Contemporary Themes

European Ethical Review Committee: the experience of an international ethics committee reviewing protocols for drug trials

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Abstract

An international ethics review committee, founded seven years ago, has several unusual features: it selects its own members, who are independent of the drug industry; it includes members with no medical or paramedical background, such as lay people and lawyers; and it reviews protocols together with the study's sponsor. Membership of 31 from nine European countries enables frequent meetings and there is a full meeting of the committee every year to review progress and consider policy.

Of the first 294 protocols for phase I, II, or III trials reviewed, 37 were admitted outright, 243 were amended (usually during the discussion of the protocol), and 14 were rejected. It is suggested that, to overcome the problem of ethics review in smaller institutions, regional health authorities in Britain might consider establishing similar committees.

Introduction

Recent coverage in the medical and scientific press has focused on the question of informed consent and the conduct of clinical trials.[1-3] Although the essential supervisory role of ethics committees has always been emphasised,[1] comparatively little information has been given on their composition and method of working. Many of the protocols considered by ethics committees are concerned with clinical trials of new drugs. In appraising the risks to the participants of such trials the members of the committee must, collectively as experts, have a wide understanding of all the characteristics of the class of drug in question and be conversant with the methods proposed for its evaluation. The following account of the European Ethical Review Committee —an international committee which has reviewed protocols submitted by pharmaceutical companies for trials with new drugs over the past six years—illustrates this aspect of medical ethics.

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Historical background

The European Ethical Review Committee was founded seven years ago by a group of experienced European clinical specialists who were conscious of the lack of ethical review committees in many parts of Europe. They were also aware of the need to ensure rapid, independent, uniform, and scientifically satisfactory review of clinical research protocols, particularly for new drugs. The committee was helped in its formation by one major international pharmaceutical company—Pfizer Limited—who in 1977 began submitting protocols for review and meeting the expenses of organising meetings. Not surprisingly, the major expenditure is the travel expenses of members, who also receive a fee for attendance. Subsequently other pharmaceutical companies submitted protocols for review and took a share of the expenses. The committee operates on this basis; it has not obtained any financial support from governments, trusts, or other independent organisations. The committee has now reviewed nearly 300 protocols for phase I, II, and III clinical trials sponsored by pharmaceutical companies in numerous European centres.

The committee helps to safeguard the rights and interests of individuals submitting to biomedical research procedures, reviewing and advising on clinical study protocols from any source in accordance with recommendations of the Declaration of Helsinki. In its composition and procedure the committee also conforms with the American regulations governing human research subjects.[4]

Composition

The committee totals 31 members from nine European countries (Belgium, France, Germany, Great Britain, Italy, Netherlands, Norway, Sweden, and Switzerland). At least 10 members attend each meeting, which allows sessions to be held frequently without placing an undue burden on individual members. Policy and planning are the responsibility of a bureau, which currently comprises a chairman, two vice chairmen, an honorary secretary, and one other member who is a toxicologist, all of whom are medically qualified. Members are chosen by the bureau and elected by the committee. Each member serves for a three year period, which is renewable. The chairman is elected by the full committee meeting in session at the annual general meeting. No outside agency has any role in selecting members and none of these are employees of the drug industry.

The five members of the bureau attend all meetings of the committee, thus contributing a continuity and uniformity to its activities. The other members represent five disciplines: clinical pharmacology, internal medicine, general medical practice, nursing, and law. There are also lay members of the committee who have no medical or paramedical background; apart from representing the interests of patients and volunteers, they play an important part in analysing the written information to be given to potential subjects asked to take part in clinical trials. One member of each of the above categories attends each committee meeting. Medical specialties represented include cardiology, metabolic diseases, paediatrics, endocrinology, and occupational health. In addition to its own members, the committee may co-opt additional experts for particular meetings if it thinks that such outside advice is necessary to enable it to reach a sound conclusion.

All members and co-opted experts are required to sign a witnessed secrecy agreement to preserve the confidentiality of the information which they encounter during their association with the committee. Before the start of each meeting all members are required to declare any personal interest which they, members of their staffs, or direct associates have in any of the protocols to be considered.

Working methods

The committee operates according to a written constitution, drawn up by the founding members and based on the Declaration of Helsinki; it can be amended only by the committee meeting in full session. It describes the aims and purposes of the committee and how it should function.

The committee has met usually monthly since it started and is required by its constitution to meet at intervals of not more than six weeks if there is business to discuss. Meetings are held either in London or Continental Europe. The usual working language is English, but French and German are also used.

Two to three weeks before each meeting the proposer of a clinical study—that is, the pharmaceutical company—submits to each member scheduled to attend the study protocol, all necessary supporting pharmacological and toxicological data, and the information sheet and consent form designed to be supplied to the subjects. Thus time is allowed for detailed examination of the documents before the meeting. At the meeting itself the clinical representative of the sponsor company introduces the protocol briefly, and remains present, along with any supporting preclinical experts who may also be present, to clarify facts and answer questions from the committee; although there is free dialogue, the representative takes no part in any decision.

Exceptionally the committee may invite the investigator who will undertake the clinical trial to attend the meeting. This may arise, for example, if the protocol entails new or complicated techniques pioneered by the investigator himself or if the committee considers that the ethics of a given experimental procedure are polemical. After discussing the proposal fully, the committee takes its decision. This may be that the protocol is ethically acceptable as presented; that it is not acceptable, and must be resubmitted with major amendments or more supporting data, or both; or, more usually, that the work can proceed subject to specific changes to the protocol being made before the work begins. Occasionally points arise that are so specialised that the committee thinks that a statement is required from a recognised authority—for example, the UK Radiation Protection Board. Required amendments are recorded in writing in detail, agreed between the proposer and the committee during the meeting, and signed by the chairman. Certificates of acceptance, specifying the members present and signed by the chairman, are issued for accepted protocols. Detailed minutes are written for each meeting and distributed to all members whether they were present or not. Permanent records of the minutes, all protocols, and the patient information sheet and consent form are kept by the honorary secretary.

An analysis of the first 294 protocols reviewed since the start of the committee showed that 37 were admitted outright, without amendment; 243 were amended; and 14 were rejected. The amendments were usually made during the discussion of the protocol.

The full membership of the committee meets annually to review progress and consider policy. Expenses for this meeting are met by the pharmaceutical companies concerned with the studies under review. All proposers of protocols presented during the previous 12 months are required to attend this meeting, and they present a final report or account of progress of studies undertaken according to these protocols. The annual general meeting also reviews policy and the views of members. Recently, for example, a lengthy discussion took place on the ethics of payments to volunteers and investigators; the consensus was that financial compensation should not be so high that it is an inducement to undergo experimentation and that any money paid to an investigator should be a correct professional fee.

Subsequently studies are kept under continuing review by the bureau members of the committee through a continuing dialogue with the project physicians of the sponsor companies, who keep the committee informed of the progress of the drug trials and any possible adverse circumstances that might lead the committee to suspend approval.

Discussion

Apart from the fact that the European Ethical Review Committee is multinational, it differs from local ethical committees and institutional review boards in several important respects: it reviews protocols in a dialogue with the sponsor of the study; its members are fully independent of the clinician undertaking the study; it comprises experts who do not usually serve on local committees—for example, a toxicologist and lawyers concerned in the legislation of medical experimentation. One of the founding members of the committee is a lawyer who was concerned in drawing up the Declaration of Helsinki.

The dialogue with the clinician from the sponsor company, who is usually responsible for the study design, is one of the most fruitful features in the protocol review. Although the committee's discussions are concerned essentially with ethics, this cannot be divorced from the scientific design of the protocol: obviously it is unethical to use one that is improperly designed. Some of the deliberations of the committee, therefore, revolve around the study design. The extensive collective experience of the members of the committee in clinical pharmacology is fundamental to the success of these discussions.

The value to the clinician submitting the protocol is that in most cases the results of the discussion allow the protocol to be modified immediately, enabling it to be accepted without delay. Roughly a quarter of protocols are accepted with slight modifications, half after one or more important modifications, and only a quarter require major modification or are rejected after discussion. Rejected protocols may, however, be resubmitted after amendment or the provision of additional data if required. Amendments have been fewer when the clinician sponsoring the study has held extensive discussions with the committee when submitting previous protocols and has, therefore, benefited from its collective experience.

The members of the committee are not usually connected with the institution undertaking the study. This independence enables them to judge the protocol without fear of alienating a colleague with whom they work every day, as may happen with local ethics committees. On the contrary, it means that the committee has no direct contact with the actual investigator although it may occasionally ask him to attend the protocol review. Interestingly the original recommendation of the Food and Drug Administration that investigational review boards should monitor clinical research studies was eventually withdrawn because it was considered that a "monitoring function is inconsistent with generally accepted scope of IRB [institutional review board] responsibilities."[7] Nevertheless, the bureau maintains a continuing dialogue with the sponsoring physician and the protocols are extensively reviewed at the annual general meeting.

The presence on the committee of members who have a special knowledge of disciplines outside medicine, but which are related to evaluating risk, is one of its special features. Because it has no direct contact with the investigator it is the policy of the committee to require a guarantee from the sponsor company that he is competent, the hospital or clinic is adequately equipped, and he will follow the protocol. Similarly special emphasis is placed on the manner in which informed consent is obtained. The committee asks the sponsor to provide the written information that is to be given to the patient or volunteer. This document, which is retained with the permanent records, is one of the main discussion points and of special interest to the lawyer members, who are concerned with the rights of the subjects. They also play a major part in advising on the sponsor's standing in law, and the committee requires the company to accept responsibility for possible injury sustained during drug trials.

The committee insists that the sponsor submits detailed summaries of toxicology studies. These are reviewed by all members and their interpretation is helped by the presence of a toxicologist. This is particularly important with protocols for volunteer studies when the drug is due to be given to man for the first time. In view of the importance of the preclinical toxicology, a toxicologist from the sponsor company is usually present to take part in the discussion of the findings.

An important number of protocols submitted to the committee are for either multicentre clinical trials or volunteer studies. With the former this is because there are still European centres without local ethics committees but, more importantly, because, even though the protocol may be reviewed by a local ethics committee eventually, the first review by a committee of experts drawn from the different countries concerned in a trial adds some uniformity to the protocol and a collective experience unlikely to be found in many local ethics committees. Similarly, it is the committee's broad collective experience that the sponsor companies wish to draw on in reviewing protocols for volunteer studies. Furthermore, those pharmaceutical companies submitting protocols for

their "in house" volunteer studies do so because they consider that such protocols should be reviewed by an external, independent committee and not an "in house" ethics committee. We fully endorse such a policy.

All this should in no way belittle review by local ethics committees, which in most cases is satisfactory. In some countries, however, local committees are not yet widely established and even when they are found there may be considerable variation in their experience, workload, and procedure.[4 5] In addition, in particular circumstances (such as multicentre studies or protocols of an unusual or specialist design) the range of representation and skill that the European Ethical Review Committee can call on is especially appropriate.

We believe that our experience is relevant to ethics committees in Britain. Present opinions about human experimentation are likely to increase the requirements for regulation. In many institutions in Britain, particularly in teaching centres, ethics review committees work well; but research is also conducted in district hospitals, which may not have the resources to construct a committee of the requisite experience. We propose that the solution to the problem of ethics review in smaller institutions lies in the regional health authorities accepting an overall responsibility for ethics review for their own hospitals and institutions. The range of resources within a health region would be ample to provide the skill required. The activities of the European Ethical Review Committee are relevant because its composition and mode of working are relevant to the type of ethics committee regional health authorities might establish—that is, a bureau of permanent members supplemented by a panel of experts drawn from an agreed range of medical disciplines and including nursing, legal, and lay members.

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Appropriate Technology

Principles of health education

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Health education is an essential component of any programme to improve the health of a community, and it has a major role in promoting:

(*a*) good health practices; for example, sanitation, clean drinking water, good hygiene, breast feeding, infant weaning, and oral rehydration;

(*b*) the use of preventive services—for example, immunisation, screening, antenatal and child health clinics;

(*c*) the correct use of medications and the pursuit of rehabilitation regimens—for example for tuberculosis and leprosy respectively;

(*d*) the recognition of early symptoms of disease and promoting early referral;

(*e*) community support for primary health care and government control measures.

Despite the potential benefits of health education, existing schemes are often inadequate and ineffective. In this article I review a range of experiences in the developing world to identify the ingredients for effective and appropriate health education. The key decisions that form the basis for any planning are decisions over *what* the desired change should be, *where* the health education should take place, *who* should carry it out, and *how* it should be done.

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What to change

The first step in planning any health education is to decide what the key problems are and what advice should be given. Well meaning attempts to introduce new practices may fail if they are incompatible with local beliefs and practices.[1] Changes advocated by health educators who are based centrally may be unrealistic locally, so a comprehensive strategy of health education both locally and nationally is necessary. Any proposal for a change of practice should:

(*a*) be simple to put into practice with the existing knowledge and skills in the community;

(*b*) fit in with existing life style and culture and not conflict with local beliefs;

(*c*) not require resources of money, materials, and time that are not available locally;

(*d*) meet a felt need of the community;

(*e*) be seen by the people to convey real benefits in the short term, not in the distant future.

To achieve success, health education programmes need to be flexible and modify their advice to fit in with people's circumstances—for example, education about nutrition should be based on foods that are available locally, aids for the disabled made from local materials, latrines built with traditional methods. Local taboos are rarely obstacles to implementing health education; indeed, many traditional beliefs are sound and may actually support the health education programme.[3]

If the change that you wish to promote cannot be modified easily to fit in with the local community, it will be hard to