GUIDELINES

GUIDELINES FOR PHASE IV CLINICAL TRIALS

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The following guidelines were approved by the Board of Directors of the Canadian Psychiatric Association on October 1, 1993

Preamble

There has been concern for a number of reasons about the conduct of "surveillance studies" or post-marketing research in medicine. Professional and regulatory bodies have been alarmed by reports of practices and procedures that do not meet standards for other types of clinical research. These concerns revolve around the aims and methods of some "trials." While probably not a widespread problem, reports of patently unscientific design and aims which are commercial rather than information-seeking are well-known.

An entire section of the Canadian Medical Association (CMA) guidelines on relationships with industry addresses this issue. CMA has identified broad principles which should be followed for the ethical conduct of research in this area. Valuable, valid information can and should be sought through properly designed trials which follow the guidelines. The CMA document, while excellent as an overall guide, is felt to lack sufficient specificity. The CPA Board, its executive and the Scientific and Research Council debated the place of specialty groups setting up guidelines in their own field. Encouragement to do so was received from the Central Nervous System Division of the Health Protection Branch (HPB) of Health and Welfare Canada. Consultation with the Canadian College of Neuropsychopharmacology indicated support for an initiative of this kind and offered to collaborate on the generation of the guidelines. A joint committee of the CPA and the Canadian College of Neuropsychopharmacology (CCNP) was struck, with the following aims: 1. To write specific guidelines for physicians engaging in Phase IV clinical trials in psychiatric practice; 2. to obtain wide-ranging input from all interested parties in preparing this document; 3. to obtain approval for the content of the guidelines from HPB; and, as a future measure; 4. to recommend a permanent committee of CPA and CCNP members to act as a central approval body for proposed Phase IV trials.

Much has already been written about the conduct of clinical trials. Professional bodies and regulatory agencies have addressed ethical and scientific principles to be followed. The application in Phase IV studies of these basic tenets is not at issue. The need for specific guidelines for carrying out Phase IV trials in psychiatry is based on the relative isolation of investigators from peer review and institutional safeguards.

Making reference points and guidance available should encourage clinicians interested in pursuing research in office practice to do so with security.

Issues to be Covered

There must be clearly stated, scientifically worthwhile aims for Phase IV trials. The investigator must be alert to sponsors who seek enrolment of large numbers of patients without posing a testable research question. Asking patients to complete self-report questionnaires on clinical change or adverse events is not sufficient. The design of a study should be such that a question like "will adverse events occur with this drug with greater than chance probability" can be tested.

Investigators must be suitably qualified to undertake the role of investigator; they must have sufficient knowledge in the area under investigation to effectively and knowledgeably use the new drug. In addition, they should be able to critically appraise the need for it and evaluate its potential to improve the current armamentarium.

Training of investigators in research methods and evaluative tools is essential. In multi-centre trials it is essential that patient ratings be reliable across centres and over time. In psychiatry this cannot be accomplished without training investigators and carrying out inter-rater reliability studies.

The issue of training is debateable because the basic design of most Phase IV studies is naturalistic and observational. The aim is to make the setting as natural as possible to contrast with early phase studies. The concern is that if investigators are trained, it is more difficult to generalize the results for routine practice.

The sponsor of a Phase IV trial must make information available to the investigator on animal and human experimental work done prior to the drug's release. All chemical and pharmaceutical, toxicological,

pharmacokinetic and pharmacodynamic information should form part of the investigator's handbook.

Sponsors of Phase IV clinical trials should operate within detailed standard operating procedures to comply with good clinical practice. These procedures must include adequate auditing procedures over and above the external audits carried out by regulatory authorities.

The investigator must have assurance that the data collected will be made available through publication. Study protocols should specify the intent to publish if the data warrant it. In all instances, the investigator must be free to communicate important clinical findings, even if these are perceived as negative by the sponsor.

The protocol made available for the trial must contain the essential components listed in the European Economic Community document "The Rules Governing Medicinal Products in the European Community." The headings are:

a) information on the sponsor, investigator and centres involved
b) justification and objectives
c) ethics
d) general time schedule
e) general design
f) subject selection
g) treatment
h) assessment of efficacy
i) adverse reactions
j) practicalities
k) handling of records
l) evaluation
m) statistics
n) financing, reporting, approvals, insurance, etc.
o) summary, supplements
p) references

Ethical conduct of research on humans is the ultimate responsibility of individual investigators. It may prove more difficult to discharge this responsibility if practising in isolation from colleagues, and if faced with unfamiliar problems. The issues addressed below are complex and difficult to legislate. According to the CMA guidelines:

"While breach of the law is generally unethical, a mere conformity with it may not be sufficient for discharge of responsibility" [emphasis added].

For this reason, all research on human subjects should be subject to scrutiny by review boards drawn from the community in which the project is carried out. Where this is not possible, CMA guidelines suggest that "agencies or bodies acting as a central clearing house" be established. These agencies should "function as a resource for physicians in assessing a study's ethical acceptability and scientific value." Ultimately, such bodies will fulfil this function, but none have yet been constituted. If such boards can be constituted for specific disciplines by specialty organizations or groups, their effectiveness will be all the greater.

The following are among the areas of special concern highlighted by the CMA guidelines:

1. The guidelines advise that "it is ethically acceptable for physicians to receive remuneration for participation in approved surveillance studies only if the participation exceeds their normal practice pattern." The guidelines go on to discuss what constitutes "exceeding normal practice patterns." This is not clearly defined, but involves consideration of "time expenditure and complexity." It can also take into account "opportunity costs," or time lost to other fee-earning activity. In psychiatric medication trials, this additional time can be calculated for activities such as explanation of the trial, obtaining informed consent, completion of rating scales, adverse-event reporting, completing clinical trial records, entering data electronically, data reconciliation with monitor and other miscellaneous tasks.

Reasonable estimates of time spent can be made with a premium for difficult or complex tasks. The financial arrangements of the trial should be scrutinized by ethics review boards in conjunction with the study protocol.

The number of patients which can be enroled in any one centre should be small to minimize the risk or even the appearance of enticement.

2. Obtaining full, informed consent in Phase IV trials is essential. It may pose more difficulties than in other settings for a number of reasons. For example, there may be a long-standing relationship with eligible patients, or the recommended route of using a physician other than the treating one may be less feasible. Imparting sufficient information about the proposed trial while reviewing other options impartially may be difficult to accomplish for the investigator. All recommended safeguards, such as using a two-stage process involving family or other advisors and using approved, written outlines, should be utilized.

3. In addition to using caution when paying investigators directly, indirect payment (for example, the purchase of equipment) should be approved by ethics review boards. Major items, such as computers, should be returned at the completion of the trial.

4. Investigators should be cautious about other indirect rewards, such as travel and expenses for educational events. The published guidelines apply.

5. Patient confidentiality must be maintained throughout. When study protocols require access to source documents, this must be fully explained to the patient. If an investigator has a number of practice locations, he or she must establish with each that access to files is permitted.

References

1. Guidelines on Research in Human Subjects Medical Research Council of Canada, 1987.
2. Physicians and the Pharmaceutical Industry Canadian Medical Association Policy Summary February 1992.
3. Conduct of Clinical Investigations Health and Welfare Canada, 1989.
4. The Rules Governing Medicinal Products in the European Community Vol. 111, 1990. "Good clinical practice for trials on medicinal products in the EEC" 57-98 and "Recomended basis for the conduct of clinical trials of medicinal products in the EEC" 115-130.