European Guidelines for Auditing Independent Ethics Committees

European Forum for Good Clinical Practice

Auditing Ethics Committees: A Concern for Quality and Public Assurance in Ethics

The growing public awareness and media scrutiny of clinical trials increasingly brings to the fore the need for ethical review and oversight of research. The importance of independent ethics committees/institutional review boards (IECs/IRBs) in the evaluation and follow-up of research protocols has become an increased focal point for public assurance that the research is sound and subjects are protected.

The European Forum for Good Clinical Practice (EFGCP) published the following guidelines in light of the recent Directive on Implementing Good Clinical Practice and the increased push toward quality and efficiency in ethical review practices. The intention of these European Guidelines for Auditing Independent Ethics Committees is to provide a framework for assisting IECs/IRBs to evaluate their practices while providing reassurance to patients, researchers, sponsors, and the general public that sound ethical oversight is in place for clinical trials.

These guidelines were developed 2000–2001 by the Audit Working Party of the EFGCP as a contribution to the improvement of human subjects protections in Europe. They have since provided a basis for a WHO guideline expected later this year.

Francis P. Crawley, Secretary General, European Forum for Good Clinical Practice.

1. Introduction

The purpose of this Guideline is to contribute to a European standard for auditing Independent Ethics Committees (Independent Ethics Committees / Institutional Review Boards [IECs/IRBs]) that review biomedical research. An increasing reliance on ethical review in Europe and abroad requires the establishment of standards for ensuring the proper and appropriate functioning of Independent Ethics Committees (IECs). Ethical review is an essential part of the biomedical research process, whose purpose it is to provide ethical guidance on research protocols and ensure the protection of trial participants.

This Guideline relies on the established standards of Good Clinical Practice as the primary reference for auditing IECs in Europe. In particular, the ICH Good Clinical Practice Guideline provides a fundamental framework for determining ethical review requirements as well as the role and responsibilities of clinical trial auditors. In considering the appropriate functioning of IECs, this Guideline makes use of the EFGCP Guidelines and Recommendations for European Ethics Committees as well as the TDR WHO Operational Guidelines for Ethics Committees That Review Biomedical Research. In considering the role and responsibilities of auditors, this Guideline is further informed by the ENGAGE Guideline: Optional Guideline for Good Clinical Practice Compliance and Quality Systems. The Declaration of Helsinki provides a general ethical framework for all persons engaged in biomedical research.

The recent EU Directive on Implementing Good Clinical Practice stresses the importance of the responsibility of the various partners in European clinical trials and introduces a legal framework for quality control. At the national level several European countries have already begun to implement audits and inspections of IECs. This Guideline is intended to assist both auditors and IECs in establishing high standards for the audit procedure as well as a cooperative approach toward the analysis of ethical review procedures.

2. The Role of an Independent Ethics Committee

In all European countries, IECs have been established to provide ethical advice to physicians and others engaged in biomedical research in order to assist in protecting potential and actual human participants in research projects. In order to fulfil this role it is essential that IECs are constituted and function according to the four principles for ethical review: independence, competence, pluralism, and transparency.

The Declaration of Helsinki and Good Clinical Practice Guidelines require the ethical review of clinical trials prior to the commencement of those trials. IECs are also expected to perform regular follow-ups to clinical trials for which they have provided a positive decision. In their decision-making, the Ethics Committees are required to be independent of the sponsor, the investigator, and any other undue influence.

In order to achieve the objectives of independence and quality in decision-making, international, European, and national guidelines require of IECs that they are appropriately constituted and that they adopt written standard operating procedures.

3. The Purpose of Auditing Independent Ethics Committees

The purpose of auditing IECs is to assist the Committees in evaluating their practices and to provide applicants to IECs and the public, assurances that the ethical review of research proposals is carried out according to established standards. An audit should provide an opportunity for an Independent Ethics Committee to receive advice on its constitution, operation, and standard operating procedures. The audit should also achieve an independent evaluation that provides information to parties having a legitimate interest in the appropriate functioning of the IECs.

IECs have a public responsibility to ensure that their reviews and decisions on biomedical research proposals are achieved according to established and current ethical and scientific practices. This requires the establishment of Good Practices for ethical review as well as the ongoing education of members of IECs.

The auditing of an Independent Ethics Committee may take place at the request of a sponsor organisation. In recent years, European IECs along with European health ministries and regulatory authorities have taken measures to improve the functioning of the Committees. In some instances these measures have included independent...
audits as a means to improve practices and achieve more confident results. There has also been an interest on the part of researchers and sponsors to have more information regarding the functioning of IECs.

At present there is no legal or regulatory framework for auditing IECs at the European level, although the framework for the inspection of clinical trials is rapidly advancing at both European and national levels. Audits may provide a more cooperative and educative model for advancing Good Practices in ethical review. This Guideline suggests such a cooperative and educative model for all parties involved, being concerned less with ‘enforcement’ of standards and more with ‘learning’ from the review of practices.

The aim of this document therefore is to indicate to Independent Ethics Committee the modus operandi of an audit conducted by a sponsor of a clinical trial.

4. The Audit Approach
ICH GCP requires that Independent Ethics Committee should review the documentation of a clinical trial before that trial begins. It also states that for each Committee or Board, there should be a reasonable number of members. Also, that the members of the Committee or Board should have appropriate qualifications and experience to review the protocol and other documents, and that they should be independent of the sponsor and investigator.

Only experienced auditors should carry out this type of audit. The members of an Independent Ethics Committee are usually senior members of society who provide their own time freely to serve on this type of committee. The auditor will be expected to communicate to the Independent Ethics Committee in a manner that will allow discussion and support but also will facilitate improvement. Both parties, the auditor and the auditee, need to find a common approach to review the constitution and practices as well as the related documentation filed with the Independent Ethics Committee, and they need to ensure that the findings are complete and accurate.

There should be open and frank communication between the auditor and the members of the Committee throughout the process, each working toward providing a supportive structure. Auditors that are not independent of sponsors should not be allowed to examine confidential documents related to other studies. In all cases, auditors should be bound by a confidentiality agreement prior to the commencement of auditing procedures.

5. Request for an Audit
A request for an audit may be made by either a sponsor or an independent party (i.e., CRO) having a legitimate interest in the quality and correctness of the review procedures followed by an Independent Ethics Committee.

6. Assigning Auditors
The auditor that meets the requirements / qualifications suitable for auditing an ethics committee will be defined in the Standard Operating Procedures (SOP) of the Sponsor. It should be specified that auditors that are not independent of sponsors would only be allowed to see those documents that do not refer to studies belonging to other sponsors.

Auditors should be persons having experience in auditing clinical trials or similar systems. The auditor should meet criteria that demonstrate both experience in auditing and maturity in communication. Auditors should be thoroughly familiar with the requirements, practices, and needs of IECs, and they should have a knowledge of the legislative and regulatory framework in which the Independent Ethics Committee to be audited is working. The specific requirements and qualifications of auditors for IECs should be established within sponsor companies as documented in standard operating procedures of the sponsor company.

7. Working Documents
The auditors will review the applicable standards, regulations, guidelines, SOPs and/or project specific requirements. In addition, the working documents of the IEC will be reviewed, including minutes of meeting and the IEC constitution.

8. Audit Plan
Standard Operating Procedures should allow for audit plans to be flexible in their design in order to permit comprehensive audits.

Each audit should be carried out according to a plan drafted by the auditor and the auditee in advance. Audit plans should be designed for each audit, taking into consideration the reason for the audit.

The audit plan should include the following:
8.1. identification and location of the auditor;
8.2. identification and location of the Independent Ethics Committee;
8.3. reason for the audit;
8.4. objectives and scope of the audit;
8.5. expected time and duration for each major audit activity;
8.6. date(s) and location of the audit;
8.7. schedule and purpose of meeting(s) to be held between the auditor and the auditee;
8.8. language in which the audit is to be conducted and any arrangements for translation;
8.9. confidentiality requirements and confidentiality statements;
8.10. identification of persons responsible for the audit (both the auditor and those on behalf of the Independent Ethics Committee);
8.11. identification of reference documents to be used by the auditor (for example, the applicable standards, regulations, guidelines, SOPs);
8.12. documents of the Independent Ethics Committee to be reviewed (for example, constitution, terms of reference, standard operating procedures, minutes of meetings, relevant correspondence);
8.13. distribution of the audit report, if applicable;
8.14. foreseen follow-up actions to the audit;
8.15. delivery of the audit certificate; expected date of the audit completion.

If the auditee objects to the audit plan, any objection should immediately be made known to the auditor. The objections should be resolved between the auditee(s) and the auditor before performing the audit.

9. The Conduct of an Audit
An audit of an Independent Ethics Committee should be conducted according to a previously agreed audit plan that follows the following procedures:
9.1. Opening Meeting
The auditee(s) would normally be official(s) of the Independent Ethics Committee. Some or all of the members of the Committee may be involved.

It is anticipated that an officer (i.e., chairperson, assistant chairperson or secretary) will be present at the opening meeting.

The audit begins with an opening meeting between the auditor and representative(s) of the Independent Ethics Committee. These representatives should be appointed in accordance with the standard operating procedures of the committee or determined by the chairperson of the committee.

The meeting can be short since the main purpose is as follows:
9.1.1. introduction to one another of the auditor and representatives of the Independent Ethics Committee;
9.1.2. review of the purpose and scope of the audit;
9.1.3. review of the audit plan;
9.1.4. confirmation of the availability of the documents and facilities to be reviewed;
9.1.5. discussion of the documents to be reviewed;
9.1.6 Discussion of the current practices of the Independent Ethics Committee and the impact of any guidelines, laws, or regulatory requirements on those practices;

9.1.7 Clarification of arrangements for contacting the representatives of the Independent Ethics Committee during the audit;

9.1.8 Confirmation of the time and date for the closing meeting;

9.1.9 Clarification of any unclear details from the audit plan.

9.2. Required Documentation for Review

The auditor is required to review the terms of reference and standard operating procedures of an Independent Ethics Committee. The auditor may also need to consider other working documents of a committee, such as the application form, decision form, specific procedures for reviewing certain kinds of protocols, evaluation forms for reviewing applications, and minutes of meetings.

9.3 Collecting Information.

A review should be made of the filing and archiving facilities where documents of the IEC are kept. The auditor should establish that filing and archiving are undertaken in a proper professional and secure manner.

Information should be in the form of Standard Operating Procedures (SOPs), minutes, and project / clinical trial specific files.

9.4 Accessing and Reviewing Documents

The auditor should review the documents required for the audit as well as the manner in which documents are filed and securely stored, including previous editions of any procedures in earlier SOPs.

9.4.1 Documents Referring to the Constitution and Standard Operating Procedures of the Independent Ethics Committee

The auditor should review the documentation referring to the constitution and standard operating procedures of an Independent Ethics Committee. These SOPs should include the following information:

9.4.1.1 The authority under which the Committee was established;

9.4.1.2 A statement that the Independent Ethics Committee operates in conformity with the Declaration of Helsinki, the ICH Good Clinical Practices Guidelines, relevant laws and regulatory requirements, and appropriate national and international guidelines;

9.4.1.3 The terms for the appointment of members (for example, duration, renewal procedure, disqualification, and resignation and replacement procedures);

9.4.1.4 The conditions of appointment (for example, withdrawal from the decision-making process if there is a conflict of interest); willingness to publicise his / her full name, profession, and gender; agreement to declare any financial reward or equivalent from Independent Ethics Committee to work to officials of the committee, and the signing of confidentiality agreements;

9.4.1.5 The procedure for making the appointment including the individual or party that makes the appointment, selection of candidates (for example, by consensus, by majority vote, or by direct appointment);

9.4.1.6 The provisions and conditions for expedited IEC review and approval, e.g. "chairman’s approval”;

9.4.1.7 The membership requirements, including the duties and responsibilities of members;

9.4.1.8 A listing of current and previous members of the Independent Ethics Committee;

9.4.1.9 The curriculum vitae of current members of the Independent Ethics Committee; a description of the requirements for holding the office of the chairperson, his / her deputy (if appropriate), secretary, and treasurer (the secretary should be defined carefully to avoid confusion between a secretary who is a voting member of the Independent Ethics Committee and an administration clerk who helps prepare the documents and arrange for dispatch of correspondence);

9.4.1.10 A description of the responsibilities and duties of the officials of the Independent Ethics Committee (for example, agenda of meetings, minutes, sending notification of decisions, filing and archiving);

9.4.1.11 The quorum requirements, including the minimum and maximum number of members of Independent Ethics Committee to be present, the minimum distribution of professional requirements, and gender requirements;

9.4.1.12 The procedures for submitting an application for the review of the proposed clinical research, including the need for the name and address of the Independent Ethics Committee required to provide the decision, the number of copies to be submitted, the language of the core documents to be submitted, the required format, the deadlines for review dates, the means by which the applicants will be informed of any incompleteness, the fee structure for considering an application and follow-up (if applicable);

9.4.1.13 The required documentation to be included in the application, including the application form, the protocol, a recent investigator’s brochure or equivalent describing recent pharmacological and toxicological data if absent from the protocol, for post-registration studies a summary of the product characteristics, recent curriculum vitae (signed and dated) of the investigator(s), recruitment of trial participants documentation including any advertisement material, all rewards and compensations to the trial participants, informed consent forms in core and local language (if appropriate), indemnity agreements for liability, other documentation that may influence decisions made by the Independent Ethics Committee (such as case report forms, diary cards, and questionnaires for trial participants), previous decisions by other IECs that may influence the decision of the reviewing Independent Ethics Committee;

9.4.1.14 The registration of applications, including the process whereby incoming material is dated, checked for completeness, filed, the applicant informed of the expected date of review, and the Independent Ethics Committee members informed of the review date;

9.4.1.15 The maintenance of records for all communications regarding the application, including written, verbal, or electronic communications;

9.4.1.16 The review procedure timelines;

9.4.1.17 The meeting procedures, including the preparation of the agenda, the minuting of the meetings, invitations of guests to the meeting (including sponsors, investigators, and specialists who may provide advice on occasions or assist in the review of a particular protocol);

9.4.1.18 The actions necessary for the enrolment of trial participants in emergency treatments, (for example, informing the local community and / or next of kin in the case of trauma or stroke);

9.4.1.19 The elements of the review of the application, including considerations such as the: completeness of the information and documentation, the suitability of the investigator(s) and supporting staff and the site, adequate provision for monitoring the conduct of the study, the adequacy and comprehensibility of the written and oral information to be provided to the trial participants, relatives and other legal guardians, or representatives, the means of recruitment of trial participants, provisions for receiving and responding to queries and complaints, provisions for compensation / treatment in the case of injury / disability / death of a trial participant attributable to participation in the study, insurance and indemnity agreements covering the liability of the investigator by
the sponsor, measures taken to ensure the confidentiality of personal participant information and the rewards and
compensation for trial participants

9.4.1.20. the decision-making procedure, including whether the decisions are by consensus or vote, the manner of specifying conditional decisions, and the manner of documenting the reasons for negative decisions;

9.4.1.21. the procedure for communicating a decision which should include a document stating the exact title of the research project / clinical trial, the documents reviewed, and their date or version number, the name and title of the applicant, the date and place of the decision, the name of the ethics committee, a clear statement of the decision made with any advice or comment. In the case of a positive decision, confirmation that all amendments have been duly regarded and brought to the attention of the full committee by the chairman, Serious Adverse Events, periodic reports and other factors requiring the decision to be reviewed, clearly defined reasons for a negative decision, and the signature and date of the chairperson of the ethics committee or in his absence by another official of the ethics committee and never a non-voting member of the ethics committee. A full committee should review all individual amendments submitted to the committee involving patient safety and welfare. Only minor administrative amendments can be dealt with outside the committee. Even here these should be indicated to the full committee at the next available meeting;

9.4.1.22. the follow-up review, including frequency determined by the nature of the study and at least yearly reviews due to unexpected SAEs or new information that may affect the benefits / risks ratio of the study;

9.4.1.23. the documentation and archiving procedures, including an inventory of all documents archived and the length of storage of the documents.

These documents should identify the author, authorisation, date of release, and the date of future review of the documents. In addition, earlier editions of these documents should be available to the auditor when relevant.

9.4.2. Documents Referring to the Applications Made to the Independent Ethics Committee

Auditors should review the applications submitted to the IECs as well as the manner in which those applications are handled. The materials that are to be reviewed should be established in the audit plan and agreed to by the Independent Ethics Committee. An auditor assigned by a research institution or sponsor may not review confidential documents from other research institutions or sponsors.

The following documents should be considered:

9.4.2.1. the materials submitted by applicants (including protocols, informed consent materials, advertising materials, information regarding potential conflicts of interest, information regarding incentives for trial participants, and the curriculum vitae of investigators);

9.4.2.2. the correspondence regarding applications, decisions, and follow-ups;

9.4.2.3. the record of all incomes and expenses of the Independent Ethics Committee (including honorariums, payments, and reimbursements made to members and staff);

9.4.2.4. the agenda of all Independent Ethics Committee meetings;

9.4.2.5. the minutes of all Independent Ethics Committee meetings (including time, date and place of the meeting, members present, third parties present, points of discussions, decisions made [including how the decision was made], signature and date of the chairperson or his / her deputy);

9.4.2.6. copies of the decisions and advice provided to applicants;

9.4.2.7. interim and annual reports during follow-up;

9.4.2.8. notifications of completion or premature study terminations;

9.4.2.9. annual reports of the Independent Ethics Committee.

9.5 Audit Observations

All audit observations should be documented. After all activities have been audited, the auditor should review all observations to determine which are to be reported as non-ICH GCP or non-regulatory compliant and / or indicative of poor business practice. The auditor should ensure that these are documented in a clear, concise manner. The audit observations should be, where possible, supported by objective evidence and reference made to requirements in ICH GCP or other appropriate documents.

9.6 Closing Meeting

At the end of the audit, the auditor should hold a meeting with the auditees, who would normally be officials of the Independent Ethics Committee and members of the committee. The main purpose of this meeting is to present audit findings to the auditee(s) to ensure that the results of the audit are clearly understood and there is no misunderstanding by either the auditee(s) or the auditor. The auditor should encourage the Independent Ethics Committee to take note of ICH GCP and of the TDR WHO Operational Guidelines for Ethics Committees That Review Biomedical Research. In many instances, the Independent Ethics Committee may not be aware that these guidelines exist. The closing meeting should be of a supportive nature rather than one of conflict.

9.7 The Audit Report

The audit report should reflect the execution of the audit. It should be dated and signed by the auditor and contain, at the minimum, the following items:

9.7.1. scope and objectives of the audit (these should include the establishment that the conduct of the Independent Ethics Committee meets those aspects of ICH GCP and local regulations relating to Independent Ethics Committee, that proper documentation has taken place, the appropriate records have been archived in a secure and suitable facility, and that the safety of the study participant has been paramount in any consideration);

9.7.2. identification of the auditor;

9.7.3. identification of the auditee and the representative(s) of the auditee;

9.7.4. audit plan;

9.7.5. identification of the facilities, persons interviewed, and the documents reviewed;

9.7.6. audit methodology;

9.7.7. findings of the audit;

9.7.8. observations and recommendations for corrective actions or areas of suggested revisions in practice;

9.7.9. audit report distribution list;

9.7.10. signature and date of the auditor.

Both the auditor and the auditee should retain a copy of the audit report for the same time period for which the Independent Ethics Committee stores essential records.

9.8 Corrective Actions

The auditee is responsible for determining, initiating, and completing corrective actions according to the findings of the audit report. These actions and a time period for the actions should be communicated to the auditor within a reasonable time period following the reception of the audit report.

9.9 Follow-up Audit

Following the completion of corrective actions, a follow-up audit may be appropriate. An audit plan should be prepared for the follow-up audit and agreed to by the auditor and the auditee. The auditee is responsible for taking corrective actions according to the findings of
The person responsible for carrying out an audit and for the operational techniques and activities under-
the follow-up audit report.

9.10 Audit Certificate
The auditor may provide the Independent Ethics Committee with an audit certificate. The purpose of the audit certificate is to confirm that an audit was performed and completed. It does not reflect a positive outcome of the audit. The audit certificate should include the following:

- name and affiliation of the auditor;
- name of the Independent Ethics Committee audited;
- type of audit (i.e., audit of an Independent Ethics Committee);
- audited system (for example, general review or specific to a project or clinical trial);
- audit dates;
- signature and date of the auditor.

The Audit Certificate is prepared and used in accordance with SOPs and may include, the date of release of the audit report and other information. (The scope of the audit certificate should be an affirmation that an audit was performed, not that the outcome was satisfactory).

The audit certificate may be appended to the Clinical Study Report (see Appendices of the ICH Guideline “Structure and Content of Clinical Study Reports” adopted by the EU as CPMP/ICH/137/95 Note for Guidance on Structure and Content of Clinical Study Reports).

Glossary

Applicant A qualified researcher undertaking the scientific and ethical responsibility for a research project, either on his/her own behalf or on behalf of an organisation/firm, seeking a decision from an Independent Ethics Committee through formal application.

Audit A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor’s standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirements(s). In the context of this document, an audit refers to a systematic and independent examination of the constitution and practices of an Independent Ethics Committee.

Audittee The audited party. In the context of this Guideline, audittee refers to the Independent Ethics Committee being audited and/or the representatives of the Independent Ethics Committee for the purpose of the audit.

Auditor The person responsible for carrying out an audit and for reporting the findings.

Audit Certificate A document presented by the auditor confirming that an audit has taken place.

Audit Findings The results of audit based on the purpose of the audit and the materials reviewed by the auditor. The audit findings should refer to specific observations made by the auditor and supported by objective evidence. Audit findings express the auditor’s conclusions regarding specific procedures or systems audited and evaluated as being compliant or noncompliant with the appropriate requirements.

Audit Plan A plan setting out the specific practices, resources, activities, and time lines relevant to a particular audit or a group of related audits.

Audit Report A written evaluation by the sponsor’s auditor of the results of the audit.

Conflict of Interest A conflict of interest arises when a member (or members) of an Independent Ethics Committee hold(s) interests with respect to specific applications for review that may jeopardise his/her (their) ability to provide a free and independent evaluation of the research with a focus on the protection of the trial participants. Conflicts of interests may arise when a member of an Independent Ethics Committee has financial, material, institutional, or social ties to the research.

Community A community is a group of people understood as having a certain identity due to the sharing of common interests or to a shared proximity. A community may be identified as a group of people living in the same village, town, or country and thus, sharing geographical proximity. A community may be otherwise identified as a group of people sharing a common set of values, a common set of interests, or a common disease.

Decision The response (positive, conditional, or negative) by an Independent Ethics Committee to an applicant following the review of an application.

Good Clinical Practice (GCP) A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and the rights, integrity, and confidentiality of trial participants are protected.

Investigator A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site conducts a trial, the investigator is the responsible leader of the team and may be called the principal investigator.

Independent Ethics Committee (IEC) An independent body (a review board or a committee, institutional, regional, national or supranational), constituted of medical/scientific professionals and non-medical/non-scientific members, whose responsibility it is to ensure the protection of the rights safety and well-being of human participants involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial participants.

The legal status, composition, function, operations, and regulatory requirements pertaining to IECs may differ among countries, but should allow the Independent Committee to act in agreement with the requirements of ICH Good Clinical Practice.

Protocol A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol reference documents.

Protocol Amendment A written description of a change to, or formal clarification of, a protocol.

Quality Assurance (QA) All those planned and systematic actions that are established to ensure that the trial is performed and the data generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirements(s).

Quality Control (QC) The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

Sponsor An individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Standard Operating Procedures (SOPs) Detailed, written instructions to achieve uniformity of the performance of a specific function.

Supporting Documents


Council of Europe. Convention for the Protection of Human Rights and...
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International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). Note for Guidance on Good Clinical Practice (CPMP / ICH /135 / 95) 1 May 1996.


World Medical Association, Declaration of Helsinki: Ethical Principles for 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; the 35th World Medical Assembly, Venice, Italy, October 1983; the 41st World Medical Assembly, Hong Kong, September 1989; the 48th General Assembly, Somerset West, Republic of South Africa, October 1996; and the 52nd General Assembly, Edinburgh, Scotland, October 2000.

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