[Section 7]

CLINICAL TRIALS

Clinical trials are most frequently undertaken in biomedical or health research, although other clinically related disciplines, such as psychology, also conduct research that evaluates interventions, usually by comparing two or more approaches. In this section, clinical trials will be discussed in the context of biomedical research with emphasis on pharmaceutical trials.

Researchers conducting clinical trials seek different research objectives under various research formats. Clinical trials may include questions that are not directly related to therapy (for example, cost effectiveness, drug metabolism), in addition to those that directly affect the treatment of the subjects. They may also take the form of case studies, cohort studies, case control studies, "n of 1" studies, or multicentre clinical trials. Although the types and forms of clinical trials naturally create methodological differences, they all can accommodate the ethical principles and procedures articulated in this Policy. Four topics of clinical trials that give rise to ethical issues are reviewed: the phases of pharmaceutical research, multicentre trials, placebo-controlled studies, and the analysis and dissemination of the results of clinical and multicentre trials.

A. Clinical Equipoise

"*....at the start of the trial, there must be a state of clinical equipoise regarding the merits of the regimens to be tested, and the trial must be designed in such a way as to make it reasonable to expect that, if it is successfully conducted, clinical equipoise will be disturbed.*"[1]

Clinical equipoise means a genuine uncertainty on the part of the expert medical community about the comparative therapeutic merits of each arm of a clinical trial. The tenet of clinical equipoise provides a clear moral foundation to the requirement that the health care of subjects not be disadvantaged by research participation.[2]

B. Phases of Pharmaceutical Research

Four conventional phases of pharmaceutical research in clinical trials are emphasized because they create different ethical issues:

- Phase I clinical trials conventionally examine the acute, dose-related pharmacological toxicities of new pharmaceutical drugs; they are often conducted in healthy subjects, but may involve patients in studies with interventions that are known to be toxic.
- Phase II clinical trials primarily examine the short-term pharmacological toxicities of—and, to a lesser extent, the efficacy of—new drugs; they are conducted in populations with specific diseases.

- Phase III clinical trials primarily examine the pharmacological efficacy—and, to a lesser extent, the short-term toxicities—of new drugs. Phase III and IV clinical trials are designed to increase the survival or the quality of life of subjects suffering from a specific disease or condition.

- Phase IV clinical trials, also known as post-marketing surveillance studies, primarily examine the long-term efficacy and toxicity of already-marketed drugs.

It should be noted that Phase I clinical trials now increasingly include persons with specific diseases—persons for whom all conventional therapies have failed (e.g., terminal cancer or AIDS). Such studies may be designated as Phase I clinical trials where, in fact, they properly should be designated as mixed Phase I/II or pure Phase II clinical trials.

Article 7.1 **Phase I non-therapeutic clinical trials shall undergo both stringent review and continuous monitoring by an REB independent of the clinical trials sponsor.**

Conventional Phase I clinical trials depend on generally healthy subjects who are paid by the sponsors of newly developed drugs. These considerations raise ethical concerns about the selection and recruitment of subjects, the process of free and informed consent, the meaning of free and informed consent under these circumstances, the membership and procedural adequacies of the REB (if any) and the duties of the federal regulator.

The development of a plethora of new pharmaceutical drugs and the private setting of Phase I clinical trials invite vigilance from an ethical perspective. As more of these trials are conducted in the academic sector, academic REBs must carefully monitor all aspects of such trials including unexpected adverse events—for example, unforeseen drug toxicity. These are matters of continuing ethical concern.

Article 7.2 **In combined Phase I/II clinical trials, researchers and REBs shall carefully examine the integrity of the process of free and informed consent. Where appropriate, the REB may require an independent monitoring process.**

Combined Phase I/II clinical trials raise particular ethical concerns because they are often conducted with desperate populations whose therapeutic options have been exhausted. Patients afflicted with terminal cancer and HIV/AIDS are examples. Such situations may distort the perceptions by patients and their families, as well as by researchers, of the balances between the harms and benefits of the research. Such factors not only relate to the process of free and informed consent, they also influence the clarity and strength of stopping and withdrawal procedures. Because of these considerations, it is essential that researchers and REBs collaborate and consult with each other throughout the course of Phase I/II clinical trials.

Phase II and III clinical trials, unlike combined Phase I/II clinical trials, often include placebo controls to detect and quantitate the acute toxicity and efficacy of an experimental drug. In such studies, and in addition to the other ethical concerns raised for combined Phase I/II clinical trials, the use of placebos (discussed below) can further stress the duty of researchers to maximize the benefit and minimize harm to subjects.

Phase IV clinical trials are usually designated as post-marketing surveillance studies. Often, however, they serve the purpose of post-marketing advertising conducted in the private practices of physicians. For example, a physician may be paid a per capita fee by the sponsor to assess the side effects and the acceptance by patients of an already-marketed drug. Such Phase IV clinical trials may compromise physicians' professional integrity with respect to finders' fees, billing practices and utilization of public resources, as well as with respect to conflicts of interest. Researchers and REBs must examine the scientific and ethical implications of Phase IV clinical trials with the same diligence accorded to other phases of clinical trials.

Clinical trials of medical devices, whether implanted in human subjects or not, raise ethical concerns similar to those encountered in the four phases of pharmaceutical research. In addition, clinical trials with some implants can create unique ethical dilemmas concerning the process of free and informed consent, as well as raise potential conflicts of interest. For example, newly developed heart rhythm pacemakers, which may cost thousands of dollars, must be implanted surgically to assess their efficacy and possible harmful side effects. In some jurisdictions, health plans pay the surgical fees, while intellectual property rights related to the experimental devices usually remain with the sponsor of the trial. In such clinical trials, and to whatever extent is practical, researchers and REBs must ensure that subjects are accorded all opportunities to exercise their rights to the initial and continuing processes of free and informed consent.

The REB must carefully examine such clinical trials to assist researchers in avoiding potential conflicts of interest concerning the selection and recruitment of subjects, and payments by sponsors to the researchers. The REB should also examine (1) the issue of continuing access after the trial, (2) the treatments, especially medical devices to which the subjects may have become accustomed or, (3) if impossible, the provisions taken to ensure adequate replacement. To discharge its duties to protect the welfare of subjects, the REB should also be aware that numerous safety standards (e.g., mechanical and electrical) apply to medical devices and receive assurances that these standards will be respected.

Clinical investigators undertaking research intended for use in seeking regulatory approval for pharmaceuticals should also generally respect the ICH Guidelines, which were developed by the United States, Europe and Japan and have been adopted by Canada.[3]

Article 7.3 **REBs shall examine the budgets of clinical trials to assure that ethical duties concerning conflict of interest are respected.**

Budgets for clinical trials usually are calculated by per capita costs—that is, the sponsor pays the researcher a fixed sum for each research subject recruited. Per capita payments raise ethical concerns because of the potential to place the researcher in a conflict between maximizing economic remuneration and serving the best health interests of subject-patients, especially if the researcher also holds a therapeutic or clinical or other fiduciary relationship with the subjects. Disclosure of the amount of the per capita payment, and other budgetary details, will assist the REB in assessing potential conflicts of interest, and may also assist the researcher in resolving them. As a general guide, per capita payments should be comparable to the physician's or researcher's usual professional fee. When trials take place within a public institution, such as a hospital or a long-term care facility, recovery of utilization costs for institutional and other resources (such as radiological and diagnostic services) should be considered essential, and should be in addition to any overhead charge stipulated by the institution.

Examination of the clinical trials within the ethical perspectives of the phases outlined above for clinical trials will assist REBs and researchers in identifying ethical issues that are both generic for all clinical trials and specific for a given trial.

C. Multicentre Clinical Trials

Multicentre clinical trials are now commonplace, and reflect not only the need for increased numbers of research subjects but also the multidisciplinary nature of contemporary human research. For REBs, multicentre trials raise particular difficulties for REBs, some of which are discussed in Section 1.

D. Placebo-Controlled Studies

Article 7.4 **The use of placebo controls in clinical trials is generally unacceptable when standard therapies or interventions are available for a particular patient population.**

Clinical equipoise is widely regarded as the moral foundation of the randomized-controlled trial. In order for a clinical trial to proceed ethically, a state of clinical equipoise must exist at the trial's inception (see Subsection A, above). Consistent with clinical equipoise, a placebo may be used as the control treatment in a clinical trial in the following circumstances:

(a) There is no standard treatment;

(b) Standard therapy has been shown to be no better than placebo;

(c) Evidence has arisen creating substantial doubt regarding the net therapeutic advantage of standard therapy;

(d) Effective treatment is not available to patients due to cost constraints or short supply (this may only be applied when background conditions of justice prevail within the health care system in question; for example, a placebo-controlled trial is not permissible when effective but costly treatment is made available to the rich but remains unavailable to the poor or uninsured.);

(e) In a population of patients who are refractory to standard treatment and for whom no standard second-line treatment exists;

(f) Testing add-on treatment to standard therapy when all subjects in the trial receive all treatments that would normally be prescribed; or

(g) Patients have provided an informed refusal of standard therapy for a minor condition for which patients commonly refuse treatment and when withholding such therapy will not lead to undue suffering or the possibility of irreversible harm of any magnitude.

When a clinical trial involving a placebo control is undertaken, the researcher and the REB must ensure that patients or authorized third parties are fully informed about any therapy that will be withdrawn or withheld for purposes of (1) the research, (2) the anticipated consequences of the withdrawing or withholding of the therapy, and (3) the reasons why investigators deem a placebo-controlled trial to be necessary (see also Article 2.4).

E. Analysis and Dissemination of the Results of Clinical Trials

In many clinical trials, the sponsors obtain contractual rights to the initial analysis and interpretation of the resultant data. Researchers and REBs must ensure, however, that final analysis and interpretation of such data remain with the researchers, whose duty it is to ensure the integrity of their research. When stopping rules are required in Phase I, II and III clinical trials, monitoring of the interim results must be done independently. It should also be remembered that, with a stopping rule in place, long-term positive or negative effects might be masked by short-term harms or benefits.

Equally important, though sometimes difficult to achieve, is the researchers' duty to disseminate the analysis and interpretation of their results to the research community. Unfortunately, negative results and outcomes of research frequently are not published or disseminated. Silence on such results may foster inappropriate and potentially harmful clinical practices or needless and wasteful duplication. Researchers and REBs may exert pressure to alleviate this deficiency in the dissemination of research results by resisting publication bans proposed in research protocols, on the basis of ethical obligations of truthfulness and the integrity of research. Research journalists, journal editors, members of editorial peer review boards, sponsors and regulators should address this as an issue of scientific and ethical urgency.

Endnotes

[1] Freedman, B., "Equipoise and the Ethics of Clinical Research", *New England Journal of Medicine*. 1987; 317: 141-143.

[2] World Medical Association, *Declaration of Helsinki.* 1964, as revised 1996, para. II.3.

[3] International Conference on Harmonization, *Guidance E6: Good Clinical Practice - Consolidated Guideline* (of ICH Technical Requirements for the Registration of Pharmaceuticals for Human Use) 1996, adopted by Health Canada in 1997: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e6_e.html.