Guidelines and Recommendations for European Ethics Committees

European Forum for Good Clinical Practice

'A Place to Meet'

Revised Edition

TABLE OF CONTENTS

PREFACE

This document is the result of research and discussion by the Ethics Working Party of the European Forum for Good Clinical Practice. It represents a proposal of guidelines and recommendations for European ethics committees involved in the evaluation of biomedical research. These guidelines and recommendations are focused on assisting in the ethical review of clinical trials involving medicinal products and substances. However, they should also prove useful to ethics committees involved in other areas of biomedical research.

The aim is to provide complementary guidance and support to the *Declaration of Helsinki* and to international Good Clinical Practice guidelines currently in use in Europe, taking into account the CPMP *Note for Guidance: Good Clinical Practice for Trials on Medicinal Products in the European Community* as well as the more recent *Guideline for Guidance on Good Clinical Practice* from the International Conference on Harmonization. The guidelines and recommendations provided here are introduced as a common standard that does not limit local autonomy. No question arises of challenging or replacing existing national or international recommendations and requirements.

Text in italics indicates recommendations from the European Forum for Good Clinical Practice, in contrast with the proposed core guidelines.

This revised edition has benefited greatly by comments received from experts throughout Europe and indeed the world. The European Forum for Good Clinical Practice (EFGCP) continues to invite comment from those having experience or a special interest in the ethical evaluation of biomedical research in Europe.

1. OBJECTIVE

The objective of these guidelines and recommendations is to establish a greater degree of scientific efficacy and procedural responsibility in the practices of Ethics Committees (ECs) in Europe. The document is intended as a basis upon which ECs can develop their own specific written procedures for their functions within biomedical research. In this regard, the document establishes minimum guidelines and recommendations for ECs to use in defining or revising standard operating procedures.

The purpose of an EC is to safeguard the welfare and the rights of human subjects in biomedical research studies, taking into account the scientific procedure and the concerns of the local community.

ECs provide timely, comprehensive, and independent reviews of the ethics of proposed studies, acting in accordance with the Declaration of Helsinki and following international standards for Good Clinical Practice.

ECs are responsible for acting with due regard to the requirements of relevant regulatory agencies, applicable laws, and in good faith with respect to both applicants and the community.

2. PROCEDURE FOR CONSTITUTING AN EC

ECs are to be constituted to ensure a competent review of all ethical aspects of the protocols they receive, and are to be constituted to ensure that their tasks can be executed free from bias and influence that could affect their objectivity. These guidelines and recommendations provide a general guide as to how ECs are to be minimally constituted. Local laws, regulations, and guidelines may provide more specific guidelines, in which case they are to be incorporated into local practices.

ECs are to specify in writing the authority under which the committee is established, membership requirements, the terms of appointment, the conditions of appointment, the offices, and the quorum requirements.

A. Membership Requirements

A statement of the requirements for candidature as a member of an EC that includes an outline of the duties and responsibilities of an EC member.

A procedure for making appointments including, but not limited to,

i. the name or definition of the party or individual responsible for making appointments and their/its affiliations
ii. the procedure for selecting candidates
iii. a definition of the method for choosing a candidate (e.g., by consensus, by majority vote, by direct appointment)

It is recommended that ECs not be appointed by individuals or institutions having a vested interest in the conduct or outcome of proposed research, such as sponsors or investigators.

B. Terms of Appointment

A statement of the terms of appointment that includes, but is not limited to,

i. the duration of an appointment
ii. the policy for renewal of an appointment
iii. the disqualification's procedure
iv. the resignation procedure
v. the replacement procedure

C. Conditions of Appointment

A statement of the conditions of appointment that includes, but is not limited to,

i. a member must voluntarily withdraw from the EC for the decision procedure concerning an application where there arises a conflict of interest; the conflict of interest is to be indicated in writing to the chairperson prior to the review and recorded in the minutes
ii. a member must be willing to publicise her/his full name, profession, affiliation, age, and gender
iii. all reimbursement for work within or related to an EC must be made known in writing to the chairperson and available (through the chairperson) to the public upon request
iv. a member must sign a confidentiality agreement covering information regarding applications and subjects

D. Officers

A statement is required of the officers within the EC (e.g., chairperson, secretary, treasurer), the requirements for holding each office, the terms and conditions of the office, and the duties and responsibilities of each office (e.g., agenda, minutes, sending notification of decisions, filing, archiving).

A statement is required of all administrative support provided by persons who are not members of the EC.

It is recommended that an EC minimally appoint a chairperson and assure the availability of a secretary.

E. Quorum Requirements

ECs are to establish specific requirements for a quorum: the minimum number and composition of members required to participate in the review of and decision on an application. Quorum requirements include, but are not limited to,

i. the establishment of a minimum number of EC members required to compose a quorum
ii. the establishment of a maximum number of EC members allowed to participate in the review of and decision on an application
iii. the professional qualifications requirements (e.g., physician, lawyer, statistician, paramedical, layperson) and the distribution of those requirements over the quorum
iv. the gender distribution requirements for the quorum
v. the age distribution requirements for the quorum

It is recommended that a minimum of five persons be required to compose a quorum. There is no widely accepted maximum number of persons, but an EC should consider that reaching decisions is more difficult when large numbers of individuals are involved. Twelve is a recommended maximum.

It is recommended that the quorum be composed as follows:

i. two physicians, sharing between them:
- *experience in biomedical research conducted according to GCP*
- *independence from the institution where the research is carried out*
- *currently practising*

ii. one layperson

iii. one lawyer

iv. one paramedical: e.g., nurse, paramedic, pharmacist

It is recommended that both sexes, a wide age range, and the cultural make-up of the local community be represented in the quorum.

It is recommended that the distribution of qualifications is to be respected over the whole of the membership of an EC.

3. PROCEDURE FOR SUBMITTING AN APPLICATION

ECs are responsible for establishing well-defined submission procedures that are readily available to prospective applicants.

A. Applicant

An application for a review of the ethics of proposed biomedical research is to be submitted by a qualified physician or dentist responsible for the scientific and ethical aspects of the research (e.g., an investigator or a representative of the sponsor).

B. Application Procedure

ECs are required to have publicly available guidelines for the submission of an application for the review of the ethics of proposed biomedical research. These guidelines include, but are not limited to,

i. the name(s) and address(es) of the EC member(s) to whom the application material is to be submitted
ii. the number of copies to be submitted
iii. the language(s) in which (core) documents are to be submitted
iv. the required application form(s)
v. the required documentation (see 3.C)
vi. the required format
vii. the deadlines for review dates
viii. the means by which applicants will be informed of incompleteness
ix. the fee structure for considering an application and the follow-up, when applicable

C. Required Documentation

All documentation required for a thorough and complete review of the ethics of proposed research is to be submitted by the applicant. This includes, but is not limited to,

i. application form(s) (when required by the EC), as defined in 3.B.iv.
ii. protocol of the proposed research (clearly identified and dated), together with supporting documents and annexes
iii. a diagrammatic representation (“flowchart”) of the protocol
iv. an adequate summary of all pharmacological and toxicological data available on the drug, together with a summary of clinical experience with the drug to date (e.g., recent investigator’s brochure, a summary of the product's characteristics)
v. recent investigator(s)’s curriculum vitae (signed and dated)

vi. material used (including advertisements) for subject (patient/volunteer) recruitment
vii. subject (patient/volunteer) information (in local language and, when required, in English)
viii. informed consent form (in local language and, when required, in English)
ix. indemnity agreements for liability
x. proof of regulatory compliance, when required
xi. case report forms, diary cards, and other patient (subject) questionnaires
xii. all significant previous decisions (e.g., those leading to a negative decision of changed protocol) by other ECs for the proposed study (whether in the same location or elsewhere)
xiii. all rewards and compensations made to subjects

It is recommended that ECs require the applicant to include a statement certifying that investigators and their families have no vested interest in the outcome of the study.
In cases where there is a potential conflict of interest, applicants are to disclose the nature of the potential conflict and describe the steps taken to minimise a bias reporting of results.
It is recommended that ECs do not require full disclosure of payments to investigators, nor that ECs uniformly require investigators to divest any financial interests they have in the sponsor's company or product.

D. Registration of Applications

ECs are required to follow a registration procedure for all incoming applications. This procedure includes, but is not limited to,

i. dating all incoming material
ii. filing all incoming material
iii. checking for the formal completeness of an application
iv. informing the applicant in the case of an incomplete application
v. informing the applicant of the expected date of review of a complete application
vi. informing all EC members of the review date of an application
vii. maintaining a record of all communications regarding applications (whether written, verbal, or electronic)

4. REVIEW PROCEDURE

All properly submitted applications are to be reviewed in a timely fashion and according to the established review procedure.

A. Meeting Procedure

ECs are to meet in accordance with published meeting dates scheduled regularly. The established quorum requirements are to be met prior to the review of applications.

It is recommended that ECs meet every 4 weeks and never less than 6 times per year.

Meetings are to follow a previously scheduled agenda, amended where appropriate.

Meetings are to be minuted. There is to be an approval procedure for the minutes.

When appropriate, the applicant, sponsor, and/or investigator are to be invited to present the protocol in the meeting.

When appropriate, outside experts (e.g., researchers with specific competencies, ethicists, statisticians) are to be invited to assist at the meeting.

When appropriate, representatives of special patient groups or interest groups (.e.g., in studies concerning pregnancy or AIDS) are to be invited to assist at the meeting.

B. Elements of the Review

The EC is to take the following considerations into account in its review:

i. the thoroughness and completeness of the information submitted and its ability to respond to ethical questions arising within the context of the study

ii. the suitability of the protocol and the data collection forms in relation to the objectives of the study (taking into account applicable rules and regulations), the statistical analysis, and the scientific efficiency, that is, the potential for reaching sound conclusions with the smallest possible exposure of subjects, and the justification of predictable risks and inconveniences weighed against the anticipated benefits for the subjects and/or others

iii. the suitability of the investigator for the proposed study in relation to her/his qualifications, and experience

iv. the adequacy of the site, including the supporting staff, available facilities, and emergency procedures

v. the adequacy of medical supervision and follow-up concerning the subjects

vi. the adequacy of provisions made for monitoring and auditing the conduct of the research

vii. the adequacy, completeness, and understandability of written and oral information to be given to the subjects, their relatives, guardians, and (if necessary) legal guardians

viii. the means by which initial recruitment is to be conducted, and by which full information is to be given, and by which consent is to be obtained

ix. the content and the wording of the informed consent form and, when applicable, the provisions made for subjects incapable of giving personal consent

x. assurances that subjects will be informed of any information of relevance to them becoming available during the study

xi. the provisions made for receiving and responding to queries and complaints of subjects during the course of a study

xii. the provisions for compensation/treatment in the case of the injury/disability/death of a subject attributable to participation in the study

xiii. the insurance and indemnity agreements covering the liability of the investigator by the sponsor

xiv. assurances that the subjects' GP's will be informed, where appropriate and with consent from the subject (patient/volunteer)

xv. the measures taken to insure the confidentiality of personal subject information

xvi. the rewards and compensations for subjects

5. DECISION-MAKING PROCEDURE

An EC's decision may only be taken when sufficient time has been made for review and discussion following the removal of all third parties from the meeting.

An EC is to assure that the documents are complete and that the elements mentioned above (4.B.) are considered before a decision is made.

An EC is to follow a pre-defined method for arriving at a decision (e.g., by consensus, by vote).

It is recommended that decisions be arrived at through consensus. When a consensus appears unlikely, it is recommended that the chairperson calls for a vote with a two-thirds majority required for decision.

An EC may append an advice to the decision that is non constraining.

In cases of conditional decisions the EC is to specify the requirements for the implementation of the decision that are constraining.

In cases where a decision is taken without the full consent of all members of the EC present, all dissenting members are to be given an opportunity to append an opinion to the EC's decision.

A negative decision on an application is to be supported by clearly defined reasons.

6. PROCEDURE FOR COMMUNICATING A DECISION

A decision is to be communicated in writing to the applicant within two weeks time of the meeting at which the decision took place.

The decision is to include, but is not limited to, the following

i. the exact title of the research project/trial reviewed
ii. the identification number and/or date of the protocol that the decision is based on
iii. the names and (where possible) specific identification numbers of the documents reviewed, including informed consent form
iv. the name and title of the applicant
v. the date and place of the decision
vi. the name of the EC taking the decision
vii. the name of the chairperson of the EC
viii. the names of the members participating in the decision
ix. a clear statement of the decision reached
x. any advice, opinions, or requirements adjoined to the decision by the EC
xi. clearly defined reason(s) for requirements
xii. in the case of a positive decision, a statement of the responsibilities of the applicant (e.g., confirmation of the acceptance of any requirements imposed by the EC; the need to notify the committee in the cases of amendments to the protocol likely to affect its decision, of serious or unexpected adverse events, of unforeseen circumstances, of the termination of the study, of the outcome of the study, of any significant decisions by other ECs)
xiii. clearly defined reason(s) for a negative decision
xiv. signature (dated) of the chairperson of the EC

7. FOLLOW-UP PROCEDURE

ECs are responsible for establishing a review procedure for following the progress of all studies (for which a positive decision has been reached) from the time the research commences through its termination.

The ongoing lines of communication between the EC and the applicant are to be clearly specified.

ECs are to indicate the quorum requirements, the review procedure, and the communication procedure for follow-up reviews, which may vary from the requirements and procedures for the initial decision on an application.

A. Follow-Up Review Intervals

The follow-up review intervals are to be determined by the nature and the events of the studies. Each protocol is to undergo a follow-up review at least once a year.

B. Instances Requiring a Follow-Up Review

The following instances or events require the follow-up review of a study:

i. any amendment to the protocol likely to affect the safety of the subjects or the conduct of the study
ii. serious and unexpected adverse events in human subjects and the response taken by regulatory agencies, investigators, and sponsors
iii. any event or new information that may affect the benefits/risks ratio of the protocol.

The EC is responsible for responding to all notifications of instances or events affecting the progress of an approved study.

A decision of a follow-up review is to be issued and communicated to the applicant, indicating either a reversal of the EC's original decision or confirmation that the decision is still valid.

C. Study Termination

An EC may decide to reverse its positive decision on a study if information emerges that adversely affects the benefits/risks ratio.

ECs are to require notification from the applicant at the time of the completion of a study.

It is recommended that ECs require a copy of the final report of studies completed.

In the case of the premature termination of a study, notification is to include the reasons for termination. A summary of any results obtained on a study prematurely terminated is to be communicated to the EC.

8. DOCUMENTATION AND ARCHIVING PROCEDURE

All documentation and communications of an EC are to be dated, filed, and archived according to written procedures. A statement is required defining the access and retrieval procedure (including authorised persons) for the various documents, files, and archives.

Documents to be filed and archived include, but are not limited to,

i. the constitution, historical documents, and the SOPs of the EC
ii. the curriculum vitae of all EC members
iii. a record of all incomes and expenses of the EC, including allowances and reimbursements made to EC members
iv. the published guidelines for submission established by the EC
v. all materials submitted by an applicant
vi. all correspondences by EC members with applicants or concerned parties regarding application, decision, and follow-up.
vii. the agenda of all EC meetings
viii. the minutes of all EC meetings including, but not limited to,
    a. time, date, and place of meeting
    b. members present
    c. third parties present
    d. points of discussion
    e. decision record, indicating how the decision was reached
    f. signature (dated) of the chairperson
ix. a copy of the decision and any advises or requirements sent to the applicant
x. all documentation and communication received or occurring during the follow-up
xi. the notification of the completion or premature termination of a study, and the summary or the reasons

It is recommended that all archived material be maintained for a minimum of fifteen years.

GLOSSARY

The definitions provided within this glossary apply to terms as they are used in these guidelines and recommendations. The terms may have different meanings in other contexts.

adverse event
Any untoward or unfavourable occurrence experienced by a subject participating in a clinical trial.

advice
Non-constraining suggestions or considerations adjoined to a decision intended to provide ethical assistance to those involved in the research.

amendment
A written description of changes to a protocol.

applicant
A qualified physician or dentist (e.g., an investigator or a representative of the sponsor) undertaking the scientific and ethical responsibility for a clinical trial, either on his/her own behalf or on behalf of an organisation/firm, seeking a decision from an ethics committee through formal application.

clinical trial
A systematic study of an investigational product or substance (usually medicinal) on human subjects (including patients and volunteers) intended to identify characteristics of efficacy and/or safety. At times this document refers to the broader term 'biomedical research', which includes clinical trials.

decision
The response, either positive or negative, by an ethics committee to an applicant following the review of the application in which the ECs' position on the ethical validity of the proposed study is stated.

ethics committee (EC)
An independent body (e.g., a review board or an institutional, regional, or national committee), constituted of medical professionals and non-medical members, whose responsibility it is to safeguard the welfare and the rights of subjects participating in biomedical research studies, taking into account the scientific procedures and the concerns of the local community.

investigator
A legally qualified physician or dentist who undertakes scientific and ethical responsibility, either on his/her own behalf or on behalf of an organisation/firm, for the scientific and ethical integrity of a clinical trial at a specific site or group of sites. In some instances a co-ordinating or principal investigator may be appointed as the responsible leader of a team of subinvestigators.

opinion
Ethical considerations adjoined to a decision that represent the views of an individual member or a group of members of the ethics committee. In most cases an opinion is used to express dissent from the whole or part of the decision. Opinions are non-constraining elements of a decision intended to express specific ethical concerns that those involved in the research should consider.

protocol
A document that provides the background, rationale, and objective(s) of a clinical trial and describes its design, methodology, and organisation, including statistical considerations.

requirements
In the context of decisions, requirements are constraining elements that express ethical considerations which the ethics committee requires or views as obligatory in pursuing the research.

sponsor
An individual or organisation/firm that takes on the scientific and ethical responsibility for the initiation, management, and/or financing of a clinical trial.

subject
An individual who participates in biomedical research, either as the direct recipient of a pharmaceutical product, medicinal substance, or invasive procedure or as a control. The individual may be a healthy person who volunteers to participate in the research, or a person with a condition unrelated to the research carried out who volunteers to participate, or a person (usually a patient) whose condition is relevant to the use of the investigational product and agrees to participate.

SUPPORTING DOCUMENTS

Bennett, P., ed. *Good Clinical Practice and Ethics in European Drug Research*. Bath: Bath University Press, 1994.

Bennett, P., ed. *Ethical Responsibilities in European Drug Research*. Bath: Bath University Press, 1990.

Byk, Christian, and Gérard Mémeteau. *Le droit des comités d'éthique*. "Collection Médecine et Droit." Editions ESKA. Editions Alexandre Lacassagne, 1996.

The Committee for Proprietary Medicinal Products (CPMP). *Note for Guidance: Good Clinical Practice for Trials on Medicinal Products in the European Community* (1 July 1991): 111/3976/88-EN.

Council for International Organizations of Medical Sciences (CIOMS), in collaboration with the World Health Organization (WHO). *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva 1993.

Council for International Organizations of Medical Sciences (CIOMS). *International Guidelines for Ethical Review of Epidemiological Studies*. Geneva 1991.

Council of Europe (Directorate of Legal Affairs). *Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine*. European Treaty Series – No. 164. Oviedo, 4 November 1997.

Department of Health (NHS Training Division). *Standards for Local Research Ethics Committees: A Framework for Ethical Review*. London: Department of Health, September 1994.

Edgar, Harold, and Ricardo Cruz-Coke. *Draft Report: Access to Treatment, Experimentation on Human Subjects and Ethics*. Paper presented to the International Bioethics Committee (IBC), UNESCO, Paris, 3-4 October 1996.

Ethics Committee Working Group, *The Working of Ethics Committees*, A Consultation Document, (Maidenhead, England), June l994.

European Commission, Directorate-General III, Industry. *Draft Proposal for a Directive of the European Parliament and of the Council on the Approximation of Provisions Laid Down by Law, Regulation or Administrative Action Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials of Medicinal Products for Human Use*. III/5778/96, final. Release date: 24 February 1997.

European Commission, Directorate-General XII, Life Sciences. *The Implementation of Good Clinical Practices: Perspectives for Research, Training and Regulatory Action*. Final Report of the Expert Group Meeting, 6 February 1996.

European Commission, Secretariat-General. *Opinions of the Group of Advisers on the Ethical Implications of Biotechnology of the European Commission*. Opinions No.'s 1-8. Brussels, 12 March 1993 - 25 September 1996.

European Ethical Review Committee, *Standard Operating Procedures,* No. 1, (Les Ouldes, France), June 1988.

FDA Regulations and Guidelines for the Monitoring of Clinical Investigations.

International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). *Guideline for Guidance on Good Clinical Practice* (CPMP/ICH/135/95) 1 May 1996.

National Research Council. *Research Involving Human Subjects: Guidelines for Institutions*. Ottawa, Canada, March 1995.

Review Committee of the Ministry for Health and Family Services. *Report of the Review of the Role and Functioning of Institutional Ethics Committees*. Canberra, Australia, March 1996.

Rogers, Arthur, and Denis Durand de Bousingen. *Bioethics in Europe*. Strasbourg, Council of Europe Press, 1995.

Royal College of Physicians. *Guidelines on the Practice of Ethics Committees in Medical Research Involving Human Subjects*. London: Royal College of Physicians, January 1990.

World Health Organization (WHO). *A Declaration on the Promotion of Patients' Rights in Europe*. Amsterdam, April 1994.

World Health Organization (WHO). "Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products." Annex 3 of *The Use of Essential Drugs*. Sixth Report of the WHO Expert Committee. Geneva: World Health Organization, 1995: 97-137.

World Medical Association, *World Medical Association Declaration of Helsinki: Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects*. Adopted by the 18th World Medical Assembly Helsinki, Finland, June 1964. Amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975; 35th World Medical Assembly, Venice, Italy, October 1983; 41st World Medical Assembly, Hong Kong; and the 48th General Assembly, September 1989. Somerset West, Republic of South Africa, October 1996.

World Medical Association, *World Medical Association Declaration of Lisbon on the Rights of the Patient*. Adopted by the 34th World Medical Assembly, Lisbon, Portugal, September/October 1981 and amended by the 47th General Assembly, Bali, Indonesia, September 1995.

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