Ethics in clinical research: searching for absolutes

Editorial

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The ethics of contemporary research practice, especially with respect to the design and conduct of clinical trials, has been subjected to considerable scrutiny in recent years. Issues related to informed consent, the use of placebo controls and the tension between the requirement for scientific evidence on the one hand and for patient autonomy on the other have all generated heated debate. In this editorial I review some recent controversies that highlight the fractious nature of the debate and point to the watershed we are approaching in clinical research ethics. Although there are no obvious solutions, it is clear that there is a need for increased patient participation in any attempt to achieve consensus on the ethical conduct of medical research.

Several months ago the *British Medical Journal* published 2 research studies involving several hundred patients from whom informed consent had not been obtained.[1,2] Both studies had been approved by local ethics committees. Moreover, both studies complied with the Declaration of Helsinki,[3] which permits physicians to waive the requirement for informed consent as long as an independent ethics committee has deemed the waiver to be justified. Divergent opinions on the ethics (and publication) of the studies were expressed in accompanying commentaries and in the unprecedented wave of letters to the journal that followed.

More recently, 2 articles in the *New England Journal of Medicine*[4,5] that questioned the ethics of placebo use in certain clinical trials generated strong criticism from members of that journal's editorial board. At issue were several placebo-controlled trials of antiretroviral treatment (to reduce perinatal HIV transmission) being carried out in developing countries. An objection to the use of placebo controls in contexts where effective treatment exists was previously raised by Rothman and Michels,[6] who documented several examples. Reaction from researchers and regulators (including members of Health Canada's drugs directorate[7]) has been equivocal, however. Those favouring the use of placebo controls put forward pragmatic (it is quicker and cheaper), statistical (it requires smaller sample sizes) and other counterarguments. In the case of the HIV transmission trials, for instance, it has been argued that, given the cost of antiretroviral drugs, patients from developing countries would not have received such treatment under the local health care system.[8] Moreover, imposing Western standards on all clinical trials conducted in developing countries would have prevented the development of many interventions such as oral rehydration, micronutrient supplementation (e.g., vitamin A) and low-cost surgical procedures (e.g., cataract surgery).[8] Finally, if the placebo arm were replaced by known effective treatment, study results might be difficult to interpret.[9] A clear consensus on the issue has yet to emerge: in at least 2 of the HIV transmission trials, the investigators have decided to drop the placebo arms,[10,11] while the *Lancet* has reversed its previous editorial opposition to the use of placebo controls.[12]

Other issues relating to placebo use, namely, the updating of informed consent and the premature termination of randomized trials, were recently highlighted in relation to the TRACE trial (on the effects of ACE [angiotensin-converting enzyme] inhibitors in patients with left-ventricular dysfunction after myocardial infarction).[13] The results of 2 other randomized trials (demonstrating a benefit for ACE inhibitors) were published before the planned termination of the TRACE trial. Brophy and Joseph[13] pointed out that the informed consent of participants

should have been updated in light of the new information. Further, they argued that proper (i.e., Bayesian) analysis would have included evidence from the other trials and led to an early ending of the TRACE trial.[13] Patients serving as placebo controls in the trial would then have received ACE inhibitors several months earlier. The TRACE investigators disagreed, basing their arguments on differences between the trials with respect to patient characteristics and drug regimens.[14]

A related problem has emerged in the context of high-dose chemotherapy for metastatic and high-risk breast cancer.[15–17] This relatively new treatment is arguably the most promising available for such disease, although experience is restricted to the results of several nonrandomized (phase I and II) trials. Results from randomized (phase III) trials, which are designed to provide evidence regarding efficacy, are not expected for another 2 years or so.[15] A unique feature is that the treatment, which involves the administration of high doses of standard antineoplastic agents (with autologous bone marrow transplant [ABMT] or peripheral blood progenitor cell [PBPC] support) is readily available in several medical institutions. Given the dismal outlook in metastatic breast cancer and the suggestion that high-dose treatment is probably the best option available, patients are flocking to institutions that will provide the treatment outside the framework of a randomized trial. It has been estimated that more than 90% of women with breast cancer treated with high-dose chemotherapy between 1989 and 1993 received the treatment in non-research settings.[16] Not surprisingly, the phase III randomized trials are accruing patients at half the expected rate. This has been termed a "disaster" and a "waste of valuable information," and some researchers advocate denying patients access to high-dose chemotherapy outside a clinical trial protocol.[16] The problem has likely been compounded by the publication of results from a randomized trial conducted in South Africa, which showed an unequivocal benefit for high-dose chemotherapy.[18] Response to chemotherapy, duration of response and survival duration all favoured the group receiving high-dose chemotherapy. However, the study has been criticized on various grounds,[19] its principal weakness being the relatively small size: the high-dose and conventional treatment arms had only 45 subjects each.

The dichotomy between patient (and physician) autonomy and the need for scientific evidence has repeatedly led to controversy. This was seen when sulfonamides were introduced in the mid-1930s and, more recently, in connection with access to zidovudine and dideoxyinosine (didanosine).[20] Public pressure persuaded the US Food and Drug Administration to relax its regulations and release the latter drugs during early phase II testing. The regulatory change also affected other drugs: tacrolimus (FK-506), an immunosuppressive agent used in transplant recipients, was placed on a fast track for evaluation. Randomized trials have since shown this agent to be a very effective immunosuppressant with several potential advantages over other drugs.[21] Nevertheless, the regulatory process, trial design and conduct problems, and the consequent multi-year delays that preceded licensing of tacrolimus led researchers and patients to severely criticize, among other things, the ethical malpractice that attends current regulatory policy.[20,22]

Although less stringent criteria for drug approval are likely to make decision-making by patients (and physicians) more autonomous, critics of fast-track approaches caution that they are also likely to make decision-making less informed[20] with regard to serious side effects and efficacy. However, arguments regarding toxicity are at least partly compromised by the fact that phase III randomized trials are not designed with a view to addressing safety issues comprehensively;[23] the most common side effects become apparent during phase I and phase II trials, while the less frequent ones are detected only during postmarketing surveillance.

One feature of high-dose chemotherapy with ABMT or PBPC support, namely, its rapid and continuing evolution, illustrates the complexities inherent in obtaining definitive evidence. High-dose chemotherapy is continually being refined. Improvements in antimicrobial prophylaxis and PBPC support (coupled with the use of hematopoietic growth factors) have resulted in a decline in infection and toxic effects. Other improvements, intended to increase efficacy, include the administration of multiple, rapidly cycled courses, techniques for purging the bone marrow, the use of newer cytotoxic agents and attempts to harness antitumour graft-versus-host responses.[24–27] This means that the results of any randomized trial, with a 2- to 3-year accrual period and a 2- to 3-year follow-up, will be several years out of date by the time they are published. Some of the randomized trials yet to be completed began recruitment in 1990–91. Even if the next reported results are negative, the information provided to patients cannot be based only on such findings. If advice is to consider the potential effects of recent improvements, it would have to include evidence of an a priori or speculative nature.

Freedman[28] argued that we cannot conscript patients to serve as subjects in clinical trials; it is a patient's right to decline participation after being completely informed about the lack of consensus within the expert community with regard to the relative merits of the therapeutic options. A patient's decision to choose a treatment that is preferred by some experts cannot be ignored, irrespective (or especially because) of the uncertainty prevailing in expert circles. Unfortunately, as the high-dose chemotherapy example shows, respect for patient choices could lead

to a delay in the completion of scientific studies. On the other hand, the standard drug approval process avoids a conflict between respect for patient autonomy and timely completion of efficacy studies by effectively denying patients their choice, at least in part: they can decline to participate but obtaining the new drug might otherwise be difficult.

Contemporary research ethics are intricate enough to defy consensus even on long-established features of randomized trials. Clearly, ethical research practice extends far beyond obtaining institutional review board approval and informed consent. These manoeuvres, while designed to protect patients' rights, can only serve as components of a more comprehensive system of safeguards. These safeguards include the investigators' commitment to maintaining the highest ethical standards and the inclination of other researchers to criticize unethical studies. Recent discussions on the ethics of clinical research have benefited from increased input from patients. Although such input may tend to make an already complex situation more contentious, the added perspective is clearly necessary. Closer scrutiny of established practices, with input from increasingly concerned and informed patients, should serve to further what has been described as the search for absolutes in a secular and ambiguous age.

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