

Avoiding Rejections by European Ethics Committees

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The Competent Authority has been notified. The clinical investigator is anxious to begin. Just when the process of conducting a clinical investigation is proceeding as planned, the ethics committee issues an unfavourable opinion. This article discusses the actions that should be taken to avoid this occurrence and how to meet other requirements related to ethics committees.

Importance of ethics committee opinions

The European Directives place considerable importance on the opinions rendered by ethics committees. For example, Article 10 of the Active Implantable Medical Device Directive (90/385/EEC) states that Member States may authorise manufacturers to start clinical investigations before the expiry of a 60-day period, provided the ethics committee concerned has delivered a favourable opinion on the investigation programme in question. A similar provision is included in Article 15, Clinical Investigation, of the Medical Device (MD) Directive (93/42/EEC). This article states that for devices falling within Class III and implantable and long-term invasive devices falling within Class IIa or Class IIb Member States may authorise manufacturers to commence the relevant clinical investigations before the expiry of the period of 60 days, if the ethics committee has issued a favourable opinion on the conduct of the clinical investigation. The same article states that for devices other than the categories mentioned, Member States may authorise manufacturers to commence clinical investigations immediately after the date of notification, provided the ethics committee concerned has delivered a favourable opinion on the investigational plan.

It should always be remembered, however, that the national regulations, which transpose the European Directives for medical devices, specify the legally binding requirements. Annex VIII, Statement Concerning Devices for Special Purposes, of the MD Directive requires that the

statement that must be drawn up for devices intended for clinical investigations includes the opinion of the ethics committee concerned and details of the aspects covered by its opinion.

In some cases, national guidance documents on medical device regulatory requirements contain more information on the role of the ethics committee opinion. For example, two United Kingdom guidance documents on clinical investigations¹⁻² state that a local research ethics committee opinion is required for all clinical investigations of devices falling within the scope of the MD Directive. It also states that the local research ethics committee opinion(s) must be sent to the Competent Authority with the other required documentation when notification of a clinical investigation is made. Other requirements related to the notification and resulting opinions of ethics committees are also discussed in these guidance documents.

Once a manufacturer understands the importance of an ethics committee opinion and the role that this opinion plays in the conduct of a clinical investigation, the process for obtaining an opinion from the ethics committee needs to be clearly understood. That is, manufacturers should understand the role of ethics committees, how ethics committees function, and the type of information that they require to render an opinion.

Definition and role of ethics committees

An ethics committee is an independent and properly



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constituted competent body with responsibility to ensure that the safety, well-being and the human rights of the subjects participating in a clinical investigation are protected. This is the definition contained in EN ISO 14155-1:2003, Clinical Investigation of Medical Devices for Human Subjects – Part 1: General Requirements, which will replace EN 540:1993 as the European harmonised standard for medical device clinical investigations when it is published in the European Official Journal. This should occur in the near future. Thus, this article will concentrate on the guidance provided in EN ISO 14155-1:2003. The definition of ethics committee in ISO 14155-1 also states in a note accompanying the definition that “ethics committee” is synonymous with “research ethics committee” or “institutional review board,” and that regulatory requirements pertaining to ethics committees may differ from country to country.

The sponsor of a clinical investigation, normally the manufacturer of the medical device, should be aware of whether or not an ethics committee has been established as an institution or whether a regional ethics committee needs to be consulted. The meeting schedule and the deadline for submitting information for consideration need to be determined. The failure to identify this information early can seriously delay defined product development milestones and timing requirements.

Ethics committee operations

Ethics committees operate in accordance with their own rules and requirements. In general, their operating procedures and practices are based on good clinical practice (GCP) guidelines such as the guideline developed by the International Conference on Harmonisation (ICH),³ which was established to provide guidance on the design and conduct of pharmaceutical clinical trials. This guideline, which is included in the list of references in EN ISO 14155-1:2003, describes

- the responsibilities of ethics committees
- the documents that ethics committees should obtain to evaluate clinical trials
- the composition, functions and operations of ethics committees
- the types of procedures that ethics committees should establish
- the records that they should maintain.

For example, the ICH GCP guideline states that ethics committees should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects and ethics of the proposed trial. Furthermore, it is recommended that an ethics committee has at least five members, of which at least one member's primary area of interest is in a nonscientific area and at least one member is independent of the institution/trial site. In addition, the guideline states that only ethics committee members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter.

Information on the proposed clinical investigation

The sponsor of a clinical investigation who wishes to minimise the chances of a negative opinion from an ethics committee should have a clear understanding of the information and documents that must be submitted to the ethics committee. The documentation should be organised to facilitate its review by members of the committee. It should also be presented in a manner that is understandable to persons who are not expert in the technological and scientific aspects of the medical device intended for clinical investigation. In general, the investigator is responsible for submitting information on the clinical investigation to the ethics committee. For this reason, the sponsor of a clinical investigation should make every effort to provide the investigator with the type and format of information that will facilitate the ethics committee review process.

Ethics committees usually develop a list of the documentation that they will require to review a clinical investigation. To meet their responsibility to safeguard the rights, safety and well-being of clinical investigation subjects they need to understand the scientific, medical and ethical aspects of the clinical investigation. Thus, the sponsor of the clinical investigation should provide the investigator with the information that will help the ethics committee meet these responsibilities. This means that the information should be in a format that will be easy to present by the investigator and easy to understand by the ethics committee. Ethics committees have responded positively to computer presentation formats that include clearly presented device descriptions and photographs and/or diagrams, medical device technical specifications, the intended use of the device, and the principle phases and design features of the clinical investigation.

In addition, an informative annex in EN ISO 14155-1:2003 lists information that should be provided to ethics committees by the sponsor, some of which should be provided for the initial review of the clinical investigation. Annex B (informative), Information for the ethics committee, lists information such as

- an assessment of the scientific merit and justification of the clinical investigation
- a summary of how the health status of subjects may be affected
- an assessment of possible risks, methods and facilities proposed for dealing with risks
- other information on various aspects of the planned clinical investigation.

Some ethics committees expect this type of information to be provided by the investigator in the form of the clinical investigation summary mentioned previously. Additional documents listed in Annex B are the clinical plan, subject information sheet, copy of the patient's insurance policy, and clinical investigator's brochure. Other information included in Annex B is to be provided at the end of the clinical investigation.

Section 3.1.2 of the ICH GCP guideline also lists documentation that should be obtained by the ethics commit- →

tee at the time of reviewing a proposed clinical trial. Some of the documentation applies more to the review of trials for pharmaceutical products. The listed information that is frequently requested for the review of medical device clinical investigations includes:

- the trial protocol(s)/amendment(s)
- written informed consent form(s)
- consent form updates that the investigator proposes for use in the trial
- written information to be provided to subjects
- the Investigator's Brochure
- investigator's current curriculum vitae and/or other documentation evidencing qualifications.


Periodic information and reports

In addition to providing information needed for reviewing a proposed clinical investigation, sponsors and investigators have other responsibilities related to the ethics committee. These are described in EN ISO 14155-1:2003. For example, Clause 6.8 of this standard requires that the sponsor, clinical investigator or investigational site inform the ethics committee promptly if a clinical investigation has been terminated or suspended and the reasons for taking this action. Clause 7.3 states that written ethics committee opinion and/or approval and relevant correspondence be maintained in investigator and/or sponsor files. Clause 8.2 requires that sponsors report all serious adverse events and all serious adverse device effects to the relevant ethics committees. This clause also repeats the requirement in Clause 6.8 that sponsors must promptly inform ethics committee(s) when a clinical investigation is prematurely terminated or suspended and the reason(s) for the termination or suspension.

Clinical investigator's responsibilities

Clause 10.3 describes the responsibilities of the clinical investigator with regard to the ethics committee, including the need to ensure that appropriate ethics committee approval has been received to start the clinical investigation at his/her centre and to provide the results from the ethics committee to the sponsor. Other responsibilities include informing the ethics committee of, and asking for its opinion and/or approval regarding any significant change in the clinical investigation plan that has been approved by the sponsor, and the reasons for the change. This clause also requires the clinical investigator to inform the ethics committee of any serious adverse device effects.

References

1. United Kingdom, EC Medical Devices Directives Guidance Notes for Manufacturers on Clinical Investigations to be Carried Out in the UK, pp. 8–9, September 1996, downloadable from www.medical-devices.gov.uk/
2. EC Medical Devices Directives Information for Clinical Investigators, pp. 4–5, 23 November 1994, downloadable from www.medical-devices.gov.uk
3. ICH Harmonised Tripartite Guideline; Guideline for Good Clinical Practice, 1 May 1996, downloadable from www.ich.org/ich5e.html 

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