

RSM 00069

Reviews of books and studies

E.E.C.: Good Clinical Practice for Trials on Medicinal Products in the European Community. Directorate-General for the Internal Market and Industrial Affairs of the Commission of the European Communities, Brussels, 1988. Code III / 3976 / 88-EN. Price not indicated.

The European Communities' notes for guidance on "Good Clinical Practice" in the investigation of medicinal products in human subjects promises to be an influential document. Particularly in view of existing differences within the European region in the extent to which trial subjects do enjoy protection, these Guidelines (which are planned to become effective in 1991) merit careful study.

On the basis of the revision Declaration of Helsinki of the World Medical Association, which is the universally accepted standard for ethics in clinical trials, the ultimate responsibility for the personal integrity and welfare of trial subjects must necessarily rest squarely with the investigator. It is obvious (though the Guidelines do not say so) that the investigator must be a physician. However, independent assurance is also required that the subjects of a study enjoy adequate protection; that is to be provided on the one hand by an obligation to ensure that informed consent has been freely given, and on the other hand by the duty to consult an Ethics Committee.

Such an Ethics Committee, as defined in the Glossary appended to the present notes, shall be an independent body constituted both of medical professionals and non-professional members, whose responsibility it is to verify that the safety, integrity and human rights of the subjects taking part in a particular trial are protected, thereby providing due reassurance to the public. Use of the term "reassurance" underlines the fact that the investigator retains the ultimate responsibility, a fact which may limit the liability of the Ethics Committee if injury does occur.

The guideline does not go so far as to require the representation on an Ethics Committee of patients or lay people, nor does it require that both sexes be represented. It would, however, seem advisable to choose the necessary non-medical members in such a way that the viewpoints of a patient or of a subject involved in a trial, which may differ from those of physicians, come sufficiently to the fore. At least in trials involving women or children the Ethics Committee handling the assessment should have a female member.

Ethics Committees should be constituted and operated in such a way that the suitability of investigators, facilities and protocols, the eligibility of subjects in the trial groups and the adequacy of the safeguards for confidentiality can all be assessed; all these issues must be objectively and impartially reviewed, independent of the investigator, the sponsor and the relevant authorities. The wide range of matters to be checked by Ethics Committees demands that their members have a wide spectrum of qualifications. The "medical professionals" as specified in the Glossary must not only be capable of determining the qualification of the investigator(s) but also of judging the adequacy of the facilities provided. the quality of the

protocol (and the feasibility of adhering to it) and the suitability of the biometric methods proposed. There seems to be agreement that failure of a study to yield useful results may constitute a waste of the goodwill of the patients or subjects volunteering for the study, and that such wastage is unethical. It follows that an Ethics Committee must consist of a sufficiently large number of experts from several medical disciplines.

Medical knowledge and experience is, however, not the only type of expertise which is demanded. Assessment of the eligibility of such trial subjects as children or elderly persons will depend upon the consent of parents or of guardians appointed by a court, and this may involve complex legal problems. The same holds true for the adequacy of the steps taken to ensure confidentiality; that will require special knowledge of the regional legislation and regulations dealing with data protection, and an Ethics Committee therefore needs continuous legal advice provided by highly qualified jurists.

The objectivity and impartiality of the review procedure, as stipulated in the Notes for Guidance, requires not only that the members of the Ethics Committee are unencumbered by any personal or financial interest in the study (or in any other study competing with that to be reviewed) but also that they have no liaison whatsoever with the sponsor or with any party having a special interest in securing fast clearance or a preferential judgement. This will render it necessary for members of a Committee having any such interest to declare it, and where necessary for such members to be excluded from the deliberations concerned. The status of an Ethical Committee as an organ of a University or of an official medical body may assure its independence both of a sponsor and of the regulatory agency. The investigator may be heard but should never participate in the decision-making process; commercial or industrial Ethics Committees can therefore no longer be regarded as acceptable. Independent of these basic requirements the legal status and constitution of Ethics Committees, Review Boards or similar institutions and the regulatory requirements pertaining to them are likely to differ from one country to another.

While, in view of the need to protect inventions under development by the sponsor, the sessions of Ethics Committees cannot be open to the public, their working procedure, membership (including the qualifications of members) and their overall performance must be available for public scrutiny.

The Commission's notes leave no doubt that potential investigators must request the opinion of "relevant" (as defined in the Glossary) Ethics Committees. Where an investigator is obliged to approach several Committees (e.g. at the national, provincial or hospital level) there will need to be an efficient mutual exchange of information and opinions if conflicts are to be avoided. The Notes for Guidance specify further that the complete clinical trial protocols (including annexes) as well as the methods and materials to be used in obtaining and documenting the informed consent of the trial subjects have to be disclosed to the Ethics Committee. There is no provision for a Committee to request pharmacological and toxicological data; one would point out that this will often be indispensable in forming a view of the ethics of the first administration of a medicinal substance or product to humans.

In addition to the provision of data prior to commencing the study, the guidelines specify that an Ethics Committee must be informed of all subsequent amendments to the trial protocol and of serious or unexpected adverse events occurring during the trial which are likely to affect the safety of the subjects or the conduct of the trial; such matters may call for a reevaluation of the ethical aspects of the study. This recommendation widens considerably the responsibility of Ethics Committees and will increase the administrative burden carried by the secretariat of such a body.

The detailed description of the tasks of Ethics Committees, as provided in these notes from Brussels, are along the lines which well-established Committees have developed in the

past, except for the fact that special emphasis is now laid on the means by which initial recruitment of subjects is to be conducted and on the extent of the information to be provided. Disclosure of the extent to which investigators may be rewarded or compensated for their participation in the study is also regarded as relevant; a Committee may have to determine whether the remuneration provided merely represents fair compensation or is such as to induce bias.

A final suggestion in the Commission's document is to the effect that the Ethics Committee should provide its opinion and advice in writing within a reasonable period of time, clearly identifying the trial, the documents studied and the date of review. This is already current practice in most Ethics Committees.

The recommendation that the information given to patients or trial subjects, as a basis for obtaining their fully informed consent, should be provided both orally and in written form is to be welcomed. This element is of particular importance where the consent has to be given by parents, relatives or guardians. There should indeed be ample time and opportunity for subjects or their representatives to ask about those details of a study which they do not immediately understand. Finally, despite the need for patient data to be scrutinized by scientists, monitors and regulatory agencies, the trial subjects must be entirely sure that no party, except for the treating physician, has access to their personal data.

These new European notes have clarified the responsibilities of Ethics Committees in a praiseworthy manner; it is clear that they will be generally appreciated by all or who are involved in these difficult tasks.

Karl H. Kimbel
Hamburg, F.R.G.