Better Access to Information about Clinical Trials

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Access to information about clinical trials is important to researchers, health care professionals, and patients. Many have argued for the establishment of clinical trials registries, citing their substantial benefits. Although some registries do exist, it has been difficult to create comprehensive, easily accessible systems. This paper briefly reviews existing registries, discusses the challenges in building registries, and reviews some of their benefits. The paper concludes with a description of a new, extensive Web–based registry called *ClinicalTrials.gov* (http://clinicaltrials.gov/), which was developed at the National Institutes of Health (NIH) by the National Library of Medicine as a result of recent legislation calling for a comprehensive, publicly accessible registry of clinical trials. The first version of the system became available in late February 2000 and contains information about approximately 5000 trials. The first release contains primarily NIH-sponsored trials, and new trials are regularly added to the system. Subsequent versions will contain information about trials sponsored by other federal agencies and by the private sector. The system was developed in accordance with basic informatics principles, including adherence to standards, usability considerations, and iterative testing and evaluation.

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> The case for registering all clinical trials . . . is now unanswerable. The public has the right to know what research is being funded. Researchers and research funders don't want to waste resources repeating trials already under way. And those conducting systematic reviews need to be able to identify all trials begun on a subject to avoid the problem of publication bias (1).

The conduct and outcome of clinical trials form the foundation of evidence-based medicine. Such trials are the primary means by which we are able to assess the safety and efficacy of new drugs and other interventions, and their results have led to improved clinical practice in many areas of medicine. Referring to the value of randomized, controlled trials, Chalmers wrote: "Randomised trials conducted over the past half century have helped to bring about a situation in which health care has been credited with three of the seven years of increased life expectancy over that time and an average of five additional years of partial or complete relief from the poor quality of life associated with chronic disease" (2).

Lilienfeld reports that the term "clinical trial" was first used early in the 20th century by the British Medical Research Council (3). He notes, however, that some formal comparative studies were already being conducted in the 18th and 19th centuries (for example, for smallpox, diphtheria, and cholera) and that some systematic trials involving controls were also conducted during those periods. The most notable of the latter seems to have been an interventional trial conducted by the surgeon James Lind in 1747 that involved 12 patients who had developed scurvy at sea (3). Perhaps the first truly randomized, controlled clinical trial was conducted in 1948 by members of the British Medical Research Council. This trial involved more than 100 patients and investigated the effect of streptomycin on the treatment of tuberculosis (4). During the latter half of the 20th century, large numbers of trials have been conducted, and current estimates suggest that many thousands are in progress at any given time. In the United States alone, approximately 13 000 new investigational drug applications are filed with the Food and Drug Administration (FDA), most involving multiple clinical trials around the country (5).

Clinical trials have enormous potential for improving medical practice. However, reports of such trials are often difficult to find and in some cases do not even exist. Because of this, many authors have called for the establishment of clinical trials registries (6–10). In a series of articles that analyzes "the gap between research and practice," Haynes and Haines (11) suggest that there are many barriers to practicing evidence-based medicine, including the volume and complexity of the research that is being conducted and poor access to information about it. Chalmers (10) says that it is "scientific misconduct" not to report the results of one's research. Not long ago, the editors of many medical journals called for an "amnesty" for unpublished trials, inviting investigators to submit trial registration forms for those trials that had previously been unreported (12). The response was disappointingly low, and the editors have recently repeated their call (13). Meinert (7) and Sim and Rennels (14) have suggested that journal editors should promote prospective trial registration by requiring

manuscripts describing clinical trials to include standard registration numbers from trial registries.

Several years ago, patient advocacy groups and others argued that information about clinical trials should be readily available to members of the public and that such availability should be required by law. Earlier legislation had resulted in the establishment of a database of information on AIDS clinical trials (15), and now the goal was to make information about clinical trials on a much broader range of diseases available through one easily accessible system. In late 1997, a section of the FDA Modernization Act required the creation of a database of information about clinical trials. Specifically, the law called for the following:

> A registry of clinical trials (whether federally or privately funded) of experimental treatments for serious or life-threatening diseases and conditions . . . which provides a description of the purpose of each experimental drug, either with the consent of the protocol sponsor, or when a trial to test effectiveness begins. Information provided shall consist of eligibility criteria for participation in the clinical trials, a description of the location of trial sites, and a point of contact for those wanting to enroll in the trial, and shall be in a form that can be readily understood by members of the public (16).

In late 1998, the National Library of Medicine (NLM) at the National Institutes of Health (NIH) undertook the development of this system, and in February 2000 we announced the first version of a new World Wide Web–based system called *ClinicalTrials.gov* (http://clinicaltrials.gov/) (17, 18). The first version contains primarily NIH-supported trials, and subsequent versions will contain data from trials supported by other federal agencies and by the private sector.

Existing Clinical Trials Registries

Because of the legislation that resulted in the development of *ClinicalTrials.gov*, it has now become possible to design and develop a broad, comprehensive registry. Although this has been difficult to do in the past, several individual registries have been developed over the years. In 1989, Easterbrook (19) surveyed approximately 60 organizations in 13 countries. She found that a total of 24 registries existed, including two early registries (the international registry of thrombosis and haemostasis trials, the Oxford perinatal trial registry) and several other registries focused on AIDS or cancer. Persons interested in information on AIDS and cancer have had access to clinical trials information for some time through two government-supported systems, AIDS Clinical Trials Information Service (ACTIS) and CancerNet (20, 21). Tonks (22) reports that many individual registries currently exist and are supported by a variety of individuals and groups around the world. She notes, however, that "Recorded details vary dramatically among registers. There is no guarantee that a register is complete, accurate, or comprehensive . . . The existing network of registers is therefore valueless to anyone but a small group of cognoscenti, and only of limited value to them."

Recently, a group of British publishers created the Current Controlled Trials Web site, which maintains links to approximately 50 on-line registries and contains a "*meta*Register" of trials submitted by six groups in Canada and the United Kingdom (22, 23). The Cochrane Collaboration, which conducts meta-analyses and creates systematic reviews of the trials literature, also maintains a register of controlled clinical trials (24). In the past few years, some medical schools and hospitals have begun to establish Web sites that list the clinical trials being conducted at their institutions, and some commercial organizations now also provide listings of clinical trials.

Challenges in Developing Trials Registries

Clinical trials registries are expensive to develop and to maintain. They require resources from all who are involved, including the developer of the registry, the trial sponsors, the review and regulatory bodies, and the investigators themselves. The currency of the information in a prospective registry is of paramount importance, and the accuracy and completeness of the data are critical. It can be difficult to identify exactly where and how many trials are being conducted at any given time, and when data are collected from a wide range of sources, there will be concerns about duplication. Standards for collecting and disseminating the information are necessary if the data are to be widely shared and easily interpreted.

Confidentiality issues may also arise. Investigators or the companies that employ them may consider information about the trial they are conducting to be proprietary and may feel that participation in a trials registry will compromise the competitive value of the information.

There will also be technical challenges in the develop-

ment of a clinical trials registry. If the goal is to create a system that is accessible to a broad range of constituents, then appropriate technology must be chosen and implemented. Tonks (22) points out that although many individual trial registries exist, they are often built with stand-alone software and are inaccessible even to researchers. Since it is an ongoing challenge to keep the data in a clinical trials registry current, it is critical that methods be put in place to ensure that the registry will be kept up-to-date.

Benefits of Clinical Trials Registries

The International Collaborative Group on Clinical Trials Registries has pointed out that the goal of trials registries is to "facilitate access to information by interested investigators and patients. This objective arises from an ethical and scientific goal, i.e. to accelerate dissemination of trial data, making the results available sooner, and enabling patients to benefit earlier from what is learned" (25). Many researchers have pointed out that the existence of clinical trials registries would address and help solve the problems associated with publication bias (6, 7, 24, 26, 27). Such bias can arise for at least two reasons. Investigators are more likely to prepare reports for publication about clinical research studies with positive, statistically significant results than those with negative or inconclusive results (10, 28). This is sometimes referred to as the "file-drawer" phenomenon (29). Studies with negative results are presumed to be uninteresting and may therefore never be published. Dickersin and Manheimer note, "There is now strong evidence that published studies are a biased sample of all studies undertaken" (24). This bias potentially leads to an overestimation of the efficacy of a particular intervention (6). Rennie (26) points out another, perhaps more deliberate reason for publication bias. The favorable results of some studies are published in various forms in multiple journals, thereby giving the impression that a particular intervention is more promising than the facts would warrant.

Comprehensive clinical trials registries would assist researchers who are conducting meta-analyses of trial results to create systematic reviews of the literature on treatments for a particular disease (30, 31). These reviews can bring the results of clinical trials to the bedside more quickly than would otherwise be the case because they usually synthesize and evaluate a large body of evidence (32, 33). Instead of depending solely on published reports, reviewers with access to a comprehensive registry would be able to collect information on all trials that have been done, regardless of whether the results were positive, negative, or inconclusive.

Table 1. **Clinical Trials Registries**

Challenges
Require extensive resources to create and maintain
Require agreement on standard data elements
Require managing data from multiple sources
Must be regularly updated and must be accurate and complete
Raise proprietary concerns
Involve technical challenges
Benefits
Serve as resources for patients, physicians, and researchers
Help patients find trials for which they may be eligible
Assist in accrual of patients
Help physicians identify treatments under study
Help in the initiation and design of new trials
Help solve publication bias in clinical trials reporting
Facilitate meta-analyses and systematic reviews

Comprehensive trials registries can also serve as valuable sources of information for researchers as they initiate and design their studies. Such registries might help them avoid unnecessary duplication of effort (which is distinct from appropriate replication). If a study has already been conducted and has conclusively shown positive or negative results, then it is wasteful and in some cases dangerous to repeat it. A comprehensive registry might also reveal areas of fruitful future investigation. For example, if few studies have been conducted in certain disease areas or for certain drugs or combinations of drugs, then investigators and funding organizations might consider these as important opportunities for research (22, 27).

Although it is not often mentioned, another substantial benefit of a publicly accessible clinical trials registry is that it may aid in the recruitment of eligible patients to clinical trials (19). Mansour (34) points out that fewer than 3% of patients with cancer participate in clinical trials. He and others give some possible reasons for this, including physician and patient reluctance to participate (34–38). As more information about ongoing and completed clinical trials is collected and critically evaluated, it should serve to educate both clinicians and patients about the risks and the benefits of clinical trials. **Table 1** summarizes some of the challenges and benefits involved in developing clinical trials registries.

Designing a Clinical Trials Registry

Because the advantages of clinical trials registries are so great and because several forces now demand their

Table 2. **Information Given in the *ClinicalTrials.gov* Record Display**

Title
Recruitment status
Sponsor
Purpose
Description of the purpose of the trial
Condition, intervention, phase (in table format)
MEDLINE*plus* related topics
Study type
Official title
Further study details
Eligibility
Ages and sexes eligible for study
Description of inclusion and exclusion criteria
Location and contact information
Names, addresses, telephone numbers, e-mail addresses
Recruitment status at specific trial locations
More information
Links to more information (e.g., related Web sites)
Publications relevant to the study (if available)
Study identification numbers (submitted by data providers)
National Library of Medicine identifier (e.g., NCT00001789)
Date study started
Date recruitment status verified
Date last updated

creation, the challenge is to develop systems that will be accessible to a range of persons and serve a range of interrelated purposes (39). Given these broad goals, several authors have suggested the types of elements that should be included in a clinical trials registry (7, 22, 25, 27). All agree on the high-level categories of information that should be present in a full clinical trials protocol (40), although there are differences in the emphasis placed on those categories. General and administrative information includes the trial name or title, a registration number, the funding source, the site at which the trial is being conducted, the name and affiliation of the investigators, the study start and completion dates, and the recruiting status of the trial. The purpose and objectives of the trial include the disease or condition being treated or evaluated, the treatments or interventions being studied, the projected sample size, the length of treatment, and the primary and secondary end points. Trial design and methods include the method of treatment assignment and other specifics of the proposed methods of analysis. Eligibility criteria describe the characteristics of the study sample and indicate which persons would be suitable given the objectives of the study. Study results might be included in the registry, particularly if they could also point to published references.

For anyone contemplating the development of a clinical trials registry, the first question to be addressed is who will provide the information. Principal investigators themselves, of course, design and implement clinical trials protocols, and they are the primary sources of the data. However, sponsors, review boards, or regulatory bodies might also assist in capturing the data and delivering it to the registry. Boissel and Haugh (9) surveyed 281 ethics review boards in seven European countries. Of the 115 boards that replied, 70% said that they would be willing to submit data to a centralized clinical trials registry, particularly if the laws in their countries were changed to mandate registration of clinical trials information.

The broad scope of the legislation that resulted in the new Web-based *ClinicalTrials.gov* system has required a carefully planned approach to a project that will be an ongoing, long-term effort. However, because a first version needed to be developed relatively quickly, it made sense to develop the system in phases, incorporating NIH-supported trials first and adding trials supported by other federal agencies and by the private sector later. In designing the system, we have been guided by several important informatics principles, including adherence to standards and iterative testing and evaluation, and have emphasized ease of use (41, 42).

Standard data elements, standard methods for labeling and transmitting the data, use of standard vocabularies, and use of standard Web technologies have all played a role in the design of the system. Discussions among the joint NIH and FDA working group about the standard data elements to be included were informed by earlier published work as well as by the results of discussions at several public meetings. **Table 2** illustrates the type of information that is displayed whenever a user retrieves a record from the database.

Twenty-one NIH institutes and centers are currently contributing data to the centralized system at the NLM. Records from all participating sources are combined in the database and are presented in a consistent way to users. This consistency is possible only because of the standard data elements that make up all records. Certain elements, such as the disease or condition name, are expressed in standard controlled vocabularies, thereby allowing better searching and browsing capabilities. The terminology component of the system uses knowledge from NLM's Unified Medical Language System (43) to assist in resolving user queries. For example, if a user queries *ClinicalTrials.gov* for trials related to "heart attack," the search will also include "myocardial infarction," which is available as a synonym in

the Unified Medical Language System. If a user misspells "glaucoma" as "glacoma," the system will offer spelling corrections.

Links to related information appear throughout the system. For example, if a trial is testing a new intervention for Alzheimer disease, a link from the record for that trial will allow users to access the topic on MEDLINE*plus*, NLM's Web-based consumer health site. If the trial record includes references to the literature, a link is automatically made to MEDLINE through NLM's PubMed system. Finally, each record is also assigned its own unique identifier, consisting of the prefix "NCT" followed by eight digits. This identifier will never be changed or reused and functions much like a MEDLINE identifier.

Testing and evaluation are always important, but they are particularly so when a system is being designed for broad use by people of many different backgrounds and technical skills. Because the primary intended audience includes patients and other members of the public, who may or may not be sophisticated Web users, we have designed the system to be as easy to use as possible and have also been concerned with accessibility. No training is required to search the system, and the results are easily understood. We conduct ongoing testing and evaluation with members of the public, health care professionals, and information specialists. Representatives from all of these groups tested prototypes of the system, and their comments have already led to many improvements and enhancements.

Discussion and Conclusions

It is too early to evaluate the impact of the *Clinical Trials.gov* system, but it seems likely that as patients and their physicians have increased access to information about ongoing clinical trials, they will be in a better position to decide whether participation in a clinical trial is appropriate. Researchers may well see an increase in the number of patients who are interested in enrolling in their trials, and they may therefore also see the advantages of registering their trials in a comprehensive registry. Although some private companies may have concerns about the proprietary nature of their clinical trials data, this may be balanced by the benefits of having their trials listed.

In addition, the system may be helpful to practicing physicians. In some cases, a physician may be aware of trials being conducted by colleagues but not of those in progress at other institutions. The links to published references related to specific trials may help provide additional insights into the goals and possible outcomes of the trials. In some cases, the results of completed trials are available on the site, most often in the form of references to published articles. This means that not only has the work been peer reviewed but also that the methods have been more fully described. The International Collaborative Group on clinical trials registries points out that although registries have many advantages, they cannot substitute for full analysis and evaluation of the research data in a clinical trial. Investigators have a continuing obligation to publish their results (21).

Because more patients are accessing the Internet for health care information, it is likely that they will be able to benefit from a reliable source of information about clinical trials. It will, of course, continue to be important to interpret this information in the context of the patient's overall medical care. *ClinicalTrials.gov* can help by providing "just-in-time" information about the particular condition or intervention under study (42), but the physician clearly plays a critical role in the application of such information. Evaluating possible participation in a clinical trial is best accomplished in a close partnership between patients and their physicians.

Clinical trials have the potential to improve people's lives. Many thousands of trials are conducted each year in the United States and throughout the world, but it is often difficult to determine what specific trials are being conducted, where they are being conducted, who is doing the work, and what the results are. Registries of varying scope and size have been developed over the years, but none has been comprehensive in its coverage. There are, in addition, significant economic, organizational, and technical issues involved in developing large registries. Many have argued strongly for the establishment of clinical trials registries over the past several decades because researchers, physicians, and patients can all benefit by having ready access to information about clinical trials.

We have recently developed and made publicly available a clinical trials registry called *ClinicalTrials.gov.* The system has been designed to be comprehensive and currently contains approximately 5000 clinical trials covering a wide range of diseases and conditions. Although this represents just the beginning of an evolving long-term project, we hope that it may be viewed as an important step toward providing better access to clinical trials information.

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