Symposium

Ethical review of multi-centred trials

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The definitive international code on the ethics of medical research recognises that 'medical progress is based on research which ultimately must rest in part on experimentation involving human subjects' (1).

History shows that doctors have always been concerned to regulate their own conduct. An outstanding early example was Thomas Percival's Code for Clinicians at the Manchester Royal Infirmary almost 200 years ago, which addressed issues raised by new methods of treatment (2). In the United Kingdom, the Medical Research Council (MRC) and professional bodies, notably the British Medical Association (BMA) and the Royal College of Physicians of London (RCP) regularly revise and issue guidelines for the conduct of research involving human subjects (3,4,5,6,7) and the Department of Health circulates advice to National Health Service Authorities (8) which is currently in process of revision.

Grounds for concern

Why is there concern about research involving human subjects, and particularly about clinical trials conducted in a large number of centres covering many different health authority districts? Four reasons can be identified:

(i) The inadequacy of local committees set up to approve the ethics of research proposals. The composition, procedures and accountability of committees is variable and the necessary expertise is frequently unavailable or unused (9,10,11,12). These defects are particularly revealed in local committees' consideration of multi-centred trials (13) which are increasing in frequency and importance.

(ii) The sheer logistics for researchers in a multi-centred trial of having to submit proposals to a large number of local committees, each of which has different requirements.

(iii) The absence of any one clearly authoritative and independent committee at a national level competent to judge the more controversial or complex multi-centred proposals denies the researchers a mechanism for justifying their intentions. Even the MRC, which has an admirable record in safeguarding the ethics of the research which it supports, has sustained vehement criticism of its national controlled trial on the relationship between spina bifida in children and the ingestion by mothers during pregnancy of folic acid supplements. This criticism is based upon the claim that it had already been shown that such supplements protect unborn children from the risk of major handicap: it must therefore be unethical to withhold them from any mother at high risk. The council's contention is that such a protective effect still required to be clearly proved. However immaculate the MRC's case in its own defence, it is inevitably weakened by the fact of its being its own judge and jury.

(iv) Individuals and consumer groups claiming to represent the interests of the subjects of research are properly vigilant and demand reassurance, especially when tragedy strikes, as in the case of the medical student who died from aplastic anaemia nine months after being paid to participate in tests on a new preparation of a benzodiazepine drug, although there was no suggestion at the inquest that the company concerned had been negligent in any way, nor that the death could have been prevented by any kind of rules (14).

It was claimed only five years ago that the situation in the UK was 'totally lamentable' and that 'the very existence' of the worst ethical committees 'may be more of a threat than a benefit to patients because they can provide the perfect cover for unscrupulous' (15).

The spur of data protection

The publication of the Bill which heralded the Data Protection Act 1984 introduced a new dimension into the national picture. Together with other far-reaching provisions for safeguarding the confidentiality of identifiable personal information, the Act gives statutory backing to the requirement for

Key words

Ethics of medical research; multi-centred trials; local research ethics committees; national research ethics committees; data protection.
research proposals to be cleared by an approved ethics committee before confidential personal health information held on computer may be disclosed. The Interprofessional Working Group (IPWG), which was set up by the BMA at the behest of the Department of Health to advise them on the operation of the Act as it relates to health care, identified in 1982/3 the need to complement a network of improved local committees, under the aegis of NHS authorities, with a national counterpart.

The IPWG's thoughts were developed by the BMA, which envisages an ungrammatically styled national ethical research committee to meet the perceived needs (6). This proposal concerns only the ethics of research proposals and is not to be confused with the more comprehensive national ethics committee mooted by Baroness Warnock (16) and others, which would be more akin to the forum for bioethical discussion created in France in 1983 – the Comité Consultatif National d'Ethique pour les Sciences de la Vie et de la Santé (17). The Department of Health and Social Security – as it then was - reaffirmed its consistent policy that the ethics of research were primarily the concern of the health professions. The BMA therefore canvassed the opinions of the health and allied professional bodies – including social work – concerned, and of recognised national representatives of the consumer interest, in extensive informal discussions during 1984/85. The Conference of Medical Royal Colleges and Faculties and the MRC elected to stand aloof at that stage, although they were kept informed of progress. There was an encouraging amount of common ground, and definitive proposals were subsequently approved by the BMA Council early in 1986 (6) and supported by the General Medical Council. Support for the proposals 'in principle' has been vouchsafed by almost all the local committees which responded to a letter from Sir Douglas Black on behalf of the BMA later that year. Consultants' representatives subsequently expressed reservations, and discussions have been conducted sporadically up to the time of writing.

A national committee for the ethics of research
Advocates of such a committee envisage a national committee as a central resource which would have three functions:

(i) To consider proposals for national or multi-centred trials in order to facilitate good research and to ensure consistency in approach;
(ii) To serve as a repository or reference library of good practice, drawing upon its own experience and that of a strengthened network of approved local committees to sift, collate and catalogue information and advice which can be disseminated to local committees upon request;
(iii) To identify experts in every relevant field and mobilise their assistance as a service to researchers, at any level, seeking advice.

The national committee need not start with a tabula rasa. There is a plethora of good advice already available in the guidelines referred to above, which merit endorsement and application (3,4,5,6,7).

No distinction is envisaged between clinical and epidemiological research because the principles – of consent, confidentiality, communication and conduct – are the same.

There is no intention to infringe the essential autonomy of local committees, which must remain free to reject any advice proffered by the national committee and to decline to participate in any multi-centred trial for their own reasons.

The most recent and authoritative contribution to the debate is the second edition of the RCP's 'Guidelines on the Practice of Ethics Committees in Medical Research involving Human Subjects', which were published late in 1989 and discussed with an invited audience of chairmen of ethics committees, directors of public health and other interested individuals on 9th February 1990 (7). Paragraph 25 merits quoting in full:

'Multi-centre studies are increasingly undertaken. They are organised by a central body which pays attention to ethical issues. They are then submitted to ethics committees in each centre. There have been occasions when a project has been approved in some centres and rejected or modified in others. This is not surprising since opinions on ethical issues can legitimately vary and this cannot be escaped. But it is undesirable that this should happen to a multi-centre project and multiple submission is cumbersome and probably unnecessary. Epidemiology studies may even be nationwide and consultation with all health districts, which often contain more than one ethics committee, is evidently impracticable. There is no satisfactory solution at present. Perhaps centres could agree to delegate a decision on a multi-centre study to a single ethics committee to represent them all, and this will be easier to arrange when modes of working and standards are more uniform. A central review body, decisions of which are agreed to be generally acceptable, does not present at present.'

No better case could be made for a central body, but not a central review body, which would imply an appellate function which would infringe the autonomy of local committees. It may be noted that there is no appeal mechanism at present from a rejection by a local committee.

Counter-arguments
What objections are raised to a central committee?

(i) The need is diminishing as local committees are improved and the forthcoming revised advice from the Department of Health may reasonably be expected to encourage further harmonisation of the remit, composition, methods and standards of local committees. The relentless march of information
technology should further reduce delays by facilitating quicker and better communication between individual local committees.

Answer: recent experience and anecdotal evidence supports only qualified optimism about local committees. In any event, improvement of local arrangements and a national resource are complementary, not conflicting objectives.

(ii) A national committee would either be toothless and redundant because autonomous local committees would thumb their noses at it, or conversely, it would be a Big Brother intimidating the locals.

Answer: it cannot be both, and note the evidence that local committees welcome the idea in principle.

(iii) A national committee would be excessively bureaucratic, whether it approved research proposals directly or through referral to a local committee appropriately experienced and resourced to deal with a specific proposal. The need to invite endorsement by all the other local committees involved would inevitably cause delay.

Answer: the new arrangements which are envisaged could scarcely be more cumbersome and unsatisfactory than the present committees. The response of local committees will be crucial.

(iv) A national committee will be costly. Who will foot the bill?

Answer: it need not be expensive relative to its value, especially if the committee is kept to a relatively small number of very senior people of distinction in their field, supported by acknowledged experts who may be expected to give their services free of charge. If such a committee is to be seen to be independent of vested professional interests, it will have to be funded by government or some other independent source.

(v) What about the need to monitor the standards of local committees?

Answer: such a function would be suicidal for a national committee. It is for local committees themselves to find the ways to do this.

The debate will surely go on.

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