facilitated by a member of the IEC assigned to act as lead reviewer. This duty is randomly assigned by the Secretary.

Distribution of papers for meetings

1.9 New applications for review must normally be received by all IEC members at least ten days prior to the IEC meeting at which the application will be reviewed.

Attendance of the Principal Investigator

1.10 The PI may be invited to attend the meeting at which his/her application is to be reviewed, in order to respond to requests from the Committee for further information, clarification or reassurance. This participation may be by remote means if the IEC Chair agrees.

1.11 When the PI is unable to attend and is not available to participate by remote means, it is acceptable for another IARC investigator or collaborator to attend instead, subject to agreement by the IEC Chair. It is not acceptable for a representative of the sponsor to attend in place of the PI.

Quorum requirements and meeting attendance

1.12 The quorum for IEC meetings is seven members and requires the presence of a majority of external (non-IARC staff) members. One external member, appointed by the other members present, may act as Chair in the absence of the IEC Chair and Vice-Chair.

1.13 The Secretary will keep a record of attendance, indicating which members were present for the discussion of each application. IEC members are expected to attend the majority of scheduled meetings each year and are required to attend at least half of such meetings. Members may attend using video-conferencing facilities.
1.14 Whenever possible the meeting should reach decisions by consensus. If a consensus is not achievable, a formal vote should be taken. All members have the right to vote including the Chair. The decision of the Committee should be determined by a two thirds majority of those members present and entitled to vote as in paragraph 1.12. In the event of a split decision, the Chair has the deciding vote.

1.15 If any member wishes to record formal dissent from the decision of the IEC, this should be recorded in the minutes.

Declarations of interest

1.16 External members must declare any general conflicts of interest they may have in relation to an application for ethical review or any matter for consideration at IEC meetings. These should be sent by each member to the Secretary on the WHO Declaration of Interests for WHO Experts form once a year. In addition, each member must declare his/her interest at the beginning of each meeting to ensure the independence of the review. Where the Chair has a conflict, that item(s) will be chaired by the Vice-Chair or in his/her absence by another external member of the quorum.

1.17 The WHO Declaration of Interests for WHO Experts defines a conflict of interest as follows: “A conflict of interest means that the expert or his/her partner ("partner" includes a spouse or other person with whom s/he has a similar close personal relationship), or the administrative unit with which the expert has an employment relationship, has a financial or other interest that could unduly influence the expert’s position with respect to the subject matter being considered. An apparent conflict of interest exists when an interest would not necessarily influence the expert but could result in the expert’s objectivity being questioned by others. A potential conflict of interest exists with an interest which any reasonable person could be uncertain whether or not should be reported”.

1.18 If an IEC member is the PI or key investigator/collaborator in a research proposal, the member may be asked to leave the meeting room and take no part in the discussion, except as outlined in paragraphs 1.10 and 1.11.

1.19 The minutes should record all declarations of interest and the decision of the IEC on the procedure followed.

Confidentiality of proceedings

1.20 Members do not sit on the IEC in any specific representative capacity (institutions, associations, departments) and must be able to discuss freely the applications submitted to them. IEC meetings must be completely confidential. Any breaches of confidentiality by members will result in termination of their membership.
1.21 The Secretary will be responsible for the collection and destruction of all applications reviewed immediately after each meeting.

Responsibilities of the Secretary
1.22 The responsibilities of the IEC Secretary are as follows:

- Preparing and issuing the schedule of IEC meetings
- Preparing the draft agenda for review/approval by the IEC
- Prior review of the applications to ensure their completeness
- Assigning lead reviewers
- Distributing the agenda and papers
- Inviting PIs
- Preparing the venue
- Recording apologies for absence prior to the meeting
- Recording attendance
- Ensuring that members have declared an interest in advance of the meeting and mentioning this interest at the beginning of the discussion of that item
- Advising the meeting as necessary on compliance with Standard Operating Procedures
- Collecting and destroying the applications reviewed immediately after the meeting
- Making a written record of the meeting
- Preparing the minutes of the meeting for review and approval at the following meeting
- Notifying applicants of decisions taken at the meeting and taking other follow-up action as necessary
- Archiving records

Minutes
1.23 The minutes of the meeting shall contain a record of the following:

- The members present and absent
- Any interests declared and the decision of the Committee on the participation of the member concerned
- The submission of written comments by members
- A summary of the main ethical issues considered
- The decision of the IEC on the applications
- In the case of an approval, any special approval conditions or additional advice to be given to the applicant
- In the case of a rejection, a list of reasons for the decision
- In the case of a conditional opinion, the additional information requested by the IEC and the arrangements for considering this information and issuing the final opinion of the IEC
- When a decision is held in abeyance, the issues for which further advice is required
When an unfavourable opinion is given on a notice of amendment, the reasons for the decision and any delegation of responsibility for giving the opinion of the IEC on a modified amendment

- The outcome of any vote taken
- Any formal dissent from the decision of the IEC by a named member, with reasons

1.24 The minutes are to be presented as the outcome of collective discussion, including written comments made by members following discussion of an application, and should not attribute particular statements to individual members, with the exception of any formal dissent.

1.25 Copies of the approved minutes of the IEC will be made available to the IARC Governing Council upon request.
Section 2

Giving an ethical opinion

Opinions available to the IEC

2.1 The IEC should reach one of the following opinions on each application reviewed at a meeting:

- Approval
- Rejection
- Conditional acceptance subject to receipt of further information or modifications
- Held in abeyance for a subsequent meeting pending receipt of further information

2.2 The Chair should ensure that one of the opinions listed in paragraph 2.1 is taken for every application considered at an IEC meeting.

2.3 Where the IEC decides that further information or clarification is required before a final opinion can be reached, the Chair will ensure that:

- The further information or clarification required is specifically identified at the meeting
- Responsibility for considering the further information and issuing the IEC’s opinion is clearly agreed upon

2.4 The IEC may delegate authority to the Chair to issue its opinion following receipt of further information or clarification from the applicant. The following information should be provided in the report:

- The opinion given on the application
- The members that were involved in considering the further information, if any

Notification of the opinion to the PI

2.5 The Secretary will notify the PI in writing of the opinion of the IEC within 10 working days of the meeting. All notification letters will be in the name of the Chair.

2.6 The following information will in all cases be included in the notification letter or in enclosures:

- A summary of particular ethical issues considered by the IEC
- A list of the members who were present for the discussion of the application or who submitted written comments on the application
Liability of IARC

2.7 Consideration must always be given to ensuring there are arrangements for dealing with liability if there is loss or injury to participants in IARC studies. The IEC should consider whether special insurance is necessary for particular studies (interventional or observational).

Communication with other bodies

2.8 It is the responsibility of the PI to inform other involved bodies/entities, such as collaborators or funding institutions, of relevant decisions taken by the IEC.

Approval to proceed with research

2.9 Approval of a project from the IEC does not imply compliance with the law of the countries involved. It is the responsibility of the PI to ensure compliance with local legal requirements and that management approval from relevant care organizations (e.g. health services) to proceed with the research has been obtained. The IEC should be notified when appropriate.
Section 3

Amendments to research approved by the IEC

Definition

3.1 A research study is considered to have commenced when the first participant or patient gives written informed consent to participate. Occasionally, the PI may propose to revise the terms of the IEC application, the protocol or other supporting documentation after approval has been given or after the study has commenced. This revision may be considered a minor, substantial or major amendment.

Types of Amendment

3.2 There are three types of amendment to an IARC study:

- Minor: of relatively little importance and therefore not considered as substantial
- Substantial: the following changes should normally be regarded as substantial:
  - Changes to the design or methodology of the study, or to background information affecting its scientific value
  - Changes to the procedures undertaken by participants
  - Any change relating to the safety or physical or mental integrity of participants, or to the risk/benefit assessment for the study
  - Changes to study documentation such as participant information sheets, consent forms, questionnaires, letters of invitation, letters to GPs or other clinicians, information sheets for relatives or caregivers
  - Change in the use of biological samples
  - A change of sponsor(s) or sponsor’s legal representative
  - Appointment of a new PI or key collaborator
  - A change to the responsibility and liability insurance coverage for the study
  - Appointment of a new PI at a research site
  - A significant change to the definition of a research site
  - A change to the definition of the end of the study
  - Any other significant change to the protocol or the terms of the original IEC application

- Major: whatever procedural changes alter the risk which participants are exposed to, or the potential benefit, constitutes a major amendment. Examples include:
  - A change in the primary purpose or objective of the research, such as introduction of additional genetic studies
  - A substantial change in research methodology
  - Introduction of new classes of investigations or other interventions (rather than simply re-scheduling or modifying those already approved)
Recruitment of a new type of participant (especially if these would be regarded as being from vulnerable groups)

However, whatever was stated in the original informed consent form should be taken into account.

3.3 Amendment involving the submission of a separate protocol should always require the submission of a new application.

**Notice of Amendment**

3.4 The IEC has the discretion to decide whether or not a proposed amendment is minor, substantial or major.

3.5 The amendment should be seen and noted by the IEC Chair. There is normally no requirement to notify the IEC as a whole. However, if the Chair considers that the amendment could affect the IEC’s previous ethical opinion, the Chair may decide to include the amendment on the agenda of items to be discussed at the next meeting of the Committee (see 3.7).

3.6 In making this judgement, consideration must be given to how the proposed changes would affect the research. Particular account should be taken of any implications of the amendment for the safety or welfare of participants and of any information that participants might require to give informed consent to continue their participation in the research as amended. Where there is any doubt about the potential implications of the amendment for participants, the amendment should be treated as substantial and ethically reviewed by the IEC.

3.7 In principle, minor amendments can go through expedited review by the IEC Chair, substantial amendments require approval by the IEC, while for major amendments, a new application for ethical review is required.

**Absence of PI**

3.8 From time to time, the PI may be absent due to annual leave, sick leave or for other reasons. For absences of up to one month, the PI is responsible for ensuring that his/her responsibilities as PI are carried out by a suitable temporary replacement and that that replacement is identified to the Secretary.

**Extension studies**

3.9 An extension study is any study using previously collected data or biological material, medical records or population study information for a new purpose or to test a new hypothesis not envisaged at the time the original consent was obtained.

3.10 It is the responsibility of the IEC Chair or Vice-Chair and the sponsor to decide if a new application is required for an extension study.
3.11 Copies of the consent obtained for the original study and any patient or participant information documents are to be sent to the Secretary of the IEC. These are to be accompanied by a brief letter from the PI summarizing the proposed changes, using language a lay person can understand. If the proposed extension is likely to affect the scientific value of the original study, supporting scientific information should be given. Any additional scientific review should be included.

3.12 The Chair or Vice-Chair, together with at least one internal IEC member, can decide on the basis of the information detailed above whether permission to proceed can be granted provided the independence of the decision can be demonstrated. They may require additional information from the PI.
Section 4

Start up of New Clinical Trials

Purpose

4.1 The purpose of this section is to define a standardized, uniform process for initiating new clinical trials at IARC.

Tracking

4.2 All IARC clinical trials shall be registered at one of the WHO Primary Clinical Trials Registries (http://www.who.int/ictrp/network/primary/en/index.html) before they are forwarded to the IEC.

Approval Process

4.3 The following documents should be forwarded to the IEC. Those marked with an asterisk are compulsory:

- Investigator Brochure: this document shows that the relevant and current scientific information about the investigational product has been provided
- Signed protocol and amendments, if any, and sample Case Report Form (CRF)*
- Informed consent form and any other written information as well as the advertisement for subject recruitment*
- Insurance statement
- Evidence of submission to regulatory authority*
- CV of the PI and other Sub-PIs*
- Pre-trial monitoring report
- Evidence of compliance of PIs with International Conference on Harmonisation (ICH) / Good Clinical Practice (GCP) guidelines

4.4 The approval of the IEC must be based at a minimum on:

- Date and document version numbers of protocol and any amendments
- CRF (if applicable)
- Informed consent form(s)
- Any other written information to be provided to the subject(s)
- Advertisement for subject recruitment (if used)
- Subject compensation (if any)
- Any other documents given approval.

Monitoring

4.5 During the conduct of the clinical trial and for the progress reports the following documents need to be established and forwarded to the IEC: any updates of
documents in 4.3 plus monitoring visit reports and signed informed consent forms, CRFs and other notifications.

Finalization or Termination

4.6 After completion or termination of the trial, the following documents shall be forwarded in the final report to the IEC:

- Investigational product(s) accountability at site
- Documentation of investigational product destruction
- Completed subject identification code list
- Clinical study report

Data and Safety Monitoring Committee

4.7 All clinical studies require safety monitoring throughout the duration of the research, but not all studies require monitoring by a Data and Safety Monitoring Committee (DSMC). DSMCs may be critical for studies intended to save lives, prevent serious disease progression, or reduce the risk of a major adverse health outcome. DSMCs are particularly important in studies where interim data analysis is required to ensure the safety of research participants.

4.8 A DSMC is often considered relevant in the following kinds of studies:

- Controlled studies with mortality and/or severe morbidity as a primary or secondary end-point
- Randomized controlled studies focused on evaluating clinical efficacy and safety of a new intervention intended to reduce severe morbidity or mortality
- Early studies of a high-risk intervention (risk of non-preventable, potentially life-threatening, complications; or risk of common, preventable adverse events of interest [especially type A drug reactions]), whether or not randomized
- Studies in the early phases of a novel intervention with very limited information on clinical safety or where prior information raises concern regarding potential serious adverse outcomes
- Studies where the design or expected data accrual is complex, or where there may be ongoing questions with regard to the impact of accrued data on the study design and participants' safety, particularly in studies with a long duration
- Studies where the data justify its early termination, such as the case of an intervention intended to reduce severe morbidity or mortality, which might turn out to have adverse effects or lack of effect, resulting in increased morbidity or mortality
- Studies carried out in emergency situations
- Studies which involve vulnerable populations

4.9 Not all studies within the above categories require DSMCs. Conversely, there may be other sound reasons for establishing DSMCs for certain studies that fall outside the above categories.
4.10 The IEC may also suggest to the sponsor that a DSMC be established for a particular study. Although the DSMC has no direct relationship with the IEC, all protocol revisions approved by the IEC should be submitted to the DSMC. Other site-specific amendments may require special treatment.

4.11 The IEC may request the PI to provide the DSMC with a periodic report.
Section 5

Monitoring of research given IEC approval

General policy on monitoring of research

5.1 IEC approval applies for the duration of the research. Nevertheless, it is the policy of the IEC that approval given to any research study should be kept under review. This normally involves the submission of annual progress reports and final reports.

5.2 However, the vast majority of studies conducted or coordinated by IARC consist of observational epidemiological studies where, after approval of the protocol by the ethics committee, the potential for causing harm to study participants or for raising other significant ethical or safety issues is negligible.

5.3 The IEC will therefore decide at the time of granting ethical approval whether each approved study is required or exempted from submitting annual progress reports and will communicate this decision to the investigators. The submission of a final report will be required in all cases.

Progress reports

5.4 In those cases where the IEC has requested the submission of progress reports, these should be submitted to the IEC annually, generally within six weeks of the anniversary of the IEC approval. The progress report consists of a simple declaration notifying the IEC of any ethical problems or adverse events which may have occurred during this period.

Safety reporting

5.5 In research, a Serious Adverse Event (SAE) is defined as an untoward occurrence that:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is otherwise considered medically significant by the investigator

5.6 An SAE occurring to a research participant should be reported to the IEC where in the opinion of the PI the event was:

- “Related” – that is, it resulted from administration of any of the research procedures
- “Unexpected” – that is, the type of event is not listed in the protocol as an unexpected occurrence
As a consequence, the study will be reconsidered.

Protocol deviations and violations

5.7 It is generally considered acceptable for a sponsor or PI to make (or permit other investigators to make) minor deviations from a protocol to deal with unforeseen circumstances. Such deviations do not need to be routinely reported to the IEC. However, if the deviation would meet the criteria for a “substantial amendment” as defined in paragraph 4.1, it should be promptly reported to the IEC. In particular, where the deviation is made to protect subjects from an immediate hazard to health or safety, this should be notified to the IEC as an urgent safety measure and reviewed accordingly.

Final reports

5.8 The IEC should receive a final report within one year of the research terminating. The final report includes information on whether the study achieved its objectives, the main findings and arrangements for publication or dissemination of the research including any feedback to participants.
Section 6

Appeal

6.1 A PI who considers that a decision of the IEC is flawed, and where there are substantial and compelling reasons, may appeal that decision in writing to the IEC within one month of receipt of the decision, stating the precise issues upon which the appeal is based.
Annex I

Site-specific assessment

Definition

3.13 Recruitment of participants or patients by external collaborators at each research site requires an assessment of the suitability of the site(s). This is not a separate ethical review, but part of the single ethical review of the research. Where there is no objection on site-specific grounds, a research site may be approved as part of the favourable ethical opinion.

The PI at each research site

3.14 In the case of any single or multi-site research, the investigator responsible for the conduct of the research at an individual research site will be known as the PI for that site. There should only be one PI at each site.

3.15 It is the responsibility of the PI at IARC to ensure that a suitably qualified professional with authority sufficient for the requirements of the protocol is appointed as the PI for each site. Any actions that fall directly within the informed consent process require the appointment of a PI at the collaborating research site.

Actions at research site

3.16 It is recommended that research site-specific PIs should normally be appointed in each case where there is delegation of responsibility to local collaborators to give information about the research to potential participants, to answer their questions, and to take written consent and/or data from them. Any actions that fall directly within the informed consent process require the appointment of a PI.

Issues relevant to the site-specific assessment

3.17 In making a site-specific assessment, the main issue to be considered is the suitability of the site for the conduct of the research. This involves consideration of the following:

- The suitability of the PI, taking into account his/her professional qualifications, knowledge of the research field, expertise in the procedures involved, previous research experience and ability to take any clinical responsibility for the local research team
- The adequacy of the local facilities available for the research
- The arrangements for notifying other local health care staff, who may have an interest in the care of the participants, about the research
- The availability of any extra support that might be required by the researcher as a result of their participation
• The local arrangements for making legal representatives available to give informed consent on behalf of minors or adults unable to consent for themselves, where this is required for the research
• The practical arrangements to be made at the site for providing information to potential participants who might not adequately understand verbal explanations or written information given in the local language, where it is planned to include such groups in the study as a whole
• Liability issues

Monitoring of research sites

3.18 The provision of ethical approval by the IEC for any study does not imply any responsibility of the IEC to assure its commencement or completion.

3.19 If information comes to the attention of the IEC that raises questions about the suitability of the site or investigator, the approval for the site must be reviewed.

Acknowledgement:

This document was adapted from that of the UK Central Office for Research Ethics Committees, Version June 2005. Available online at www.corec.org.uk