Report from the Panel on The Case for Registers of Clinical Trials at the Eighth Annual Meeting of the Society for Clinical Trials*

Prepared by Kay Dickersin, for the panel

Panelists and topics

Thomas C. Chalmers, MD (Boston), Chairperson: Reasons for building and maintaining registers

R. John Simes, MBBS, SM (Sydney): Evidence of publication bias, using a clinical trials register

Kay Dickersin, MA (Baltimore): The Oxford Database of Perinatal Trials

Jean-Pierre Boissel, MD (Lyon): The International Committee on Thrombosis and Haemostasis Registry

Curtis L. Meinert, PhD (Baltimore): Options available for developing a comprehensive trials register

ABSTRACT: A plenary session at the Eighth Annual Meeting of the Society for Clinical Trials addressed "The Case for Registers of Clinical Trials." There are a number of reasons for having registers of clinical trials: to promote collaboration and communication among investigators regarding new and ongoing clinical trials, to provide a basis for methodologic research, and to facilitate meta-analysis by the availability of a system of trial identification that is independent of the published literature. The experience gleaned by those involved with two existing trial registers, the International Committee on Thrombosis and Haemostasis Registry and the Oxford Database of Perinatal Trials, can be used to provide insight into the issues generic to trial registration. The time perspective to be used, inclusion and exclusion criteria, the practicability of comprehensive prospective registration, and funding are central considerations for these and other registers.

KEY WORDS: *clinical trials, clinical trial registers, meta-analysis, publication bias, research design*

The value of data registries has been known for centuries. Church records of marriages, births, and deaths were the forerunners of the modern computer-based databanks. Centralized data collection and management has always been a key element of such databases, initially perhaps for practical

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reasons, but eventually providing an ideal framework for research of all sorts. Today, a wide variety of databases are maintained, for example, databases of nucleic acid sequences [1], active cancer treatment protocols [2], publications in health promotion [3], and cumulative results from fetal surgery [4].

It is an appropriate, if not overdue, time to ask how registers of clinical trials can be developed. A plenary session at the Eighth Annual Meeting of the Society for Clinical Trials, May 17–20, 1987, addressed "The Case for Registers of Clinical Trials." Although the discussion often centered on the difficulties of such an undertaking, the need to initiate the effort was emphasized. An overview of the concerns and issues expressed at that meeting is presented here.

There are a number of reasons for having registers of clinical trials. The first is to promote collaboration. The opportunity to exchange ideas related to a particular research question will ultimately promote clinical trials, and increase the impact of the trials' results by making them more accessible to clinicians.

The second reason is to provide a basis for methodologic research concerned with the way in which trials are undertaken. At the least, the availability of register data would allow regular descriptions of the state-of-the-art of clinical trials.

The third reason is to facilitate meta-analyses of clinical trials. At present, most meta-analyses are based solely on the published literature, thereby being subject to the risk of publication bias—a tendency to differentially publish study findings depending on the size and direction of the results. There is evidence that such a bias exists in the medical literature [5,6]. In a study employing information provided from The International Cancer Research Data Bank (maintained by the National Cancer Institute) [7], Simes found that a meta-analysis of published trials of treatment for ovarian cancer showed a survival advantage for combination therapy, whereas the meta-analysis using trials registered with the International Cancer Research Data Bank did not show such an advantage [5]. The results of a survey by Dickersin and colleagues [6] showed a significant difference in outcome between published and unpublished trials conducted by the same investigators.

It has been suggested [8] that a logical extension of trial registration is the registration of all patients in trials, allowing collection of critical follow-up information. For instance, follow-up of patients diagnosed and treated for acute myocardial infarction and enrolled in clinical trials might provide useful information on long-term harm and benefit of the therapies employed. Although patient registration may make sense as a corollary to trial registration, the proposal requires additional attention to practical issues (such as funding of the follow-up effort) and issues related to patient confidentiality before implementation.

There are several known registers of clinical trials, and this summary describes the operations of two of them (see Table 1). The International Committee on Thrombosis and Haemostasis (ICTH) Registry [9], now chaired by Jean-Pierre Boissel, was started in 1974, to register trials involving haemostatic or antithrombotic drugs in order to "make the research design of the various ongoing trials more easily accessible to those researching in the same area of experimental medicine" and "to help the researchers who are planning or designing new trials, or performing meta-analysis." The Registry is prospec-

Table 1 Comparison of Two Clinical Trial Registers: The International Committee on Thrombosis and Haemostasis Registry (ICTH) and the Oxford Database of Perinatal Trials (ODPT)

Register	Inclusion Criteria	Time Perspective	No. of Trials	How Identify New Trials?	How Available	Funding
ICTH	Multicenter; randomized; thrombosis & haemostasis field	Prospective	150	Mailing list; questionnaire	Journal (Thrombosis & Haemostasis)	None
ODPT	Randomized; perinatal period	Prospective and retrospective	4000	Survey of obstetricians & gynecologists; literature searches	Classified Bibliography; floppy diskette	WHO; Oxford University Press

tive, listing more than 150 randomized, controlled, multicenter trials. The Registry focus has changed over the years: from 1974 to 1985, it included trials of certain treatment regimens, whereas it currently includes trials of specific diseases (e.g., atherosclerosis, ischemic diseases, hemorrhagic disorders, arterial or venous thrombosis). Although the Registry is sponsored by the ICTH, the costs of its operation are absorbed by the office of the chairperson of the subcommittee in charge of the Registry.

In addition to having problems inherent in the organization and operation of any register, those coordinating the Registry have not had feedback on whether Registry information has been found useful. A system for receiving such feedback would be valuable.

The Oxford Database of Perinatal Trials (ODPT), developed by I. Chalmers and coworkers, has been described previously in this journal [10]. Controlled trials are entered into the database only if they involve random or quasirandom treatment assignment and the treatment or intervention is applied in the perinatal period. The database has five components: registers of published reports of perinatal trials, of unpublished, ongoing and planned perinatal trials, and a library of meta-analyses of results from perinatal trials. Published reports for the Database are identified via MEDLINE, manual searches of journals, and communication with colleagues. Registration of unpublished, ongoing and planned trials has begun recently. Eligible trials have been identified by communication with colleagues and, recently, by a worldwide survey of obstetricians and pediatricians. Formal mechanisms for ongoing prospective registration will be developed over the next two years.

Funding for the development of ODPT has been provided by the World Health Organization (WHO) and Oxford University Press (OUP) (which will publish the Database, available on 5.25 inch floppy diskettes).

The two examples of registers presented underscore several issues important to registration. First, definitions of inclusion and exclusion criteria are more difficult to apply than might be imagined: what design features are required for trial inclusion? What area will the register cover and how will the limits be defined?

Second, registration of trials may be organized either retrospectively or prospectively. Retrospective registers, relying either on published reports of completed trials or responses to surveys designed to identify unpublished trials, have limitations. They represent incomplete information on the population of all trials. In addition, knowledge of study results could, conceivably, influence selection for inclusion in the register. Also, because a trial is by definition underway or complete at the time of entry into a retrospective register, certain methodologic research (e.g., comparison of original study design characteristics to design at the end of a trial) and serendipitous collaborative efforts may be unfeasible.

Prospective registration, that is, registration of trials as they are started, is preferable, if there is a way to ensure that they are caught in the register net. Prospective registration by way of passive surveillance, that is, depending on investigators to register trials without notification or requests from register administrators, is likely to miss some trials. Active surveillance may do a better job of enticing registration, yet not knowing which investigators to survey is a limitation of this approach.

Third, register type can be defined by the disease entity of concern, the specific treatments employed, the medical discipline encompassed (e.g., the perinatal field), or even by a design characteristic (e.g., multicenter trials).

Once a decision is made to initiate a register, information to be collected must be decided on. The desire to "have it all" must be balanced with practical issues and consideration of the ways in which the register will be used.

What steps need to be taken in the development of registers? The first step is to begin registering existing registers. Descriptive surveys on resources already available are needed to augment this information. Second, indexing of clinical trial reports available in the medical literature must be improved; two recent articles have described the difficulties of identifying clinical trial reports [11,12]. Improved indexing could be partially realized if journals set standards for trial reporting. Third, workshops where information is exchanged on developing registers are needed. And finally a multinational effort to develop a comprehensive register or registers of clinical trials, encompassing all diseases and disciplines, should be initiated.

Funding of registers is a major issue. Possibilities include government grants and contracts, private funding by foundations or industry, and self-supporting mechanisms using registration and subscriber fees. As the value of registers becomes appreciated, government and other agencies will be willing to fund such an undertaking. At present, funding agencies are likely to view the main benefit of registers as a resource for meta-analysis. In fact, this is an important consideration: for example, from Sime's data [5], it appears that women with ovarian cancer have received an unpleasant treatment that would not have been thought beneficial, had all trials been considered.

As noted by the panel, however, there are many additional potential gains from registration of trials: funding agencies could use available information on ongoing research to make maximum use of research funds; institutional review boards would know of work going on in the same area and perhaps encourage collaboration rather than duplication, when appropriate; and last, but certainly not least, this resource would provide methodologists with an abundance of material.

An undertaking as ambitious as prospective trial registration is admittedly a gambol into unmapped territory. The argument by meta-analysts to have a resource free of publication bias may be the point on which many are willing to further the register effort. In fact, the greater gain will be in the resource itself, both in terms of improved medical care and the improved research upon which that depends.

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