International Agency for Research on Cancer

World Health Organization

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 by IARC staff or external investigators using IARC samples and/or data. Through its international composition and the inclusion of members with a variety of backgrounds, the IEC ensures, to the extent possible, the international consistency and completeness in ethical approval.

These Standard Operating Procedures (SOPs) provide a framework and guidance for the IEC, the Secretariat, and the investigators submitting an application. They should be read in complement with other relevant documents such as the IEC Rules and Procedures.

List of abbreviations

COI: Conflict of Interest
DTA: Data Transfer Agreement
EAV: Ethics Advisory Group
IEC: IARC Ethics Committee
MTA: Material Transfer Agreement
PI: Principal Investigator
SOPs: Standard Operating Procedures

Section 1

Meetings of the IARC Ethics Committee

1.1 IARC Ethics Committee (IEC) meetings are arranged by the Secretariat, which is responsible for all administrative aspects of the ethics review process including the pre-screening of applications. The Secretariat of the IEC is provided by the Director's Office.

1.2 Meetings to review applications are held 5 times per year at IARC. Members that cannot be physically present may attend the IEC meetings remotely by videoconference.

1.3 The **quorum** for IEC meetings is seven members. Meetings require the attendance of a majority of external (non-IARC staff) members and of at least one lay member[1]. In the absence of the IEC Chair and Vice-Chair one external member appointed by the other members attending, may act as Chair.

Declarations of interest of Committee members

1.4 To ensure the IEC complete objectivity in its proceedings, the following is required:

- On an annual basis, external IEC members must declare any generic potential Conflict of Interest (COI)[2] by completing a "Declaration of Interests for IARC/WHO Experts" form. They are required to inform the Secretariat of any changes that may occur in the intervening time.
- In advance of each meeting and at receipt of the review assignment, each IEC member must declare any potential COI in relation to specific applications being evaluated (e.g. he/she is the Principal Investigator – PI, a collaborator, or is in any other way linked to the study being evaluated).

1.5 If an IEC member has declared a COI in relation to a particular study, he/she takes no part in the decision on that study. Where the Chair has a potential COI, that item(s) will be chaired by the Vice-Chair or by another external member of the committee in his/her absence.

1.6 The minutes should record all declarations of interest and decisions of the IEC on the procedure followed.

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[1] The composition of the IEC is described in Section III of the Rules and Procedures.

[2] The IARC Guidelines for Declaration of Interests (IARC/WHO Experts) defines a conflict of interest as "any interest declared that may affect or reasonably be perceived to (1) affect the expert's objectivity and independence in providing advice to IARC/WHO, and/or (2) create an unfair competitive advantage for the expert or persons or institutions with whom the expert has financial or business interests (such as adult children or siblings, close professional colleagues, administrative unit or department)."

Review of applications

1.8 The review of each application is led by two members of the IEC assigned to act as lead reviewers. The *primary reviewer* provides a full assessment of the study; the *deputy reviewer* supplements as needed and acts as primary reviewer in case of his/her absence.

1.9 The lay members will not be appointed as primary reviewers and may be appointed as deputy reviewers. They will participate fully in all discussions and will evaluate aspects relevant to study participants (e.g., purpose of study, potential risks and/or discomfort for the study subjects, the likelihood of getting useful results, mechanisms put in place to ensure privacy and confidentiality, etc.). In particular, they will review in-depth the Informed Consent Forms, as well as projects with expected high impact on the population and unexpected ethical concerns.

1.10 Whenever possible the Committee 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 and Vice-Chair. In these cases, the decision of the Committee should be determined by a two thirds majority of those members present and entitled to vote as in paragraph 1.5. In the event of a split decision, the Chair has the deciding vote.

1.11 Any member that wishes to record formal dissent from the decision of the IEC can ask for this to be recorded in the minutes.

Attendance of the PI

1.12 The PI may be invited to attend part of the meeting, also by remote means, at which his/her application will be reviewed, in order to respond to requests from the Committee for further information or clarification. The PI should not be present during the deliberations of the Committee.

1.13 When the PI is unable to attend, another IARC investigator or collaborator, but not a representative of the sponsor, may attend instead, subject to agreement by the IEC Chair.

Confidentiality of proceedings

1.14 Members must be able to discuss freely the applications submitted and the discussions held during IEC meetings must remain confidential. Any breaches of confidentiality by members will result in termination of their membership.

1.15 Minutes and decisions of the IEC shall remain in restricted circulation and should not attribute particular statements to individual members, except when requested by a member (see paragraph 1.11).

1.16 Documents circulated by the Secretariat should be treated as confidential by

the IEC members.

Responsibilities of the Secretariat

1.17 The responsibilities of the IEC Secretariat are as follows:

- preparing and issuing the schedule of IEC meetings;
- issuing announcements and calls for applications;
- receiving applications and reviewing them to ensure completeness;
- contacting PIs in case additional information relevant to the discussion of their application is needed;
- assessing and issuing notifications, in collaboration with the IEC Chair and Vice-Chair as needed;
- assessing submissions eligible for expedite review and circulating them to the IEC Chair and Vice-Chair for review, and to the assigned reviewers if applicable;
- preparing the draft agenda for the meetings. The agenda will include: the assigned reviewers based also on potential COIs, list of submitted projects including a brief description of the study and any issue preliminary identified and discussed with the PI, and any other topic of interest to the IEC;
- distributing the agenda, project submissions and other meeting documents;
- arranging travel and accommodation for external IEC members, if needed;
- meeting logistics;
- recording attendance to the meeting and verifying that the quorum is met;
- advising the meeting as necessary on compliance with IEC's RAPs and SOPs;
- providing support to, working in conjunction with, and advising the IEC Chair, Vice-Chair and Committee members on administrative and procedural matters;
- preparing the minutes of the meeting (see paragraphs 1.18-1.20);
- notifying PIs of decisions taken at the meeting within 15 working days of the meeting;
- following-up on PIs' replies to IEC decisions;
- maintaining, updating and developing the IEC database and the IEC governance documents;
- advising and following up on ethics training of IEC members and liaising and maintaining the EAV, composed of senior external experts in support to the IEC; and
- horizon-scanning for potential new members and for possible changes required in the IEC procedures due to changing international or IARC/WHO practices.

Minutes

1.18 The minutes of the meeting shall contain a record of the following:

- attendance of the members;
- any declared COI and the decision of the Committee on the participation of the member concerned;
- a summary of the discussion of the main ethical issues considered for each study;
- the decision of the IEC on the applications: 'Approved', 'Conditionally

approved' or 'Not approved' (see paragraph 4.1);
- the comment(s) to be given to the PI;
- the outcome of any vote taken and any formal dissent from a decision of the Committee by a named member, if any;
- any other topics discussed by the IEC and action items.

1.19 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.

1.20 Copies of the approved minutes of the IEC will be made available to the IARC Governing Council upon request but shall otherwise remain confidential.

Section 2

Submission of applications

2.1 Applications for IEC review are submitted by the study's PI. The closing date for applications is no later than 15 working days prior to each IEC meeting.

2.2 The IEC will only review complete applications, including the study proposal, informed consent forms and local ethical approvals (as detailed in Section 3). Before applications are submitted to the IEC, they will be reviewed by the Secretariat and any incomplete application will be returned to the PI for completion.

2.3 The following categories of application are available to the PIs (see Section 3 for detailed description and documents to be included with each application):

- Regular submission;
- Expedite review; and
- Notification.

Applications submitted by IARC PIs

2.4 The PI is responsible for:

- submitting all documents in English as the working language of the IEC. Studies conducted in French language must submit the IEC questionnaire in English but additional study documents may be submitted in French (given it is also an official language of IARC). Documents submitted in other languages will not be reviewed by the IEC;
- submitting a full application, including all relevant enclosures (see Section 3);
- collecting relevant information and documents from all the study sites and in particular the Informed Consent Forms, local ethical clearances, approval under the applicable national law, and processing Material and Data Transfer Agreement (MTA/DTA) forms[3] with the relevant IARC Units;
- preparing and submitting an Annual Progress Report, when applicable;
- ensuring that the implementation of the study at the local sites complies with the ethical standards and with any applicable good clinical[4] or epidemiological practice standards;
- ensuring that the use being made of personal data and samples and the conditions for their storage and process, are consistent with:

[3] IARC MTA/DTA Templates available at http://intra.iarc.fr/policies-and-procedures/Standard-Agreement-Templates

[4] Clinical intervention trials should be conducted according to the IARC/WHO Policy on clinical trials registration and public disclosure of results.

- the IARC/WHO Policies on data protection[5];
- the relevant national regulations; and
- overall the transparency and security about data processing, the participants' right to access, restrict, rectify or erase personal data, and the data protection by design and by default[6];

- ensuring that local PIs and project personnel are trained at an appropriate level to conduct the study and have been trained in the study procedures;
- being prepared to respond to specific requests from the IEC in person on in writing;
- informing other involved bodies/entities, such as collaborators or funding institutions, of relevant decisions taken by the IEC; and
- accepting responsibility, together with collaborators and their institution(s), for the conduct of the study and ensure that adequate insurance is in place to cover any eventual liability.

2.5 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 will consider whether special insurance is necessary for particular studies (interventional or observational).

2.6 The IEC should be immediately notified by the PI of any ethical issues that have arisen in the course of the study, for example serious adverse events or concerns raised by local ethics committees.

2.7 In the case of prolonged absence from work, the PI is responsible for ensuring that his/her responsibilities are delegated to a suitable temporary replacement, and that that replacement is identified to the Secretariat.

2.8 Approval by the IEC does not attest compliance with the law of the countries involved. It is the responsibility of the PI to ensure compliance with local legal and ethical requirements, and that administrative approval to proceed with the research has been obtained from relevant organizations (e.g. health services).

[5] Confidential information must be processed in compliance with the IARC Information Classification Policy and relevant WHO Policies.

[6] In agreement with General Data Protection Regulation, Art. 25.

Applications submitted by non-IARC PIs

2.9 Samples or data collected for IARC studies may occasionally be used for additional studies that have no direct involvement of IARC scientists[7]. In these cases, the application for IEC review might be submitted either by the external PI of the new study or by the IARC staff member responsible for the samples or data (IARC Custodian) on behalf of the external PI.

2.10 In addition to the standard procedures and required documents (see Section 3) applications submitted by external PIs should include:

- the IEC questionnaire completed and signed by the external PI;
- memo to the IEC from the IARC PI/Custodian of the original IARC study confirming his/her agreement for the use of the samples/data;
- IEC references of the original IARC study and copies of the ethics approval of the original IARC study, and of its Informed Consent forms; and
- copy of the 'transfer agreement forms'[3] submitted to IARC with the request for access to the samples or data.

[7] See "IARC Policy on Access to Human Biological Materials" and the "Sample access standard operating procedure" (available on the IARC Biobank website - http://ibb.iarc.fr/) for the principles and procedures governing access to samples stored in the IARC Biobank.

Section 3

Type of submission to the IEC

Regular Submission

3.1 The following types of study should be submitted to the IEC through the regular submission procedure:

- **new studies or collection of new material** (including descriptive studies, surveys, studies on cancer registry data, and studies on outcomes other than cancer);
- **studies on previously collected data and stored samples**, including data from questionnaires, from previous biomarker analyses, or from medical records **submitted by a non-IARC PI** (if EPIC studies see paragraph 3.3);
- **studies on stored samples** from studies previously approved by the IEC for their initial use/application and **that will perform new biological analysis and/or make use of new technologies** (if EPIC studies see paragraph 3.3); and
- **pooled analysis of data** from studies not previously approved by the IEC;
- **substantial amendments** (procedural changes that may alter the risk or the potential benefit to study participants and may have important ethical implications) to studies previously approved by the IEC:

    a. changes in the use and/or quantity of biological samples;
    b. a change of sponsor(s) or sponsor's legal representative;
    c. appointment of a new PI or key collaborator, either at IARC or at a local research site;
    d. a change to the definition of the end of the study;
    e. a change in the purpose or objective of the research, such as introduction of additional genetic studies;
    f. a substantial change in research methodology;
    g. a change to the responsibility and liability insurance coverage for the study;
    h. introduction of new classes of investigations or other interventions (rather than simply re-scheduling or modifying those already approved); or
    i. recruitment of a new type of participant, especially if these would be regarded as being from vulnerable groups; and
    j. protocol violations (accidental or intentional changes to the approved study protocol which may increase risk or decrease benefit to the research participants and that may affect their rights, safety or welfare and/or on the integrity of the data) should be notified to the IEC as an urgent safety measure, and in particular, where the change is made to protect subjects from an immediate hazard to health or safety.

Procedure for regular submission

3.2 The PI should submit a memo to the IEC. The memo should be accompanied by:

- completed IEC questionnaire;
- study outline/protocol (including sample size and power calculations where appropriate);
- informed consent forms, where appropriate;
- national and local ethics committees' approvals, including comments and conditions, or evidence of submission;
- an account of national legislation on human research ethics and data protection, where appropriate;
- any other relevant documentation;
- for resubmissions or amendments provide all previous IEC references/registration numbers related to the study; and
- for multicentric studies pooling previously collected data provide, in addition to the generic documents above, a flow-chart showing how data and/or samples will be managed and shared between the different centres, and clearly state in the application the role of IARC in the study.

Expedite review

3.3 The following categories of studies which are judged not to present potential threats in terms of the rights and welfare of study participants may be submitted to the IEC through the expedite review procedure:

- **on special request by the PI** (e.g. if there is an urgent grant deadline);
- **European Prospective Investigation into Cancer and Nutrition (EPIC) studies** that will perform new biological analysis and/or make use of new technologies and/or that are submitted by a non-IARC PI; and
- **minor amendments** (procedural changes that are unlikely to alter the risk or the potential benefit to study participants and that do not entail ethical implications) to research previously approved by the IEC:

    a. small changes of negligible impact on the main study protocol that are made prior to the start of study recruitment;
    b. minor amendments that do not involve changes to the protocol;
    c. small changes to the design or methodology of the study, or to background information affecting its scientific value;
    d. small changes to the procedures undertaken by participants;
    e. small 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; or
    f. protocol deviations (accidental or intentional changes to the approved study protocol to deal with unforeseen circumstances, which do not increase risk or decrease benefit to the research

participants and do not have a significant effect on their rights, safety or welfare and/or on the integrity of the data).

3.4 In cases where the Chair and Vice-Chair, and the assigned reviewers if applicable, judge there are no potential ethical implications of the minor amendment or new study, they may approve the proposal. Approval will be communicated to the members of the IEC at the following meeting.

3.5 All requests not given expedited approval will be required to be submitted as a regular application (see paragraphs 3.1., 3.2).

Procedure for expedite review

3.6 The PI should submit a memo to the IEC requesting the expedited approval of the study. The memo should be accompanied by:

- the reason of the request for an expedited review;
- any implications of the proposed request for the safety or welfare of participants;
- the detailed proposal (for EPIC Studies: the PF1) and the protocol;
- the relevant national and/or local ethics committees' approvals (for EPIC studies: approval by the EPIC Steering Committee);
- any changes that affect the terms or the appropriateness of the original Informed Consent or of other original information documents given to the study participants;
- in cases whether a re-consent may be required, the possibility of tracing and re-contacting the study participants, or the waiver of consent approved by the local ethics committee; and
- IEC reference of the original IARC study and copies of the ethics approval of the original IARC study and of its Informed Consent forms (if applicable).

Notification

3.7 The following categories of studies which are judged not to present potential threats in terms of the rights and welfare of study participants may be submitted as a notification to the IEC Secretariat:

- **studies having received a previous ethical approval, using only previously collected data** (including data from questionnaires, from previous biomarker analyses, or from medical records) for a new purpose or to test a new hypothesis not envisaged at the time the original consent was obtained. This applies to studies submitted by an IARC PI (regular submission is required for studies submitted by a non-IARC PI; see paragraph 3.1);
- **methodological and quality assurance studies** which do not present any potential ethical implications;
- **studies collecting anonymous data** without any identifiers associated or linked to an individual and that do not present issues related to privacy and confidentiality. The protocol must demonstrate

that such studies are permissible by national law; and
- **studies on population aggregated information**.

3.8 In cases where the Secretariat identifies minor potential ethical implications, the study will be submitted to the Chair and Vice-Chair for review. Approval will be communicated to the members of the IEC at the following meeting.

Procedure for notification

3.9 The PI should submit a memo to the IEC, accompanied by:

- an abstract of the proposed study summarizing its objectives, research hypothesis, scientific rationale and methodology (for EPIC Studies: the PF1);
- power and sample size calculation (if applicable); and
- IEC reference of the original IARC study and copies of the relevant national and/or local ethics committees' approvals (for EPIC studies: approval by the EPIC Steering Committee), and of its Informed Consent forms (if applicable).

Section 4

Decisions available to the IEC

4.1 The IEC should reach one of the following decisions on each application:

- *Approved*
    - the IEC may set minor recommendations;
- *Conditionally approved*
    - the IEC sets requirements to submit additional information, clarification or modification, and
    - may set recommendations;
- *Not approved*
    - the IEC sets the requirement to substantially revise and re-submit at a subsequent meeting.

4.2 The decisions may be accompanied by two types of comments (a summary of the ethical issues considered by the IEC):

- **recommendations** or advices given by the IEC which do not condition the approval of the study; and/or
- **requirements** to provide additional information/documents, clarification or modification which condition the approval of the study.

4.3 Where the IEC decides to set comments, the Chair or Vice Chair will ensure that this information is specifically identified and included in the minutes. The wording and content of the comment to the PI should be agreed upon during the meeting, specifying the ethical principles underlying the decision whenever possible.

4.4 A project that is 'conditionally approved' may be partially initiated (e.g. at specific centres), if the approval IEC requirements are provided by the PI.

4.5 The PI's answers to the requirements or recommendations set in case of a 'conditional approval' or 'approval with minor recommendations', may be expedite reviewed by the IEC Chair and Vice-Chair, and assigned reviewers if applicable, or submitted for review at the next Committee meeting as needed.

4.6 A project 'not approved' might be resubmitted through the regular procedure, if the IEC reasons for the decision and required further information or action are provided by the PI.

Notification of the IEC's decision to the PI

4.7 The Secretariat will notify the PI in writing of the decision of the IEC. All notification letters will be in the name of the Chair.

4.8 The decisions should be communicated to the PI within 15 working days of the meeting. In case of delay in preparing the full notifications, PIs may request informal access to the decision from the Secretariat, with the understanding that the full notification will be sent as soon as feasible.

4.9 The following information will be included in the notification letter or its enclosures:

- the decision of the IEC;
- the comments/summary of the ethical issues considered by the IEC;
- requirement for annual reports, if applicable, and the due date for its submission.

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. 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.

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. These studies do not warrant a regular follow-up by the ethics committee during their progress.

5.3 The IEC will 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.

5.4 Categories of studies that would typically require the submission of an annual progress report include:

- intervention studies and clinical trials[8] (participants may be subject to risks/adverse events);
- studies using new emerging technologies (may lead to incidental findings, false positives/negatives);
- studies with implications on confidentiality (potential identifiability of subjects); and
- studies with potential for incidental findings.

Annual Progress Reports

5.5 Studies required to submit an annual progress report should done so generally within six weeks of the anniversary of the IEC approval. For studies that must also submit an annual report to a Data and Safety Monitoring Board (DSMB) or to the funding agency, the PI may request that the calendar of reporting to the IEC be aligned with the DSMB's/funder's schedule.

5.6 The annual progress report consists of a simple declaration from the PI notifying the IEC of any ethical problems or adverse events which may have occurred during this period.

[8] The IEC follows the NIH definition of a clinical trial: "A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes".

5.7 For intervention studies and clinical trials the annual report should also include:

- a copy of the DSMB report;
- the scheduled inclusion of subjects versus the actual inclusion;
- the trial ID or registry identifier code/number;
- the final version of the protocol; and
- overall compliance to the IARC/WHO Policy on clinical trials registration and public disclosure of results.

Safety reporting

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

- 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; or
- is otherwise considered medically significant by the investigator.

5.9 A SAE occurring to a research participant should be reported as soon as possible by the PI to the study's DSMB and to the IEC, together with his/her assessment of whether the event was:

- related/unrelated (resulted from administration of any of the research procedures); and
- expected/unexpected (the type of event is not listed in the protocol as an expected occurrence).

5.10 The IEC will review the DSMB's assessment of the SAE and determine if the study's ethics approval needs to be reconsidered.

Section 6

Appeal process

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

6.2 The IEC will have the option of inviting the PI to explain his case and, if necessary, referring the appeal to an external group of experts for an opinion (see RAPs document).

6.3 The IEC will provide a written reply to the PI within 15 days addressing the issues raised, and either confirming and justifying its position or issuing a revised decision.

Acknowledgement:

The first version of this document (18 May 2006) was originally adapted from the UK Central Office for Research Ethics Committees (June 2005, available at http://webarchive.nationalarchives.gov.uk/20130107105354/http://dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4112417.pdf).

Annex 1: Types of submission to the IEC

	Type of submission		
Type of study	**Regular**	**Expedite**	**Notification**
New study or collection of new material* **including descriptive study, survey, study on cancer registry data, or on outcomes other than cancer*.	X		
Methodological and quality assurance study. Study on population aggregated information. Study on anonymous data* **the protocol must demonstrate that such study is permissible by national law*.			X
Amendment to already approved protocol/study.	Substantial amendment and/or request not given expedite approval by the IEC.	Minor amendment	
Study on previously collected data* where consent for storage and future use was specifically provided. **such as data from questionnaires, previously measured biomarkers, or medical records*.	➢ Only if: • The study is proposed by a non-IARC PI; • Pooled analyses of data from studies not previously approved by the IEC.	EPIC study submitted by a non-IARC PI	X
Study on previously collected data/stored samples that will perform new biological analysis and/or make use of new technologies.	X	EPIC study	