Medical Ethics

Proposal for ethical standards in therapeutic trials

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Ne dis pas, "Quel silence," mais dis, "Je n'entends pas."¹

The passage of new drugs from animal study to routine treatment can occur only through trials in man, in which three phases are distinguished. These trials must not only follow scientific rules they must obey ethical laws: (a) they must not expose the patient to any risk that is not imposed by the clinical condition, and the treatment concerned must be one that gives the patient a chance of improvement; and (b) the patient must have the right to be fully informed and to make his own decisions after advice from his family doctor, who must be given all the necessary facts.

Although some of our committee are jurists, this study considers only the philosophical perspective of these trials, excluding the medicolegal and juridical problems of relations between human experimentation and malpractice.² This delicate and arduous task requires conciliating individual medical ethics with collective ethics, both of which are essential as medical research has to improve not only the general state of medicine but also that of any patient submitted to any treatment.

We report the conclusions of an informal pluridisciplinary committee after independent and open discussion of the methods applied to clinical trials as they are designed and carried out in practice.

General rules

No trial or therapeutic study of any kind can be carried out on a person who has not been consulted or who has not understood after an examination that his state requires the treatment under study. Trials carried out on healthy subjects who either are not informed or are forced to participate are a breach of the rights of the individual.² The Nuremberg Code, the subsequent Tokyo Declaration of the World Medical Association, and the Helsinki Declaration of the same association, according to which "the physician may justify experimentation on humans only if it has a therapeutic value in terms of the subjects," all condemn trials on healthy subjects, although they do not directly prohibit them. In France "most jurists reject the legality of the issue, estimating that the contract existing between the experimenter and the subject is illicit as a result of the existence of risk without benefit."²

Although trials have been conducted on uninformed subjects, all physicians today recognise the need for obtaining informed consent from the patient before carrying out any type of trial.³ A case reported in the *Lancet*, of a patient who died during a trial unnecessary to her wellbeing to which she did not consent and to which her husband was totally opposed,⁴ emphasises the unacceptability of unethical trials and their risks to patient survival. Peto

stated that the "essential of informed consent is merely a legalistic trick to circumvent that which should be the responsibility of only the physician towards his patient."⁵ This is a regrettable attitude. Similarly, Fost is wrong in considering informed consent to be "an obstacle to research."⁶

Consent must obviously be written with the possibility of a subsequent juridical debate in mind, but it must consist of more than just signing an esoteric questionnaire. This means that the patient, a member of his family, and his family doctor must receive detailed explanations of all the reasons for the trial, the possible risk of toxicity, the time the patient will have to devote to the trial, other available treatments that might be beneficial but that he will not receive, and the possible benefit he may receive from the treatment studied and its integration into the therapeutic regimen proposed for him. Clearly, the following two rules concerning all trials are absolute, as they not only cover basic ethics but belong to the basic principles of natural rights: (a) the patient must have nothing to lose by subjecting himself to the therapeutic trial; and (b) there must be some hope of the treatment proving beneficial.⁷

Phase I trials

There are three phases of therapeutic trials. The phase I trial defines the first therapeutic study of a new treatment process in man. We will discuss only the case of new drugs. The phase I trial imposes an essential rule: it must have been preceded by all possible animal studies, which must have furnished all the necessary data to ensure that the trial conducted on humans is of the necessary quality and offers the subjects maximum safety. These studies must have been meticulously carried out on several species. Inevitably, some unknown factors will persist, particularly with regard to extrapolation of favourable and harmful effects from the experimental models to man.

There is no justifiable scientific or medical reason for exposing to risk a subject who has no medical reason to participate in a trial and who can expect no benefit from it. Hence we condemn not only all phase I trials conducted on normal subjects² but also those conducted on patients with a disease other than that for which scientific, experimental, and cognitive data have suggested that the treatment might have a beneficial effect. In other words, the phase I trial is to be conducted only on patients suffering from one of the diseases on which the physician may hope to obtain some effect. The existence of unknown factors in the extrapolation of toxicities from animals to man, and of favourable effects and the attendant risks, prohibit the simultaneous submission of more than one subject to the study.⁷

It remains to analyse the ethics of the methods. We will limit ourselves to phase I trials in which interpatient dose escalation is used,⁸ as they are traditionally carried out in most disciplines. Clinical pharmacologists administer extremely low doses to the first subjects. These doses are much lower than those presumed to be effective from preclinical data. Doses are increased progressively according to the Fibonacci plan (or one similar) so that those doses expected to be effective are administered only to the sixth or even the 10th subject in the trial. Thus the patients subjected to the early doses in the plan are only experimental objects or guinea pigs. No

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excuse can be given for making them play this part, even when they have advanced disease, as phase I protocols clearly define that the general conditions of those subjects included must meet certain criteria on the Karnofsky scale (quantification of the general state) and exclude those whose general health is unsatisfactory. Hence the methodological and scientific conditions of phase I studies, as they are traditionally carried out, do not satisfy the ethics held to in this paper. Nor do they satisfy the patient. The trial referred to above, in which, with her husband's support, the patient refused to take part, and subsequently died, was a phase I trial.⁴

Mathé proposed a new type of phase I trial using inpatient dose escalation, whereby the increase in dose would be applied to every subject.⁹ Each would thus finally receive the dose expected to achieve some favourable effect. They would also have the maximum protection from possible toxicity by the study of the effects of the low and intermediate doses administered initially. This proposal reflects the concern of jurists consulted for their opinion on the ethics of trials, but the method poses delicate problems concerning cumulative toxicities, and so detailed examination of this factor is required in several animal species.

Phase II trials

Phase II trials are devoted to determining the potential pharmacological activity of a new treatment. This treatment is applied at the dose and according to the modalities of administration determined by the phase I trials, which evaluated the toxic cost of its useful activity. Phase II trials do not initially appear to pose major ethical problems.¹⁰ Nevertheless, it is evident that their conditions are ethically satisfactory only in theory, as several problems are encountered in practice: (a) only those patients with a certain score on the Karnofsky scale can be subjected to phase II trials, as their general health state can affect the results obtained; and (b) it is exceptional to prove—even in patients whose illness is considered to be incurable and resistant to all existing treatments—that the illness is not influenced by any of the available agents, or by any of the numerous combinations that are available. This explains why pointless trials, such as those with an insufficient number of patients to enable conclusions to be drawn, must be proscribed. Also to be proscribed are conventional phase II trials that include hundreds of patients with different types of illnesses but in which each type is represented by insufficient patients for valid conclusions to be drawn.

Oriented phase II trials, in which the number of patients necessary to answer the question posed for each type of illness is consistent with that defined by Gehan,¹¹ are the only ones that are ethically convenient. It would be scientifically unacceptable if the trial included one patient less than the number required for statistical evaluation of the results according to Gehan, which would disobey the collective ethic. At the level of the individual ethic, it would be equally unacceptable to include in the trial one more patient than necessary, as a patient with something to gain if treated individually would be exposed to the risk inherent in all trials (especially as the protocol would have been drafted before the first results became known). The phase II trial of chlorozotocin in which hundreds of patients received the drug for several diseases for which it had not been justified by preclinical studies¹² was as unethical as was the fact that the studies in which the drug worked did not include the number of patients scientifically required by Gehan.

An exception to this rule is phase II trials with "predetermined expected results" comparable with a previous trial and conducted according to the method of Lee and Wesley.¹³ This method of simple comparison according to the predetermined expected result appears ethically and scientifically satisfactory. It may thus be considered for most comparative studies (see below).

Comparative trials

The third type of clinical study concerns comparative trials. It is often desirable to determine if one drug is more useful than another.

This comparative phase II trial with a predetermined expected result is often sufficient,¹³ especially as the value of comparing various drugs and their action should be modulated by their qualitative difference.

DURATION OF EFFECT

Treatments of certain states, either perceptible or occult, are measured by the duration of their effect. This is the case in the prevention of relapses or in the attempt to increase survival by prophylaxis.

The final analysis is the evaluation of the effects of treatments on the duration of life. All progress is historic, which explains the basic value of comparing the patients in the trial with "historical controls."¹⁴ The data are collected from archives or a new analysis done before the trial of the new means of treatment. This technical assessment is relative and will not be discussed. The comparative method of Gehan using historical controls does not pose a basic ethical problem as it concerns only a prolonged phase II trial. The only difficulty for a non-statistician is the need for a very large patient population to obtain sufficient precision in the comparison. He questions whether too many subjects are being included in order to prolong the trial until its significance or negation is established. Understandably he cannot ignore the fact that the study will require an increasing number of subjects as the difference sought or determined gets smaller. Those ignorant of statistics—namely, the patient, the moralist, and the physician—may ask if a trial must be systematically extended—that is, placing the patients in unnecessary positive (toxicity) and negative (depriving him of another treatment) circumstances of risk simply to calculate the significance of such a small difference. This is all the more true as the accepted probability (95%) is a choice not justified by any medical, social, economic, or even statistical criterion (why 95% and not 94%?)

Every patient in a clinical trial is at risk of an accident, and the physician must remember that he is the sole responsible party. Every protocol thus includes a risk related not only to the collective nature of its application, its rigidity reducing the acceptability to each patient, and to the probable lack of knowledge at the moment of its drafting but also to the fact that corrections for individual cases are not always anticipated when not prohibited. In a trial in Memphis nine children developed leucoencephalitis before the treatment was stopped; this is ethically and juridically unacceptable.¹⁵ A joint French-Swedish study conducted under the auspices of the Centre National de la Recherche Scientifique has shown the advantages, both economic and medicohuman, of casuistic treatments based on each individual case in comparison with treatments fixed by statistical protocols.¹⁶

RANDOMISATION

Discussing the ethical problem of the large number of patients often required in comparative trials helped us to approach the basic problem in comparative trials—namely, the ethics of randomisation of patients who will receive the treatments to be compared.^{17 18} The process is initially a shock to the patient and according to Kassiner seems insulting to the individual.¹⁹ After analysis related to psychosomatic factors, once patients are informed of the possible beneficial effects of a placebo and harmful effects of no treatment (nocebo),^{20 21} it is clear that an evaluation of the importance of these factors on treatments may be useful, providing the possible delay in developing a more effective treatment does not menace patients' wellbeing. Furthermore, it is difficult to see how a placebo and no treatment may be used with the full consent of the family member, the family doctor, and the patient.

The random choice of administering a given treatment or no treatment to compare the effects may possibly be useful in certain cases. It is not our purpose to criticise the reasons for this, or to establish an inventory of the technical defects of the randomisation methods. We may, however, propose conditions to limit the insult to the individual represented by the randomisation pro-

cedure. When two treatments are to be compared they must be considered to be the two most effective in combating the disease in question; there must be no known difference between them but there must be a reason for expecting one. If an old treatment is known to be effective, notably because it was compared with no treatment, it is unethical subsequently to compare a new treatment with no treatment: the new treatment must be compared with the old. In several trials the control has not been a treatment previously shown to be more effective than no treatment: after a trial of three drugs as adjuvant chemotherapy in breast cancer Rossi *et al* claimed a considerable benefit,²² which was not confirmed by Howell *et al* in the United Kingdom.²³ The two randomised trials on patients with osteosarcoma, which only confirmed the 60% beneficial effect of chemotherapy known for 10 years,^{24,25} as well as the randomised trial of treatment with acyclovir, which only confirmed its well known effect on prevention of cytomegalovirus infection²⁶ are also ethically unacceptable.

There is another condition concerning comparative trials with randomised controls: the selection processes must not be invalidated because of the heterogeneous distribution of patients within the groups compared, as assessed by the variables that may determine the results. The value of a heterogeneous system can be determined only by large numbers of patients—for example, 3000 to detect a 20% difference⁵ and even large numbers to affirm that a small difference is significant. These figures would be perfectly acceptable if used in conditions of homogeneity, which are necessary for all comparisons established a posteriori. They are neither ethically acceptable nor pragmatically realistic for a priori studies.

The jurist who is consulted about the study may advise against using a large control number in a priori studies as that might hinder the dynamics (speed with which the study is carried out) of the established method. Nevertheless, he must bear in mind that the clinical trial may develop into a "glass bead game"²⁷ for statisticians, if it has not done so already—an end unto itself. This is especially so if he listens to Peto, who advocates the use of large numbers in phase II trials that simply search for sufficient efficacy to justify development of the product.⁵ It is impossible not to be horrified by Peto's proposal that options in clinical trials should be placed "in the hands of a small supervisory committee, including statisticians and physicians, none of whom must have included patients in the trial."

Conclusions

In conclusion, legal specialists asked by physicians for their ethical views want the dilemma over clinical trials on man to be resolved by conciliating the scientific method with the rights of each patient. This will ensure that the defence of patients will be guaranteed a priori by ethics, rather than being debated a posteriori by the law. We prefer to propose prophylactic health ethics instead of the adaptation of a medicolegal code to clinical trials, the latter being an inevitable outcome if ethical considerations are abused and disregarded.

Many workers, both doctors and statisticians, recognise that although many comparative trials are programmed in a way that requires a random choice of controls, few produce the quality of results required for the physician. The argument for the adjuvant chemotherapy effect claimed by Rossi *et al* on the survival of women with premenopausal breast cancer,² which was not found in an identical trial in the United Kingdom, does not hold, as the many women who received the treatment were later affected by severe bone marrow sequelae, including those who would have been cured without it, illustrating the poor scientific quality of randomisation. This explains why many practitioners have little confidence in such trials, especially when we realise that the physician must and can give psychological comforts as well as just increased length of life.

Thus, with caution and reservations alluded to above and knowing that we cannot abandon clinical trials at this time of medical advances, we should not be unrealistic. We believe that physicians cannot and do not wish to assume more individual responsibility. On the other hand, we affirm that jurists cannot answer all ethical problems. The committee of ethics, methodology,

and economy has convinced us of the value and the necessity of a three pronged solution: (a) reduce the number of those trials whose success is low from the start or whose quantitative importance does not merit the disregard of medical ethics that are inevitable if randomisation is included; (b) monitor that physicians are respecting individual ethics; and (c) decide on the application of the trials in the light of the balance between their practicality, their quality, and the individual and collective ethics.

A mixed committee must work towards this objective in each hospital. It would include two physicians, one for and one against the trial discussed, who are able to analyse and discuss the questions posed by the study; a statistician, who may consider the differences being sought and calculate the number of patients required to attempt to show them; a lawyer, who would be responsible for defending individual ethics; and a judge, who would attempt to conciliate the conflicting aims of individual and collective ethics born out of research. An international association of patients who refuse to be randomised for any purpose has been founded by GM.

In this way we may be assured that the interests of both research and patients will be reconciled. This means favouring medical research so that patients can be cured and society benefited.

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