Ethics of clinical research: lessons for the future

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The *Bulletin of the Institute of Medical Ethics* published an anonymous article by an aggrieved patient complaining that she was entered into two clinical trials without informed consent.¹ The editor decided that all concerned should remain anonymous in order to concentrate on issues rather than personalities. The article was preceded by a fierce editorial depicting the perpetrators as being equivalent to Nazi war criminals and the patient to a survivor of Auschwitz. The rest of that issue of the *Bulletin* contained a carefully selected series of papers, letters, and reviews, all supporting the editorial prejudice.

This case captured the attention of the media, and the cloak of anonymity was dropped when Adam Raphael of the *Observer* newspaper published an article on 9 October 1988 entitled, "How doctor's secret trials abused me." Implicit in the accusations were charges against the Cancer Research Campaign and the ethics committee of King's College Hospital. The story then ran for a couple of weeks in the correspondence columns with a clear difference of opinion emerging between the armchair ethicists and the proponents of clinical research. An abortive debate between the editor of the *Bulletin* and MB on TV AM on Monday 10 October did nothing to clarify the issues. It was left to the BBC2 programme "Antenna" on 4 January 1989 to make a serious attempt to set the record straight with an evenhanded discussion of these sensitive issues when both leading proponents were interviewed.

We present more of the facts of this case, followed by a discussion of the ethical issues of consent in randomised trials, and ending with recommendations for the future conduct of trials that may allow a way forward out of this morass.

The clinical trials

The first trial in which this patient was entered was a multicentre collaborative study concerning adjuvant systemic treatment in managing early breast cancer. In their first submission to the ethical committee the investigators argued on ethical and compassionate grounds for waiving informed consent. Their working party argued that "all patients will be offered local therapy as good as the best available whilst the addition of cyclophosphamide or tamoxifen is unlikely to be harmful and could conceivably produce lasting benefit."² Their applications argued against seeking informed consent to avoid causing unnecessary distress to the patient in making her aware of the precise prognosis of her condition and the uncertainty of surgeons about the appropriate treatment for such disease and to avoid giving the impression that half of the patients entered into the trial would receive no treatment for the cancer that may remain after mastectomy. After a full deliberation the ethical committee responded by refusing to waive the requirement for informed consent, and at a special meeting between the chairman of the ethics committee and the chairman of the trial protocol committee an agreement to proceed with the trial was reached on the understanding that a full explanation to the patient (and, where appropriate, to her partner) would be made and informed consent sought. The patient could withdraw

from the trial at any time and accept conventional treatment, which in 1980 did not include adjuvant medical treatment.

An explanatory leaflet was prepared to present to all patients being considered for entry into the trial. This was considered to be commendable and the trial proceeded. It is interesting that 33 of the 35 participating centres in the United Kingdom thought that informed consent was not appropriate for patients entering the trial. Within two months of the start of the trial with the requirement of informed consent at our hospital, the ethical committee called a special meeting because it was concerned to learn of the additional stress that "informed consent" was causing patients

Autonomy is not the only ethical imperative . . .

and their near relatives—after the shock of learning that they had cancer and needed to have a mastectomy then to have to consider being included in a trial of adjuvant treatment within a few days of their operation seemed to be an additional burden. The chairman of the protocol committee, therefore, strongly pleaded for a review of the attitudes of the ethical committee. It was thought that in the special circumstances of the trial informed consent should not be required but the rationale for the treatment would be explained in detail to the patients who were randomised to receive either tamoxifen or the short course of cyclophosphamide. This decision, which was unanimous, was taken to allow this desirable trial to proceed without causing further distress to patients. Paradoxically, the complainant was randomised to receive the best of the options as determined by a recent published report seven years after the start of the study.³

A separate application was made 18 months later to the ethical committee to investigate a method of improving the psychological adjustment of women to mastectomy by the intervention of a professional counsellor. The protocol was approved and informed consent was not required. The trial was carried out because, although counselling cancer patients might help them to cope with the disease, a counter argument was that those who were counselled might come to rely on the counsellor as a psychological crutch rather than use their own resources (as can be expected in 70% of patients). It was therefore important to assess scientifically the value of counselling. As the counselling was limited because only one part time counsellor supported by research funds was available a clinical trial was proposed. Instead of individual randomisation, however, the study was arranged so that at fortnightly intervals patients who presented to the clinic had a 50:50 chance of meeting the nurse counsellor. At this time only one other clinic in the United Kingdom offered a counselling service. Furthermore, any patient who was identified by the senior surgeon as developing psychological problems during treatment was offered psychological support and counselling.

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Patients were, of course, receiving the medical and nursing care which in our hospital has a long tradition of providing support and explanation throughout protracted illnesses. The results of this study have only recently been published⁴ and agree reasonably well with those obtained in a similar study carried out in a different part of the United Kingdom. A network of nurse counsellors has now been set up in an attempt to carry this worthwhile service into all health districts.

Shift in attitudes

Over the past 30 years we have witnessed a dramatic shift in the attitudes of doctors and patients to medical science and ethical behaviour. Since 1950 attitudes, medical knowledge, and doctors' relationships with patients have changed, and the patient has become more enlightened, more aware of health, and more demanding over medical decision making. Inevitably tensions have developed, and the case under discussion is but one expression of the clash of ethical imperatives that is now to be expected.

Randomised clinical trials

No one would deny the need to make progress in the care and management of patients with cancer. Most new ideas that improve our understanding of the malignant process and suggest innovations in treatment arise from tissue culture in the laboratory or experimentation on rodents. It would be naive, foolish, and dangerous to translate these experimental ideas directly into standard medical practice without carefully controlled development. Clinical trials (often stigmatised as "human experimentation") are conducted in three phases. The first phase explores the toxicity and methods of delivery using human volunteers. The second seeks evidence of activity among a predetermined set of patients with a specified cancer. Never has there been any debate about the need for full informed consent among these two groups of volunteer subjects. It is when we come to phase three trials that confusion and moral dilemmas become explicit.

Once sufficient evidence has accumulated from a phase II trial that the treatment is not only effective but may in theory be better than standard treatment the time has arrived for the randomised control trial. In

medical circles this point is described as "equipoise."⁵ To mount national trials there has to be first of all a professional equipoise where roughly equal numbers of the profession favour either the standard treatment or the novel treatment. For a physician to enter a patient into the trial a personal equipoise must exist, expressed as a genuine uncertainty about which treatment would offer the better chance for that patient. From the outset, by their own code of conduct clinical researchers recognise the moral dilemma and the hazard of moral compromise in attempting to consider the needs of future generations of patients while doing the best for the patients sitting in their consulting rooms.

Ethical models

Until about 10 years ago the majority viewpoint among doctors was based on the beneficent model of doctor-patient relationships. If full informed consent for randomisation was sought it was believed that the expression of uncertainty about the best treatment and the description of the uncertainty of the outcome of their cancer would be too much for the patient to bear. Therefore, provided that no one was denied the best available treatment the fact that an alternative treatment that was already tried and tested in phase I and phase II studies would be offered as part of a random decision was judged to be irrelevant. Indeed, the Medical Research Council's guidelines at the time of the initiation of the trials mentioned above accepted this approach for patients with "a possibility of fatal illness."⁶ It is worth noting that physicians and surgeons who were practising in the same climate of knowledge and uncertainty, yet did not enter the patients into clinical trials, would also be guilty of withholding total information by not disclosing that half of the medical profession might favour an alternative treatment to that which they offered.

There has been an enormous shift in medical opinion favouring increased autonomy for patients, which is partly a result of the work in the Cancer Research Campaign Clinical Trials Centre at the Rayne Institute. This group was acutely aware of these ethical and moral dilemmas and invited a lay ethicist and moral philosopher to join a working party in 1980. They listened, respected her opinions, and published an article in the *BMJ* in 1983 under joint authorship

advocating a policy of full informed consent in cancer trials, in particular where a patient has a rational and justifiable reason to calculate his or her own utilities in the face of the alternative treatment options.⁷ These issues were particularly poignant when considering the trial mounted by the Cancer Research Campaign to compare mastectomy with conservation of the breast for the early stages of disease that had to be closed after recruiting only 150 patients because the insistence on full informed consent frightened off both surgeons and patients.

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Autonomy, however, is not the only ethical imperative that should be considered, and perhaps an exaggerated regard for this single principle will put at risk not only the practice of scientific medicine but the whole concept of the doctor-patient relationship. Traditionally, the duty of doctors is to do their best for their individual patients and not just to provide a list of alternatives from which the patients (now the consumer) select according to their needs and desires. If doctors are to continue to have the duty of care they must also bear in mind other ethical principles when they treat each patient. For example, non-maleficence—could informed consent come into this category since further information and uncertainties are forced upon patients at a time when they are feeling most vulnerable? Justice—should information be given about treatments which if available would drain the resources of the health service so that future patients may have to remain untreated?

Informed consent does not absolve the doctor from duty of care nor does it always help the patient to come to a decision about how she would like to be treated. What will help patients to determine their treatment priorities is advice from the medical profession that is based on well documented data. It is the "risk-reduction approach of controlled experimentation [that] serves to keep to a maximum the numbers of patients who receive optimum treatment at any particular point in the evolution of therapy."⁸

Recommendations for future conduct of clinical research into treatment

We believe that the solution to this dilemma lies not in international declarations or codes of conduct but in a practical solution where the rights and responsibilities of the individual are given full consideration while scientific medical practice is encouraged with the aim of reducing the burden of human suffering in the future. We all want to encourage greater patient awareness, and ethical committees have a responsibility for safeguarding the interests of patients when taking part in clinical research. The idea of setting up a national ethics committee (for topics other than reproduction) has already reached the correspondence columns of the *BMJ*,^{9,11} and we wish strongly to support this proposal. After five years of serious consideration with both internal and public debates on this matter the Cancer Research Campaign Clinical Trials Centre and the ethical committee of King's College Hospital wish to make the following proposals.

(1) When clinical research is non-therapeutic and in phase I and phase II drug trials, where patients or subjects are volunteers only, and the issue of informed

consent is not controversial it must be sought in each case.

(2) When a group of clinicians wish to ask by a randomised controlled trial a minor question in a single district general hospital—for example, comparing two types of sutures or two types of non-steroidal anti-inflammatory drugs—then obtaining informed consent is traumatic neither to the patient nor to the doctor, and the morality of the study can safely be left to the local ethical committee.

(3) In considering national multicentre randomised controlled trials asking major questions and funded by national bodies such as the Medical Research Council or the Cancer Research Campaign a radical change of emphasis is needed. We advocate having a national ethical committee with both professional and lay members. Appointment to this committee should be seen as a singular honour, and the members should be knowledgeable about the principles and practice of medical ethics. Once a large trial has been funded and its protocol approved by this committee the trial should be launched with public notices in the learned journals and the news media. All eligible patients being treated for the disease at any hospital in the UK should then be given full information on the national trial and have the right to decide to enter or not enter the trial. So in fact there would be only one consent procedure, nationally approved, for all patients whether they are in the trial or not.

In certain cases the committee may take the decision that for a particular trial, in consideration of all the issues, the principle of non-maleficence should override that of autonomy. In such cases informed consent need not be sought since a true national equipoise exists, and given current knowledge and circumstances the best medical care is randomisation into a trial. In some trials an extension of this argument may also allow the committee to decide that patients randomised to the control group that is to receive standard treatment should not need to be informed of all the possible risks and benefits of the newer treatments under test in the other arms of the trial.

Finally, all patients should retain the option to abrogate their responsibility and right to autonomy, leaving the clinician to make the final decision, which might indeed be determined at random. Patients, however, must also be reassured that at any time they may withdraw from a trial but will still receive the care required for the treatment of their disease.

Inevitably this makes increasing demands on patients when they are weak and vulnerable. Bearing in mind that most of us become patients at some time before we die, this is the penalty we have to accept unless we wish to return to the dark ages when treatment was determined by conceptual rationalism rather than scientific method.

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