

Ethics of randomised clinical trials

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Editor's note

Dr Giertz discusses the principles of controlled trials and their potential for objective assessment of advantages and disadvantages of new drugs or other clinical methods. He points out that trials in which another method is compared with placebo or inaction, while potentially yielding valuable information, may also give rise to moral objections.

The Helsinki Declaration

Up to now there are no generally accepted ethical guidelines for controlled studies. The issue is hardly discussed in the Helsinki Declaration even in its last version. The reason might be that in many of these studies it is difficult to determine whether to classify them as 'mere patient-care' or as research. If they are to be considered as mere patient-care, the doctor is under the obligation to answer for his action to the medical authorities involved, but if they are to be characterised as research experiment they have, in accordance with the Helsinki Declaration, also to be scrutinised by an independent ethical committee.

The original version of this Declaration (1964)—that in its essential features has been adopted in most countries, at least in Europe—addressed itself directly to the clinical investigator, who it was assumed would himself make the necessary ethical deliberations. Under these circumstances it was immaterial whether a measure was designated as patient-care or as research. With the very setting up of ethical committees and with the very introduction of scrutiny in the new version of the Declaration, the question has emerged in a partly new light.

Even in its new version the Declaration is formulated as if it were directed towards individual doctors engaged in practical clinical work. Thus, the Declaration prescribes that a doctor among other things must have the right to utilise a new method if he considers that he can thereby help his patient. A medical measure of this kind need not have anything to do with research, but even in such a situation a doctor may need to be able to fall back on generally accepted principles of action.

An ethical evaluation presupposes knowledge of the ethical issues involved. We doctors have to

study these issues with the same interest and dedication as we use in the study of pure medical procedures. Our ambition must be to guide the evolution even in this field and not to lose the initiative to lead—as I see it—other groups with less qualification for this delicate task. To this end, the Swedish Society of Medical Sciences has established a Commission on medical ethics. The function of this Commission is to give advice and to formulate general statements concerning medical ethics when asked to do so, but also to act on its own initiative. The Commission is composed of ten members, five society members, including doctors from various specialities, one member from the State Medical Research Council and four laymen elected by various public bodies. It is primarily as chairman of this Commission that I have been confronted for the past ten years with many of the difficult ethical considerations facing medicine today. The State Research Council has in cooperation with this Commission tried to direct the control of medical research in Sweden. Ethical committees have been active since the end of the 1960s at the six medical schools in the country.

Own studies

In an effort to obtain a general view of how matters stand in practice, I carried out two studies at the request of the Research Council.

a) An examination and compilation of the somewhat more than 700 papers from all fields of medicine reported in the summary book from the Annual General Meeting of the Swedish Society of Medical Sciences in 1974.

b) A follow-up of all the projects assessed by the ethical committees in Sweden up to and including 1974.

The aim of the first investigation was to try to elucidate what should reasonably be characterised as patient-care and what should be characterised as research. About half of the papers dealt with problems where patients were involved.

Under the heading 'Mere patient-care', 127 studies were assembled where the clinical questions were entirely dominant and the scientific element was of such a kind that it was clear that ethical assessment was not necessary.

In 75 of the papers, reports were made of experiences with new diagnostic aids and therapeutic methods. The new procedures were applied in routine medical care and no more comprehensive steps were taken for demonstrating the value of the measures.

In most of these cases, the doctor in question considered the adopted measures to be medically indicated. The measures thus did not entail any departure from what was justified from the patient-care angle. Since this was a matter of medically based measures performed under medical responsibility, these cases ought not, in my opinion, to be introduced under the concept of biomedical experiments. It would probably lead to untenable consequences if we in Sweden were to get a number of authorities—the ethical committees—assigned to decide which measures were in line with the requirement of the medical regulation for—as we say—‘science and tested experience’. In Sweden this is a task for the National Board of Health and Welfare.

However, situations exist where testing can be required. Such is the case when a doctor wishes to use a new method whose reliability he feels unable to judge and where he is thus himself doubtful of the value of the method in question.

The basic rule ought to be that the doctor in charge should be entrusted with the duty of himself deciding when a medical-care measure needs to be evaluated from an ethical view-point. The situation varies however, in the evaluation of surgical and similar procedures and of some medical principles of treatment. As regards operative technique it is—at least in Sweden—most often primarily the operator in cooperation with the staff of the clinic who, on the basis of their experience and knowledge, are best equipped to judge the situation in question. As regards new drugs, the individual doctor or clinical staff would usually find it difficult to assess their advantages or disadvantages. Therefore in most countries, as in Sweden, the testing of new drugs is surrounded by special regulations.

In 115 of the papers, studies were reported where measures were adopted which were not necessary solely from the standpoint of the patient's situation, but where the aim undoubtedly was to elucidate the nature of the disease concerned or to create a basis for improved diagnostics and therapy. Thus, patient-care and research were here so closely interlinked that it was not infrequently difficult or impossible to draw a borderline. The less troublesome an intervention is and the greater its value for the patient is judged to be, the less is the need for further ethical evaluation.

In our experience it is relatively unusual for trials to be carried out on patients where the aim did not have any relationship with the patient-care situation. This type of research has no connection with the problems here discussed.

The follow-up study

Applications and committee minutes were examined and, moreover, all heads of experimental staff were asked to what extent their particular project could be implemented in the way planned and whether any complications arose. With a few exceptions, all the information asked for was obtained.

The report submitted in 1977 briefly elucidated the diverse ethical problems confronting medical research. In the report emphasis was placed on an appendix comprising reviews of most of the projects assessed. It was hoped that this compilation would serve as a valuable support to members of our ethical committees or other interested persons who feel the need for orientation on the views adopted by the committees in various situations.

The number of projects assessed was 520, of which 175 involved healthy human subjects and 345 patients. Of the projects about 50 could be characterised as controlled clinical trials. In 24 placebo was used.

Controlled clinical trials

Now, where do the controlled studies fit in? Are they to be considered a natural element of patient-care work or ought they to be characterised as research experiments?

This is, of course, an important matter from an organising view-point. But are the ethical considerations different if such an intervention is looked upon as mere patient-care or as research? I do not think so. In controlled studies there is—or at least there should always be—an effort to do the very best for the patient. The problem is that the doctor does not know—and in most instances no one else knows—what is the very best. Despite this, the doctor has to make his decision. The scientific element is merely that he organises his decisions making it possible to draw conclusions concerning the best therapy as soon as possible. If there is a risk involved, the risk is not due to the scientific approach but due to the risk involved in any medical action.

The main ethical problem concerning controlled studies is thus not the risk involved but the difficulty in not violating the patient's integrity. In proposed new Swedish law the principle of informed consent is established. Getting proper information is looked upon as one of the fundamental rights of the patient. When, how and to what extent information is to be given must, however, be the decision of the responsible doctor.

The patient's need of information can be different depending on his situation, the kind and seriousness of the illness and on other circumstances. The extent of information might thus vary from patient to patient. In one case, the patient might need very comprehensive information to be able to decide if he wants to accept a proposed treatment or not.

while in another case, more limited information might be pre-supposed justified. As this cannot be gathered in regulations, it is stated in the proposed law only that the need of information has to be satisfied.

I totally agree with these viewpoints. Before a doctor starts a treatment he has to inform the patient concerning the advantages and disadvantages with the therapeutic methods available. The doctor has this duty whether the action is looked upon as 'mere patient-care' or as research. The basic elements of information to be imparted are:

- a) A proper explanation of the procedures to be followed and their purposes.
- b) A description of the benefits reasonably to be expected.
- c) A description of any attendant discomforts and risks reasonably to be expected.
- d) A disclosure of any appropriate alternative procedure that might be advantageous.

It should be noted that the proposed law gives the doctor the right to limit the information given to the patient, if he deems this necessary. In my opinion this would happen:

- a) When the doctor judges that complete information would be psychologically damaging to the patient.
- b) When it is obvious that the patient has not the ability to profit from the information, either because of the character of his illness, or because the information is of a medically complicated nature.
- c) When the information is obviously of no significance to the patient.

What in this connection is decisive is that information should not be kept from the patient if it is of value to him. Taking this into consideration, my conclusions are:

- a) It cannot be accepted that the patient is withheld any information of value.
- b) If the doctor considers the new treatment to be equal to or better than those in common use and if he is prepared to give proper information, there can be no objection to a controlled study.
- c) If the doctor is in doubt concerning the benefit and risks of a new method, the patient must be given all information of value. Alternative possibilities should be presented. As I see it, no review committee should put this principle out of running without very strong reasons.
- d) If the doctor considers the new treatment equal

to, or better than those in common use, he might, in performing a controlled study, be entitled to limit his information if this information seems to be insignificant to the patient. Doing so, he ought to have the sanction of a review committee.

These standpoints are more restricted than some of the assessments made by the review committees in Sweden up to 1974. As I see it, it is the patient-doctor relationship which is the crucial point when dealing with controlled studies. Especially today in the light of the loss of faith in doctors, it is essential that we have an honest and frank relationship with our patients. To restore the confidence in the profession seems just now to be more important than the progress that might be created by some controlled trials. My impression is that these studies are often too highly esteemed. Thus, over the years, I have got a more and more restrictive attitude towards the use of randomised clinical studies where these entail that patients are inadequately informed.

Postscript

After this paper was presented we discussed the matter in a group chosen by the Ethical Commission of the State Research Council. The group made the following statement:

'When a doctor is confronted with alternative methods which are equal to one another he, as a rule, first makes up his mind what treatment he is going to recommend. Only after this has been done does he discuss the situation more closely with the patient. He suggests the action he has decided upon but also presents the alternative possibilities. It is part of the art of medicine to give such information in a way that inspires confidence.

In a controlled study the difference is that the decision is not made by the doctor in an arbitrary way, but through a scientifically planned randomised distribution. There is no need to tell the patient that such a method has been used. It has been shown through experience that doing so can give rise to anxiety and insecurity. The prerequisite for randomising is, however, that the doctor, after deciding on the method of treatment informs the patient exactly in the same way as if he had made the decision himself. Even if participating in a controlled study – apart from the randomisation – can be looked upon as 'mere patient care' the group recommends that these type of studies are scrutinised by the ethical committee'.