

Clinical-trial registration: a call for its implementation in Canada

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Résumé : Pour empêcher la partialité dans les publications et l'approbation d'essais dont les résultats peuvent ne pas être publiés, on devrait rendre obligatoire l'enregistrement des essais cliniques dès le début. Au Canada, les conseils d'éthique en recherche sont dans une position unique pour promouvoir cet enregistrement. Les journaux, les organismes de subvention et les groupes de défense des droits des patients peuvent aussi jouer un rôle. L'enregistrement fournira un index de renseignements sur les essais, ce qui permettra d'en évaluer l'impartialité, l'équité et l'exhaustivité.

The results of randomized controlled trials (RCTs) are the most reliable evidence upon which to assess the efficacy of health care interventions.¹ Since the publication of the first "modern" controlled trial, in 1948,² almost half a million RCTs have been completed. It is difficult to be more precise about the number of trials, because investigators have never been required to register their trials. This has led to publication bias, research ethics boards' approval of protocols without assurance that the results will be written up and made available, and granting agencies' inability to determine the direction of the research being conducted.

Investigators are more likely to report RCTs that have positive direction and results³ — publication bias. Not surprising, the results of many RCTs are never written up because the investigators are discouraged by the findings.⁴ The publication of selected RCTs can lead to systematic errors in the evaluation of treatments. Simes⁵ showed the existence of publication bias through his analysis of studies obtained from clinical-trial registries. He analysed trials of alkylating agents versus multiple-agent cytotoxic chemotherapy in the treatment of ovarian cancer. Published trials yielded statistically significant results in favour of the multiple-agent therapy. This conclusion was not supported when the results of all trials, both those published and those registered but not published, were analysed.

The results, positive and negative, of well-designed trials are important contributions to the literature. When patients participate in RCTs, investigators must ensure that the collected data are reported. Ethically, it is inappropriate to allow patients to undergo experimental therapy, with its sometimes life-threatening side effects, and not report the results.⁶ Failure to make such data available for public scrutiny has been considered scientific misconduct.⁷

The only way to ensure the availability of all evidence from clinical trials is to register each trial at its inception. The first clinical-trial registry was developed approximately two decades ago.⁸ Over the last 10 years the number has steadily increased.^{9,10} There are now approximately 30 registries covering many areas of medicine, including AIDS, cancer, perinatal medicine, stroke and vision. These registries aim to gather information about the RCTs at their inception. Typically the information collected includes the trial name and objectives, the name of the principal investigator and ways of communicating with him or her, inclusion criteria, sample size, type and method of randomization, type of masking and statistical analysis, and trial sponsorship.

For the successful implementation of clinical-trial registration, several groups need to participate: research ethics boards, journal editors, granting agencies, the pharmaceutical industry and consumer groups. Some of these groups will be part of a conference on trial registration, to be held Dec. 6 to 7, 1993; the conference is sponsored by the Office of Medical Applications of Research, National Institutes of Health, Washington (Dr. Kay Dickersin: personal communication, 1993). It is hoped that by bringing these groups together, a consensus will be reached that all trials must be registered at their inception. A clinical-trial registry can be a data source for these groups; if further information is required the registry would provide a link to the primary trial data through the principal investigator.

In Canada research ethics boards are in a unique position to promote, foster and, indeed, require trial registration, because all human research — basic and clin-

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ical, peer-review funded or not, single centre or multi-centre, with or without informed patient consent — must be reviewed by a research ethics board before it begins. Thus, the boards are the conduits through which to gather complete information for registering RCTs.

Research ethics boards follow the Medical Research Council of Canada (MRC) guidelines for reviewing protocols.¹¹ These guidelines have ensured the continuing high standard of review. They emphasize that the boards should integrate scientific and ethical evaluation into the review process. Now is an opportune time for research ethics boards to insist that all RCTs under their review be registered at inception. The boards have a moral and ethical responsibility to ensure that all patient data be available. If conclusions are to be made about the efficacy of therapy, they must be based on evidence from all relevant trials. RCT registration at trial inception is an important and timely new requirement that would meet the MRC's scientific and ethical guidelines.

Recently, there has been concern about the underrepresentation of women in clinical trials.¹² Similar concerns may be raised about other groups. Without a database of trials it is difficult to evaluate whether clinical trials are fair and equitable and include all groups in society. Mandatory trial registration at inception would provide the appropriate database to address these pressing issues.

Journals, granting agencies and patient advocacy groups have important roles in promoting clinical-trial registration. Whenever journals publish RCTs they could include the registration number of the trial. This would promote the use and development of registries. Currently, most granting agencies do not maintain registries of trials. However, there is a movement to improve this situation (Dr. Francis Rolleston, MRC: personal communication, 1993). If granting agencies promoted and funded registries they would avoid spending limited fiscal resources on needlessly duplicated trials and could establish the direction in which additional research is most likely to be beneficial. The end result would be more effective research funding in health care. Finally, when patients agree to participate in trials they should be encouraged to ask the investigator whether the trial has been registered and request a summary of the trial results. Patient advocacy groups might facilitate this process. As a result, investigators would be compelled to report trial results.

The developments in computer technology and electronic communications have allowed information from paperless registries such as the Ottawa Stroke Trials Registry to be easily shared around the world at minimal cost. This technology could also be used to link clinical-trial registries maintained by research ethics boards, journals and granting agencies.

The International Collaborative Group on Clinical Trial Registries is committed to the implementation of

clinical-trial registration through the development of registries, the standardization of their content, the registration of all trials and the promotion of communication between registries.¹³

In conclusion, the implementation of mandatory clinical-trial registration at inception ensures that a comprehensive trial registry will quickly develop. In Canada this is most likely to be achieved by research ethics boards. Granting agencies could be more effective by linking with such registries. Current technology will keep the costs of implementing registration to a minimum. Finally, registration will provide an index of trial information that can be assessed for fairness, equitability and inclusiveness.

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