

The Society for Clinical Trials supports United States legislation mandating trials registration¹

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The official position of the Society for Clinical Trials is to support legislation in the United States and internationally that mandates registration of all controlled clinical trials at or before enrollment of the first participant. The major trial sponsor would be responsible for ensuring contribution of trial information. The mechanism for registering trials would be through research ethics review boards, and registration would be required for ethics approval and before trial initiation. Standardized data and a unique identification number would be available for each registered trial. *Clinical Trials* 2004; 1: 417–420. www.SCTjournal.com

“The Society for Clinical Trials is an international professional organization dedicated to the development and dissemination of knowledge about the design and conduct of clinical trials and related healthcare research methodologies” [1].

The Society supports legislation in the United States (US) and internationally that mandates centralized registration of all controlled clinical trials at or before enrollment of the first participant. The Board of Directors of the Society has had a growing interest in publicly supporting policy issues of interest to its members and has elected comprehensive registration of clinical trials as its first issue. Clinical trials registration has been a topic of debate and discussion at the Society’s annual meeting [2] and in the pages of our Journal [3–5], and our organization’s leaders and members have been longtime advocates of registration [6–9].

Why register trials?

Healthcare decisions require access to all relevant information, not just what is available in the biomedical literature and the media. The Cochrane Central Register of Controlled Trials, which at this writing contains over 400 000 published clinical

trial reports, regardless of language, is an attempt to assemble the world’s clinical trials literature in one place [10]. But information about unpublished and ongoing trials is not collected or archived systematically. Arguments for developing and maintaining a system for comprehensive trial registration have been enumerated elsewhere [11] and will be summarized here.

The results of clinical trials are disseminated mainly through publication in scientific journals. If trial findings are never published, then knowledge is effectively lost. Perhaps half of all trials are never published [12,13] and considerable evidence indicates that studies with results demonstrating beneficial effects, or absence of adverse effects, are more likely to be published compared to studies with “negative” results, or those documenting adverse effects [13]. This publication bias has practical and serious results, since the overall benefits of an intervention may be overestimated and the adverse effects underestimated.

The overall effect of an intervention is best estimated using a compilation of all relevant findings, not just those that have been published. Those making healthcare decisions depend on systematic reviews and meta-analyses of the results of trials to provide such compilations. Systematic

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reviews focusing on the published literature alone can be influenced by publication bias, however, and the authors may incorrectly conclude that an intervention is effective and safe.

Central registration of trials at inception would document that a trial had been initiated and would allow those interested to find out more about the trial's design and results. Registration would also be a means of documenting that a trial had ended and could provide information about access to its results.

A number of ethical arguments also support trial registration. For example, individuals participate in trials on the understanding that they are contributing to scientific knowledge. If the results of a trial are not published, no such contribution exists and the participant–investigator and participant–ethics committee trust is betrayed. When the trial sponsor stands to profit from the trial findings (e.g., approval of a new drug), but has never published the trial results or made them public, this breach of trust is of special concern. Indeed, failure to publish studies has been called scientific misconduct [14].

Trial registers also serve to inform sponsors, research ethics review boards and others about all trials undertaken, which helps to prevent unnecessary duplication of effort and waste of resources. Registers also provide information about ongoing trials to patients and their doctors, thereby offering the potential to speed enrollment and advance new treatments.

Consequences of failure to register clinical trials

There are numerous examples of how failure to publish has led to increased patient suffering. Most recently, a systematic review of antidepressant trials in children revealed unfavorable harm–benefit profiles for four commonly used drugs after data from unpublished trials were included [15].

In another example, many scientists believe that a trials registration system could have led to earlier recognition of inappropriate use of antiarrhythmic drugs for secondary prevention of myocardial infarction. In the US alone in the 1980s, this therapy is estimated to have produced 20 000–75 000 deaths each year [16]. Beginning with a 1983 systematic review of 14 trials of class 1 antiarrhythmic drugs [17], a number of meta-analyses showed a lack of a beneficial effect and an increase in sudden death for coronary patients with ventricular arrhythmias. Yet trials continued to be conducted (over 50 trials involving more than 23 000 people were conducted), and the drugs continued to be used in practice until the 1990s. One study, completed in 1980, was not published until 1993 [18], and some

scientists believe that if there had been earlier knowledge of this trial and its results, it could have greatly expedited the recognition of the dangers posed by the biologically rational therapy [19].

Examples of trials registers

Disease-specific trials registers have been in existence at least since the 1960s [11, 20–22], with leadership taken by individual champions and the US government as well. Most registers have at least some aspect that is publicly accessible and are generally compiled by the register organizer. Currently, hundreds of small and large trials registers exist in the US [23] [e.g., the National Cancer Cooperative Group's TrialCheck, AEGIS (a major AIDS trials register)], yet no comprehensive register or centralized access point exists. Whether in the US, the United Kingdom or elsewhere, the closest we have come to comprehensive registration is coverage of government-funded trials in government-maintained registers [24, 25]. In 1997, the FDA Modernization Act mandated trials registration in the US for trials for serious and life threatening diseases, regardless of funding source. Yet with lack of funding appropriations and enforcement authority, this register (www.clinicaltrials.gov) only contains an estimated 50% or less of potentially eligible trials [26,27]. Lack of compliance with the law is primarily associated with industry-sponsored trials [27].

We believe that comprehensive, centralized, publicly accessible clinical trial registration, including a minimum standardized data set with information about each trial, should be legislatively mandated to provide a resource for systematic reviews of intervention effectiveness and for members of the public and doctors interested in trial participation. *All* controlled clinical trials involving human participants and collecting information on defined participant outcomes should be registered, regardless of the topic, the trials' perceived importance or funding source. Legislation should mandate that specific minimum information about each trial's design and findings should be recorded centrally and made freely available to the public. Governments have a moral responsibility to require and support registration and to fund the effort. Further, the legislation should include provision for enforcement and sufficient financial support for the register.

Countrywide trials registration in Europe is gaining ground [28, 29]. So far, many of the existing European registers, including the European Clinical Trials Database (EUDRACT) for medicinals, are not public, but it appears that changes are likely soon. Support by the European Science Foundation [30]

and other influential groups has helped European and country-specific efforts. Perhaps most importantly, the World Health Organization (WHO) has recently announced that it has registered and obtained from *Current Controlled Trials* a unique registration number for trials approved by its own ethics review board, and that it will promote development of an international unified clinical trials register [31]. The interest of WHO in the problem of global access to health information indicates worldwide concern. The Society for Clinical Trials is also international in scope and goals and is committed to taking a leadership role in this global effort.

Proposed plan

Work should begin immediately in the US to implement mechanisms for registration. The most direct way to comprehensively register trials is through research ethics review boards [32, 33]. As part of this effort, a unique identifier should be assigned to each trial, as is currently being done by *Current Controlled Trials* in their meta-Register [34]. Current information technology makes trials registration feasible and cost effective. By not maintaining a register we incur the potential cost of needless duplication of effort and loss of study participant trust.

Statement of support for United States legislation mandating registration of all controlled clinical trials

The Society for Clinical Trials seeks legislation in the US and internationally that mandates registration of all controlled clinical trials at or before enrollment of the first participant. The proposed register would exist in perpetuity. The legislation would be enforceable and sufficient funds would be appropriated to support the register.

Controlled clinical trials eligible for registration are research investigations of health or healthcare interventions that compare at least two parallel groups of human participants for effectiveness of interventions or other outcome. Trials may be randomized or not. Clinical trials in which participants serve as their own control, for example crossover trials in which participants are allocated two or more interventions sequentially, and paired organ trials would also be included.

The responsibility for ensuring contribution of trial information rests with the major sponsor. The mechanism for registering trials would be through research ethics review or institutional review boards, since controlled clinical trials typically are

approved by such boards before initiation. Trial registration would be required for ethics approval. Ethics review boards include, but are not limited to, private and public boards associated with institutions or organizations and independent boards.

Research ethics review boards would in turn contribute the information for each initiated trial to a central register organized by the US Department of Health and Human Services and housed and maintained by the National Library of Medicine.

Information contributed by the sponsor to the trials register would include at least: the name of the individual supplying the information, name of the trial sponsor(s), protocol number given to the trial by the sponsor(s), purpose of the trial, all interventions and trial arms, title of the trial, acronym, disease or condition under study, eligibility criteria, phase of the trial, location of recruiting sites, recruitment status, date study enrolled first participant, sources of funding (all known funding sources and reference numbers given to the trial by each funding agency), and lead principal investigator or person with overall authority (name, full address, telephone and fax numbers, and email address).

Each trial on the central register, including multicenter trials, would have a unique registration number. Trial information (e.g., stage of completion, publications) would be updated once each year. Trials would remain on the register when completed to serve as an archival resource and date of completion would be noted. Effectiveness and safety information should be made publicly available in a timely manner.

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