Registering a Clinical Trial in ClinicalTrials.gov

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Chest 2007;131;909-912; Prepublished online February 15, 2007;
DOI 10.1378/chest.06-2450

CHEST Postgraduate Education Corner

MEDICAL WRITING TIPS

Registering a Clinical Trial in ClinicalTrials.gov

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(CHEST 2007; 131:909–912)

Key words: compliance; computer; epidemiology

Abbreviations: ICMJE = International Committee of Medical Journal Editors; IRB = institutional review board; NIH = National Institutes of Health; PRS = Protocol Registration System

The registration of clinical trials has been the focus of attention within the medical literature,[1–4] as well as in the lay press and the US Congress.[5,6] Clinical trials registries are Web-based databases of clinical trial information that serve both ethical and scientific functions. Registries serve the ethical function of ensuring that the public has information about ongoing and previously conducted trials. Registries also provide researchers, journal editors, and reviewers with the context for understanding research results; by providing a complete list of clinical studies, they can alert researchers to studies that do not have published results. Trial registries differ with regard to a number of criteria, including the sponsoring organization, the focus (general vs disease specific), and the trial information that they contain. Many groups, including the International Committee of Medical Journal Editors (ICMJE), endorse the principles that registries should be managed by a nonprofit organization and should be free of charge for both registrants and users. Trial registries differ from results databases: the former generally include protocol and recruitment information, whereas the latter include study results.

Currently, the largest international clinical trials registries that satisfy the ICMJE criteria are the US-based ClinicalTrials.gov, which has approximately 35,000 trials, and the UK-based International Standard Randomised Controlled Trial Number Register, which has approximately 5,050 trials. This article focuses on registering a trial in ClinicalTrials.gov. However, most of the principles discussed will apply to the registration of trials in other registries, so that the information is clear and useful.

Background

ClinicalTrials.gov is a registry that is operated by the National Library of Medicine of the National Institutes of Health (NIH).[1] The registry contains listings of publicly and privately funded clinical trials from around the world. ClinicalTrials.gov was initially developed to help potential subjects with life-threatening illnesses find trials in which they might want to participate. Since that time, the registry has come to serve many other purposes for a variety of users (Table 1). Registering trials with ClinicalTrials.gov is free of charge for both US and non-US registrants. Use of the registry is freely available to anybody with Internet access.

What Policies Regulate Clinical Trials Registration

A number of policies and regulations create specific incentives for trial registration. Some key policies are listed in Table 2. In addition, the NIH registers all trials that it funds. Although this is generally done by the NIH staff, investigators should check their trial records to ensure the accuracy and completeness of the information.

Which Trials Should Be Registered

ClinicalTrials.gov accepts (and encourages) the registration of any biomedical or health-related re-

*From the National Library of Medicine, Rockville, MD.
The authors have no conflicts of interest to disclose.
Manuscript received October 6, 2006; revision accepted November 27, 2006.

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DOI: 10.1378/chest.06-2450

Table 1—*Trial Registry Purposes for Various Groups*

Registry Purpose	Group That Benefits
Fulfill ethical obligations to participants and community	Patients, general public, research community
Provide information to potential participants and referring clinicians	Patients, clinicians
Reduce publication bias	Users of the medical literature
Help editors and others understand the context of study results	Journal editors, users of the medical literature
Promote more efficient allocation of research funds	Granting agencies, research community
Help IRBs determine appropriateness of a research study	IRBs, ethicists

search study that is conducted in human beings as long as the following conditions exist: (1) the study has been approved by an institutional review board (IRB) [or equivalent]; and (2) the study conforms to the regulations of the appropriate health authority, when applicable. Trials that are currently under

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review by an IRB can be registered pending IRB approval. The registry currently includes both observational and interventional studies of any intervention type (*eg*, drugs, devices, procedures). However, only a subset of these trials is required under the policies shown in Table 2. Trials may be registered at ClinicalTrials.gov at any time, including after completion. However, many policies require registration prior to enrollment of the first subject.

How Do I Register my Trial?

The ICMJE statement requires that trials are registered "at or before the onset of patient enrollment."[9] Other policies mentioned in this article require registration within 21 days of the first patient's enrollment.

ClinicalTrials.gov uses a Web-based protocol registration system (PRS) [http://prsinfo.clinicaltrials.gov]. In order to minimize the chance of duplicates, and to ensure quality control, trials are generally registered through "organizational accounts." The PRS Web site provides a list of current organizational accounts and will guide the user through the process of identifying the appropriate trial account. For example, if the trial has received external funding from either a public source (*eg*, NIH), a private source (*eg*, a pharmaceutical company), or a foundation, then that organization's account should be used. New accounts can be set up as necessary, according to the instructions in the PRS. Many trials are conducted at multiple locations. It is critical that these trials be registered only once, with all locations listed. Investigators and sponsors need to coordinate and be clear about who will be registering the trial. Inquiries about problems with identifying or using accounts should be directed to register@clinicaltrials.gov.

Table 2—*Trial Registration Policies*

Policy Name	Policy Mandate	Trials Covered by Policy		
		Trial Design	Intervention Type*	Policy Details
Food and Drug Administration, section 113[7]	US legal mandate	Intervention trials	Drugs only	Mandates registration with ClinicalTrials.gov of all investigational new drug efficacy trials for "serious and life-threatening diseases"
ICMJE statement[8,9]	Policy of journals as condition for publication of research results	Intervention trials with at least one prospectively assigned concurrent comparison arm	Any intervention type*	Covers all trials that are "clinically directive"†; uses "minimum data set" defined by World Health Organization
World Health Organization International Clinical Trials Registry Platform[10]	Statement of WHO policy principles	Intervention trials	Any intervention type*	Calls for registration of all interventional clinical trials and defines a "minimum dataset"
Association of American Medical Colleges, "Principles for Protecting Integrity in the Conduct and Reporting of Clinical Trials"[3]	Statement of principles	Intervention trials with at least one prospectively assigned concurrent comparison arm	Any intervention type*	Calls for registration of all trials meeting ICMJE requirements

*Examples include drugs, surgical procedures, devices, and behavioral treatments.
†Defined as "all trials whose primary purpose is to affect clinical practice."

Once the account has been identified and the account administrator contacted in order to receive log-in information, the "quick start guide" can be viewed, which will "walk" the user through the process of trial registration.

A list of all the data elements in ClinicalTrials.gov can be found by clicking on *Trial Registration Requirements* link at the PRS information page [http://prsinfo.clinicaltrials.gov]. The user will note that some data are required by ClinicalTrials.gov; registration cannot be completed unless the appropriate information is entered in these fields. Other elements are optional but may be required under other policies (*eg*, the ICMJE).[11] We encourage users to complete all data elements because this will provide the most information about the trial. Registrants report that this process takes from 10 to 20 min.

Once entry of data elements is finished, the quality assurance staff at ClinicalTrials.gov will review the submission. The applicant may be asked to clarify some items or to make corrections. Following this, the record will be public within 2 to 5 business days.

Records contain information about recruitment status and therefore must be updated as often as necessary. ClinicalTrials.gov staff will prompt the user to update the record every 6 months during the recruitment phase, but records should be amended as soon as recruitment status or protocols are changed, or when other information becomes available (*eg*, links to publications). All changes are dated and tracked on an archival site, which is available to the public at www.clinicaltrials.gov/archive. The record on ClinicalTrials.gov main site displays the information from the most recent update.

Key Issues To Consider When Registering a Trial: Avoiding Most Frequent Problems

Clinical trials registries may be used by people with many different backgrounds and interests, as described in Table 1. For example, patients may want to consider participating in the trial and/or may want to consider all of their possible options. In general, potential participants will find a trial by searching by condition or intervention; therefore, it is important that this information be accurate and complete.

IRBs may use the registry to help evaluate a particular trial. The registry could provide a listing of past research (published or unpublished) that is relevant. In addition, the registry could help them to identify ongoing research (*eg*, prior to publication) that may overlap or be relevant to the protocol under current consideration.

Journal editors and reviewers may use the registry to determine whether or not a submitted manuscript adheres to the protocol design that was described in the initial registration (protocol amendments are also recorded in the registry, and are publicly accessible). In addition, journal editors may wish to understand the research context, which would include ongoing and previously unpublished research on the same topic.

Systematic reviewers may use the registry to identify all published and unpublished research on a given topic and to identify key protocol elements, such as specific intervention. The quality of the information in the registry and the efficiency and logic underlying the search engine are critically important for making the registry useful to these different types of users. Here we discuss some frequent problems that arise with trial registration:

Deciding Whether or Not To Register a Study

It is sometimes unclear whether a specific clinical study must be registered according to the law, or according to ICMJE or other policy mandates. As long as the study meets the ClinicalTrials.gov requirements (human subjects with health or biomedical outcome measures), it is generally better to register it. If there is doubt about the applicability of a study to the registry, contact register@clinicaltrials.gov.

Multisite and Complex Study Designs

A multisite study is generally regarded as a single study if the sites use the same protocol, and if the data are intended to be pooled for analysis. Each such study should be registered only once, regardless of the number of sites. For some studies, it may not be clear whether or not they should be registered as one or several studies. For example, some vaccine studies re-randomize participants from the first phase for possible participation in a subsequent phase. When questions arise about how to register a study, contact register@clinicaltrials.gov for guidance.

Study Type

Registrants must note whether their trial is interventional or observational in design. This item is critical because it determines what other design features are queried by the registry. Detailed definitions are available in the data element definitions at http://prsinfo.clinicaltrials.gov/. Interventional studies are those in which the investigator intervenes and prospectively assigns subjects to receive a specific intervention. The assignment process may or may not be random. In observational studies, the investigator simply observes the outcomes in a predefined

group of subjects but does not determine what interventions they receive. This item frequently confuses investigators because either study type may involve the use of medical interventions. In addition, diagnostic, therapeutic and other types of interventions could be studied with either interventional or observational designs.

Condition

One or more conditions that are the focus of the study should be listed here. Medical subject headings (*ie*, MeSH) terms should be used whenever possible. Medical subject headings are a controlled terminology developed by the National Library of Medicine for indexing medical texts. Prevention studies should generally list the condition that is being prevented. Health services research studies do not always involve a specific medical condition. The focus of the study should be used; examples include "medical errors," "number of prescription medications," or "discharge rates."

Intervention

Randomized controlled trials, or other trials with two or more arms, should list the interventions separately for each arm of the study. Drug interventions should be identified by a generic name if available; when there is not yet a generic name, the company serial number or the chemical name may be used. Devices should be described as fully as possible, using a formal nomenclature whenever appropriate (*eg*, Global Medical Device Nomenclature; GMDN; Radley, Oxford, UK).[12] Biologics, including vaccines, should also be fully described. Although "pneumococcal vaccine" may seem specific, there can be multiple versions of such a vaccine, and it would be important to know which version is being tested. In all cases, once a marketed name is available, the records should be modified to include the marketed name (along with previous names).

Primary and Secondary Outcome Measures

Outcome measures should include the specific measure (*eg*, a specific rating scale) along with the time of measurement. For example, "cardiovascular mortality at 1 year" is superior to "mortality" as an outcome measure entry. Although entries in this field are highly variable, we have found that using the outcome measure description that one would use in a structured abstract of a journal article typically provides an appropriate level of detail.[1]

Conclusion

The registration of clinical trials serves many different purposes. Sponsors and investigators are encouraged to register their trials and to provide the most informative entries possible so that the public has access to a full listing of medical or health-related research involving human subjects.

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