Issues in the Registration of Clinical Trials

Deborah A. Zarin, MD
Nicholas C. Ide, MS
Tony Tse, PhD
William R. Harlan, MD
Joyce C. West, PhD
Donald A. B. Lindberg, MD

Public concerns about the perils associated with incomplete or delayed reporting of results from clinical trials has heightened interest in trial registries and results databases. Here we review the current status of trial registration efforts and the challenges in developing a comprehensive system of trial registration and reporting of results. ClinicalTrials.gov, the largest trial registry with 36 249 trials from approximately 140 countries, has procedures in place to help ensure that records are valid and informative. Key challenges include the need to minimize inadvertent duplicate registrations, to ensure that interventions have unambiguous names, and to have a search engine that identifies all trials that meet a user's specifications. Recent policy initiatives have called for the development of a database of trial results. Several issues confound the implementation of such a database, including the lack of an accepted format or process for providing summaries of trial results to the public and concerns about disseminating data in the absence of independent scientific review.

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HIGH-PROFILE DISCLOSURES OF "hidden" data from clinical trials have led the public to realize what some researchers have known for a long time: ethical and scientific problems arise when trial results are either delayed or not completely revealed to the public or other researchers.[1-6] Ethical problems arise if volunteers consent to a trial with the understanding that the study will inform medical knowledge and the results are then not made publicly available.[3] Future volunteers are at risk for being misled and harmed when their consent and the trial design are not fully informed by prior research. Institutional review board (IRB) members cannot fully weigh risks and benefits when some unknown proportion of the relevant data is unavailable for review.[4]

Researchers have documented that up to 37% of clinical trials presented in abstracts never result in a full journal article[7]; that even when published trial results exist, some prespecified outcome measures may be omitted[8]; and that various selection factors influence which results are published.[5,6,9,10] As a result, health care and policy decision makers are left to rely on a biased subset of the totality of evidence for a given intervention. This could lead to inefficient resource allocation and suboptimal health care decisions.[11]

The registration of clinical trials in Web-based, publicly available databases has become a key tool in addressing some of these issues.[12-14] Many disease-specific and sponsor-specific registries have been developed, with the intent of providing information for the public, clinicians, and researchers.[13,15,16] Registries such as the International Standard Randomized Controlled Trial Number Registry and ClinicalTrials.gov were developed to cover the full range of clinical conditions from a broad group of trial sponsors. There recently has been a heightened appreciation and sense of urgency to use trial registries to facilitate more consistent, timely, and comprehensive public disclosure of trial information.[1]

While trial registration has gained momentum in the last several years as the result of a few key policy initiatives, an unknown number of trials are still not being registered.[17-20] Even if universal registration were achieved, however, it would not be sufficient to resolve the problems associated with incomplete disclosure of results.[21] This has led many to advocate for the systematic, public dissemination of trial results, whether published or not, as a way to ensure that all trials involving human volunteers contribute to medical knowledge.[22,23] Additional impetus has been the recognition that infrequent, but clinically impor-

Author Affiliations: National Library of Medicine (NLM) (Drs Zarin and Lindberg) and Office of Biotechnology Activities (Dr Tse), National Institutes of Health, US Department of Health and Human Services, Bethesda, Md; and American Psychiatric Institute for Research and Education, Arlington, Va (Dr West). Mr Ide is a contractor with Thoughtful Solutions Inc, McLean, Va, through which he works full time with the NLM. Dr Harlan is a self-employed contractor to the NLM. Dr Zarin was formerly at the Technology Assessment Program at the Agency for Healthcare Research and Quality. Dr Tse was formerly a staff scientist at the NLM.
Corresponding Author: Deborah A. Zarin, MD, ClinicalTrials.gov, National Library of Medicine, 8600 Rockville Pike, Bldg 38A, Room 75705, Rockville, MD 20894 (dzarin@mail.nih.gov).

tant, unanticipated adverse effects may not be recognized due to relatively small sample sizes and incomplete publication of results from preapproval studies.[24,25] Aggregation of data from all trials, whether published or not, could be helpful in detecting significant adverse effects.

In this article, we review the current status of trial registration and recent experiences with the largest public trials registry, ClinicalTrials.gov. We also discuss progress toward a comprehensive system of trial registration and reporting of results.

Current Status and Uses of ClinicalTrials.gov

Several US and international policy recommendations, regulations, and statutes have created incentives for trial registration (TABLE 1). For instance, section 113 of the US Food and Drug Administration (FDA) Modernization Act[26] called for the creation of ClinicalTrials.gov and mandated registration of all efficacy drug trials for "serious or life-threatening diseases and conditions" conducted under FDA Investigational New Drug application regulations. The International Com-

Table 1. Selected Policies That Require Trial Registration*

Policy Name	Policy Type	Intervention Type	Policy Scope	Inclusion of Provisions for Results
FDAMA, Section 113,[26] 1997	Federal law	Drugs and biologics	Efficacy trials for "serious or life-threatening diseases or conditions" regulated by the FDA	No
Fair Access to Clinical Trials (FACT) Act,[29] 2007	Bill introduced in US Senate by Senator Dodd (Conn)	Drugs, biologics, and devices	Ongoing trials for "serious and life-threatening diseases and conditions" regulated by the FDA except phase 1 safety trials; registration prerequisite for IRB approval.	Yes
Enhancing Drug Safety and Innovation Act,[28] 2007	Bill introduced in US House of Representatives by Representative Waxman (Calif)	Drugs, biologics, and devices	Most "safety or effectiveness" trials for approved and unapproved products	Yes
Food and Drug Administration Revitalization Act,[27] 2007	Bill introduced in US Senate by Senator Kennedy (Mass)	Drugs, biologics, and devices	All drug trials, other than phase 1, regulated by the FDA and all device trials intended "to determine safety and effectiveness of a device" and regulated by the FDA	Yes
ICMJE Statement,[18] 2005	Publication policy	Any†	Interventional controlled trials; defines criteria for "acceptable registries"	No
WHO ICTRP,[22] 2006	WHO policy	Any	"All medical studies that test treatments on patients or healthy volunteers"	Yes
Centers for Medicare & Medicaid (CMS): Proposed Clinical Research Policy,[30] 2007	Proposed CMS Medicare policy	Any	All "qualified" research for which Medicare covers routine care costs	Yes
PhRMA Clinical Trial Registry Proposal,[32] 2004	Recommendation	Drugs and biologics	"All company-sponsored hypothesis-testing (non-exploratory) clinical trials conducted on drugs and biologics marketed in the US or intended for marketing in the US, regardless of disease studied or the location of the trial"	Yes
Ottawa Group,[4] 2005	Recommendation	Any	"Prospective controlled or uncontrolled research study evaluating the effects of one or more health-related interventions assigned to human participants"; defines criteria for "acceptable registries"	Yes
AAMC Principles,[31] 2006	Recommendation	Any	"All trials meeting the ICMJE requirements"	Yes
IOM Report:Drug Safety,[23] 2006	Recommendation	Drugs only	"Industry sponsors. . .at a minimum, all Phase 2 through 4 clinical trials, wherever they may have been conducted, if data from the trials are intended to be submitted to the FDA as part of an NDA, sNDA, or to fulfill a postmarket commitment"	Yes
Maine State Law,[33] 2005	State law	Drugs and biologics	Trials of "prescription drugs in this State" (of Maine); includes "biological products"	Yes
Prescription Drug Right-to-Know Act, New Jersey State Bill,[34] 2006	Bill before state legislature	Drugs and biologics	"Each clinical trial that the company conducts or sponsors for each prescription drug that the company sells, delivers, offers for sale or gives away in this State" (of New Jersey)	Yes

Abbreviations: AAMC, Association of American Medical Colleges; FDA, US Food and Drug Administration; FDAMA, FDA Modernization Act of 1997; ICMJE, International Committee of Medical Journal Editors; ICTRP, International Clinical Trials Registry Platform; IOM, Institute of Medicine; IRB, institutional review board; NDA, New Drug Application; PhRMA, Pharmaceutical Research and Manufacturers of America; sNDA, supplemental New Drug Application; WHO, World Health Organization.
*Several policies by legislative or other bodies were selected to illustrate a range of policy initiatives.
†Includes drugs, biologics, devices, surgical procedures, and behavioral treatments.

mittee of Medical Journal Editors (ICMJE) established a policy, effective July 2005, that requires prospective trial registration as a condition of publication.[17] The ICMJE policy lists criteria for acceptable registries, including being publicly available at no charge; being managed by a nonprofit organization; and registering interventional trials regardless of condition, intervention, sponsor, or location. In addition, the ICMJE criteria require inclusion of the Trial Registration Data Set defined by the World Health Organization.[22,35]

The registries currently accepted by the ICMJE are listed in TABLE 2.[36] ClinicalTrials.gov, operated by the National Library of Medicine, includes both observational and interventional studies. Each record is assigned a unique identifier (NCT number) and includes summary information on study protocol, patient recruitment status, and site location, as well as administrative data. Records are updated by the registrant as the protocol or recruitment status changes; all changes are dated and tracked on a public archival site.[37]

As of January 2007, ClinicalTrials.gov contained 36 249 recruiting and completed studies sponsored by the public and private sectors for all intervention types, including phase 1 trials and observational studies, from more than 140 countries. Approximately 38% of registered trials include sites outside the United States. Trial sponsors or investigators use a Web-based system to register trials through organizational accounts.[38] Both the individual responsible for the specific trial record and the organizational account administrator must sign off before a registration or a change to the record becomes public. Overall, as of January 2007, there were 3646 organizational accounts, including 1288 from industry, 93 from US federal agencies (including the National Institutes of Health [NIH]), and 2265 categorized as "university" (ie, from "university, foundation, or other").

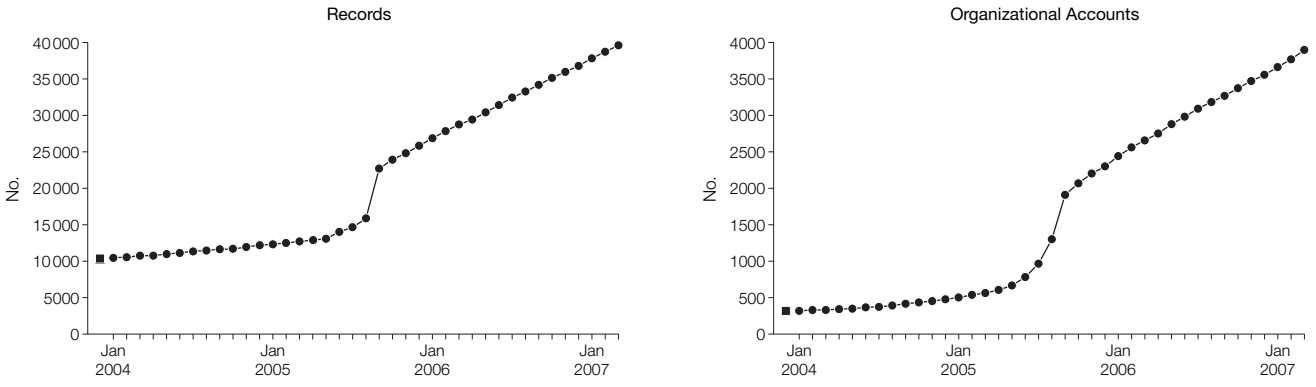
A marked increase in ClinicalTrials.gov registrations occurred around the time of the implementation of the ICMJE policy on September 13, 2005.[39] The FIGURE indicates continued growth in the numbers of records (trials) and organizational accounts. ClinicalTrials.gov received an average of 30 new trials per week prior to September 2005, and 220 new trials per week since then. The creation of new organizational accounts provides insights

Table 2. Registries Accepted by the International Committee of Medical Journal Editors[36]

Registry Name	URL	Auspices/Funding	No. of Trials (As of 1/17/07)	Is Recruitment Status Recorded and Updated?	Can Users Search for "Open" Trials?
ClinicalTrials.gov	http://clinicaltrials.gov	US Federal Government (National Library of Medicine at the NIH)	36 657	Yes	Yes
ISRCTN	http://isrctn.org	Not-for-profit entity administered by Current Controlled Trials Ltd fees collected from registrants	5281	No (anticipated closure date is recorded)	Not currently
Australian Clinical Trials Registry	http://www.actr.org.au	Grant from Australian National Health and Medical Research Council (University of Sydney)	1350	Recorded (plans to allow for updates by mid 2007)	No (planned by mid 2007)
Netherlands Trial Registry	http://www.trialregister.nl	Grant from Dutch Ministry of Health (Dutch Cochrane Center)	797	Yes	No
UMIN Clinical Trials Registry	http://www.umin.ac.jp/ctr/	Grant from Japanese Ministry of Education	534	Yes	Yes

Abbreviations: ISRCTN, International Standard Randomized Controlled Trial Number; NIH, National Institutes of Health; UMIN, Japanese Ministry of Education; URL, uniform resource locator.

Figure. Number of ClinicalTrials.gov Accounts and Records Since January 1, 2004, by Month



First data marker (square) in each plot represents all available data prior to January 2004.

into sources of new trial registrations. In 2006, an average of 328 new organizational accounts were opened each quarter—and 787 (60%) of that year's total of 1312 were for non–US-based organizations. Over the past 2 years, the proportion of all trials submitted from the NIH has decreased, while the proportion of trials from the university and industry categories have increased (TABLE 3). Drug studies continue to dominate the registry, with only very small numbers of device trials registered. The site receives approximately 30 000 unique visitors per day, 39% of whom are referred directly by search engines and 28% via links from other sites.

The quality and completeness of trial records have improved since October 2005.[40,41] Prior to that time, 10% of industry records used vague terms such as "investigational drug" in lieu of an actual drug name. There have been no such new entries in the past 6 months, and most older records with vague drug name entries were corrected by the sponsor, so the registry now has fewer than 20 records (out of a total of 23 367 interventional drug trials) that lack a meaningful drug name.

In addition, completion of the primary outcome measure field, required by the ICMJE, has increased. (Primary outcome measure is defined by ClinicalTrials.gov as the specific measure that will be used to determine the effect of the intervention[s]. The description should include the time at which the measure will be taken.) The percentages of registrations since January 1, 2006, that have an entry in the primary outcome measure field, by organization type, are: NIH (74% [63% of the NIH trial registration records with missing data in this field have the information included elsewhere in the record]), other federal (88%), industry (88%), and university (89%). A review of records in 2005 showed heterogeneity in quality of entries for primary outcome measure, with only 31% specifying both a measure and time frame.[39] A new data entry format anticipated to be in place by summer 2007 should improve the quality of these entries by structuring the separate listing of measure and time frame.

Table 3. Studies Registered in ClinicalTrials.gov as of January 2005, 2006, and 2007*

Variable	No. (%)		
	January 2005	January 2006	January 2007
Total	12 187	25 195	36 249
Type of study			
Observational	2077 (17)	3684 (15)	5286 (15)
Interventional	10 110 (83)	21 511 (85)	30 963 (85)
Type of interventional trial (data provider category)			
National Institutes of Health	7904 (78)	9415 (44)	10 828 (35)
University†	196 (2)	5696 (26)	10 007 (32)
Industry	1715 (17)	5714 (27)	9273 (30)
Other US federal	295 (3)	686 (3)	855 (3)
Intervention category‡			
Drug	8711 (86)	16 682 (78)	23 367 (75)
Procedure	5028 (50)	6995 (33)	8923 (29)
Behavior	505 (5)	1819 (8)	2622 (8)
Device	121 (1)	890 (4)	1631 (5)
Vaccine	241 (2)	667 (3)	1075 (3)
Interventional study location			
Only in the United States	7203 (71)	12 265 (57)	16 397 (53)
Not in the United States	734 (7)	5064 (24)	8918 (29)
United States and other country	1399 (14)	2205 (10)	2928 (9)
Missing§	774 (8)	1977 (9)	2720 (9)

*This table summarizes data as collected on April 17, 2007.
†Refers to university, foundation, and other organizations.
‡A trial record may include more than 1 intervention type.
§Some sponsors remove location information once a trial closes to recruitment.

Challenges in the Registration of Clinical Trials

Registries are useful to the extent that they can assure users that the trial records are valid and provide an accurate list of all trials that meet a user's specifications. Meeting these demands is difficult, and the current approaches and most vexing issues are discussed below.

Validating Trial Registry Data

Tension exists between the desire for broad and up-to-date coverage of trials, which requires a simple registration process, and the need to ensure valid entries with useful information. ClinicalTrials.gov combines a straightforward, Web-based registration system with a system of organizational accountability. After being approved by the organizational account administrator, registered data are put through a series of automated and manual checks for completeness, appropriateness, internal consistency, and the functioning of any inserted links. We request and inspect 1 IRB approval letter per trial. Reminders to update records are sent to registrants every 6 months while the trial is open. Contact information for recruiting trials is confirmed by phone at up to 3 sites per trial, although it is collected for every site. However, without access to trial protocols it is not possible to determine, with complete certainty, that all data are accurate.

Establishing a Search Engine to Serve the Needs of Heterogeneous Users

Providing users with an accurate and complete listing of trials that meet their specifications is the function of the search engine. Registries that do not provide this function can be frustrating for users.[20] For example, a patient wishing to enroll in a trial would want to search open trials by condition or possibly intervention, along with site location.[42] Approximately 47% of ClinicalTrials.gov trials are currently

Table 4. Features of Search Engine in ClinicalTrials.gov

Search Engine Feature	Example
Identify and limit search to recruiting (open) studies	Potential trial participants would want to search only open trials
Spelling correction and relaxation of search terms	Misspelled words prompt a query; eg, a search for "Alzimer's disease" would prompt a query about "Alzheimer's disease"
Use of synonymy from UMLS[45]	A search for "heart attack" would find trials that list other terms, such as "myocardial infarction" or "cardiac syndrome"
Ability to search within a specific field	Search terms can be limited to specific fields; eg, a search for "diabetes" would find trials for diabetes but not trials that list diabetes as an exclusion criterion
Use of hierarchy from MeSH[43]	A search for "inflammatory bowel disease" would find trials of specific types of inflammatory bowel disease, such as Crohn's disease.
Relevancy ranking	Trials that are most related to the user's query are listed first

Abbreviations: MeSH, Medical Subject Headings; UMLS, Unified Medical Language System.

open to enrollment, though this percentage will decrease over time as open studies transition to closed studies. Researchers are often interested in all trials conducted on a given topic, whether open or completed.

ClinicalTrials.gov uses a search engine that makes use of several National Library of Medicine products, including Medical Subject Headings,[43] to identify trials that might be of interest to each user.[44] Incorporating synonymy into the search system helps users. For example, more than 60% of the studies in ClinicalTrials.gov about heart attacks do not contain the phrase "heart attack" but use a term (eg, myocardial infarction) that the system identifies as a synonym. TABLE 4 lists key features of the search engine, along with examples that illustrate how the feature would be helpful.

Preventing Duplicate Trial Registrations

Ideally, each registered trial in ClinicalTrials.gov is represented only once, resulting in a one-to-one correspondence between the NCT number and a single trial protocol. Large numbers of duplicate registrations would undermine the credibility of the registry by producing inflated search results. For example, researchers would be unable to determine the true number of trials for a given drug (and the aggregate number of participants studied), and potential trial participants could be frustrated by their inability to determine how many options they actually have. One common cause of duplicate trial registration is lack of coordination between organizations and investigators participating in multisite trials.[40] This potentially is a substantial problem, because 47% of registered trials at ClinicalTrials.gov have more than 1 listed site and 10% list more than 25 sites.

ClinicalTrials.gov attempts to prevent duplicates by requiring sponsoring organizations to sign off on each new record. In addition, ClinicalTrials.gov uses software tools to regularly scan the registry database to identify trial records that are "highly likely" to be duplicates. This involves looking for similarities in identification numbers, sponsor names, study titles, and other data elements. However, final decisions about duplicates must be made by staff, usually after direct communication with individuals involved in the trial. Software alone will never be sufficient, since trial descriptions in duplicate pairs may be quite different, and conversely, nonduplicates can look very similar (TABLE 5). Most potential duplicates are prevented at the organizational level. To date, 850 duplicates (out of approximately 37 000 trials) have been identified, after they were registered, through the ongoing process of identifying and eliminating duplicates. In 2006, 169 duplicates (1.5% of registered trials) were detected. Once a duplicate record is identified, 1 record is suppressed and the 2 NCT numbers are linked, and the archival site reflects these changes. In addition, the source of the duplication is analyzed in an effort to avoid future problems. The World Health Organization is considering the implementation of a Universal Trial Registration Number.[46,47] If such a number were assigned at the inception of every clinical trial throughout the world and used consistently, it would greatly reduce the problem of duplicates.

Defining and Naming Interventions

A common use of the registry is to identify all trials involving a specific intervention. To do this, the interventions must be identified in trial records as specifically as possible. Each intervention type poses particular naming or identification issues. Marketed drugs have a generic name; in the United States, these are registered through the US Adopted Names Council, linking them unambiguously to chemical structures.[48,49] Although drugs can usually be unambiguously identified by their chemical structure, intellectual property concerns may limit sponsors' willingness to reveal such details prior to drug approval. Instead, companies sometimes use company-specific serial numbers. These identifiers are not tracked by any external agency. The FDA uses its own internal identification system that is never made publicly available. Companies may change the serial number or may use several serial numbers for a given investigational product. Eleven percent of drug trials from all data providers and 20% of industry drug trials in ClinicalTrials.gov list a company serial number as the "drug name," including 43% of phase 1, 35% of phase 2, 11% of phase 3, and 1% of phase 4 trials.

The ClinicalTrials.gov search engine uses known synonyms (eg, searching "SU011248" also yields "sunitinib" studies). However, this naming problem significantly reduces the like-

lihood of finding all studies related to a given drug, because the National Library of Medicine may never be able to identify all relevant serial numbers. Manheimer and Anderson[20] have noted similar difficulties in searching by investigational drug names across registries. Drugs may also have more than 1 generic or brand name, but these names are tracked by external agencies and thus are easier to identify. A component of the Maine law (Table 1),[33] effective March 1, 2007, requires drug companies to list all names and aliases of drugs through the ClinicalTrials.gov data-entry system. This information will be publicly available and will be used by ClinicalTrials.gov to improve search functions. However, serial numbers (and trials) of drugs that are never approved may remain "masked" in the database. This could be important if, for example, trials reveal important safety or efficacy problems that could be relevant either to marketed drugs or to other drugs currently being evaluated.

The system of human subjects protection requires that investigators, IRB members, and, eventually, potential participants know about relevant safety information. This system is undermined to the extent that prior research is not revealed. For example, a recent "first in human" study of a new immune modulator, known as TGN1412, had catastrophic effects on 6 volunteers; their participation should, at a minimum, inform future related research.[50] However, without knowing the identity of this agent, it would not be possible to warn investigators, IRB members, or potential participants about possible relationships to other agents being studied. An approach to resolving this problem is to have an external agency track company serial numbers in a system that would eventually require full disclosure.

Although marketed vaccines and other biologic products have unique names, they may not have publicly accessible premarket identifiers and cannot always be unambiguously described by chemical structure, as with active drug compounds. It is not clear how to ensure meaningful names that allow for differentiation between different versions of a biologic product (eg, pneumococcal vaccine). Currently in ClinicalTrials.gov, entries vary from "experimental HIV vaccine" to "meningococcal ACWY conjugate vaccine" and "rgp120/HIV-1 SF-2."

The identification of specific medical devices is complicated by a single device having several components and by each component changing incrementally without a concomitant change in the device name. The issue becomes even more complex when combinations of drugs or devices are considered. While nomenclatures have been developed (eg, Universal Medical Device Nomenclature System, Global Medical Device Nomenclature),[51-53] none provides for a unique listing of different versions of a device or its components. Naming problems also exist with procedures (eg, a new method of removing a gallbladder) and with behavioral interventions.

Coordinating Trial Registration Internationally

Currently, most trial registry users must search multiple registries, each with different search capabilities, to find all trials meeting their search criteria, and researchers must navigate

Table 5. Examples of Trials Identified in ClinicalTrials.gov: Duplicate Trials With Different Trial Descriptions and Nonduplicate Trials With Identical Trial Descriptions

	Trial Registry Unique Identifier	
Trial Description	NCT00399139	NCT00086684
	Duplicate Trials With Different Trial Descriptions	
Title	An Effectiveness and Safety Study of Pentosan Polysulfate Sodium for the Treatment of Interstitial Cystitis	Efficacy and Tolerability of ELMIRON
Official title	A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Evaluation of the Efficacy and Tolerability of Two Different Doses of Elmiron for the Treatment of Interstitial Cystitis	Multi-Center, Randomized, Double-Blind, PBO-Controlled Parallel Evaluation of the Efficacy and Tolerability of ELMIRON
Condition under study	Interstitial cystitis	Interstitial cystitis
Interventions	Pentosan polysulfate sodium	ELMIRON
Sponsors	McNeil Consumer & Specialty Pharmaceuticals, a Division of McNeil-PPC Inc	Johnson & Johnson Pharmaceutical Research & Development LLC; McNeil Consumer & Specialty Pharmaceuticals, a Division of McNeil-PPC Inc; Ortho-McNeil Pharmaceutical
	NCT00168298	NCT00168324
	Nonduplicate Trials With Identical Trial Descriptions*	
Title	A Study of the Safety and Efficacy of a New Treatment for Macular Edema Resulting From Retinal Vein Occlusion	A Study of the Safety and Efficacy of a New Treatment for Macular Edema Resulting From Retinal Vein Occlusion
Condition Under Study	Macular edema associated with retinal vein occlusion	Macular edema associated with retinal vein occlusion
Interventions	Dexamethasone	Dexamethasone
Sponsors	Allergan	Allergan

*Although the data items in the ClinicalTrials.gov records are identical, on inquiry by ClinicalTrials.gov the sponsor reported that the trials use the same protocol but are 2 separate trials and will be conducted at different sites.

conflicting and overlapping registration requirements. Other biomedical information systems (eg, PubMed/MEDLINE and GenBank) meet the needs of users and researchers from around the world, yet currently there is no single international trials registry. While the development of an incentive structure to promote trial registration may best be accomplished nationally or regionally, the collection, validation, organization, and display of the data may require international collaboration. The World Health Organization is collecting data from a number of trial registries, including ClinicalTrials.gov, and plans to provide a search portal for the assembled information.[19] Other rudimentary search mechanisms already exist, including the ability in Google to search from a customized list of sites.[54] This could be used, for example, to search the ICMJE-approved registries.

Some countries have recognized the benefits of using existing infrastructure. For example, Israel has mandated the use of ClinicalTrials.gov.[55] Such a policy enables users to search and display trials from their own country as necessary to meet their needs. Many countries, however, are developing new registries, partly motivated by the desire to have information in their native language. However, to accomplish most of the scientific goals of registration, it will be necessary to also have a version of the information in an English-language–based registry. Although there are significant costs associated with developing and operating a registry, the marginal cost for ClinicalTrials.gov to register additional trials is minimal. ClinicalTrials.gov welcomes collaboration with other countries in creating a universal trial registration system and will continue to register trials from all countries.

Extending Registries to Include Trial Results

Given the persistent gap between the number of trials conducted and the number for which complete results are reported,[5,7,8,56-59] many groups are calling for the systematic inclusion of trial results in a publicly accessible database (Table 1). In the United States, only the Maine law[33] currently requires the posting of unpublished as well as published results. While the Maine law does not specify a particular results database, it does require that a federal government–sponsored database be used if and when one is developed. Legislation under current consideration in the United States[28,29] would require results, including narrative summaries, to be made available in a government database (Table 1).

Sources of Clinical Trial Results

Scientific review of trial results by individuals not associated with the research is believed to be critical to ensure accuracy and maintain confidence in the data and subsequent conclusions.[2] Trial results and associated conclusions that are published in peer-reviewed literature undergo independent editorial and scientific review. Results that are included in a New Drug Application undergo rigorous review by statisticians and other scientists at the FDA who have access to the complete protocol and raw data.[10] Reports of these FDA reviews for some, but not all,[23] approved drugs are available at Drugs@FDA.[60] Other trial results can be found in one of 12 pharmaceutical industry–sponsored databases (eg, http://www.clinicalstudyresults.org/), but these sites are generally not reviewed by experts external to the company. Cohen et al[61] have found that when conclusions were listed in these databases, they tended to be more favorable for the company's product than those found in published articles or FDA reviews of the same trials.

Current Registry Practices

ClinicalTrials.gov records include links to published articles, entries in Drugs@FDA, or, occasionally, proprietary sites for study results. In addition, the use of NCT numbers in journals and the indexing of these numbers in MEDLINE creates a seamless link between trial records and publications. However, neither ClinicalTrials.gov nor any of the other ICMJE-approved registries allows direct reporting of unpublished results. Sim and Detmer[62] have described a system for trial registration and reporting of results in parallel with journal review and publication. Neither the usefulness of this system for other uses nor the feasibility or sustainability of this approach has yet been evaluated.

Challenges in Expanding Access to Trial Results

Legislation under consideration in the United States calls for reporting both published and unpublished data in a government-run results database.[27-29] Unfortunately, no generally accepted standard format or process exists for providing this type of information to the general public. The Consolidated Standards for Reporting of Trials statement[63] and the International Conference on Harmonisation E3 Guideline[64] are possible frameworks for a results database,[47,65] but neither was designed to communicate technical trial results to the general public. Both comprise sets of standard data elements for reporting of results and are designed to allow expert reviewers (eg, editors and regulators) with access to additional contextual information (eg, full protocols) to evaluate the data.

It is not clear how the accuracy of non–peer-reviewed results and the appropriateness of the statistical analyses and interpretations could be validated with existing methods or resources. Concerns also exist about relying on sponsors or other data providers with vested interests in how the results are portrayed to submit narrative summaries of results.[2] None of the policy proposals under discussion would provide registry staff with access to protocols or raw data, making the independent scientific review of database entries impossible. Without the ability to validate entries, selective reporting of trial results could still occur, thus undermining the key purpose of a results database.

In addition, basic principles of evidence-based medicine require consideration of study design and quality, as well as of all other relevant research results, prior to drawing conclusions from a single study (eg, see http://www.cms.hhs.gov/FACA/Downloads/recommendations.pdf and http://www.cochrane.org/resources/handbook/). Finally, the development of treatment recommendations involves other considerations, such as the risks and benefits of treatment alternatives.[66,67] Individuals who use a results database entry for a single trial to make judgments about an intervention's benefits or harms may be misled.

Other possibilities for expanding access to trial results have been discussed. Turner[10] has called for the timely posting of reviews for all marketed drugs on the FDA site, Drugs@FDA. The IOM [Institute of Medicine] Drug Safety report notes that most drugs that were approved since 1998 have some entry in Drugs@FDA, though the amount of information available is highly variable.[23] The linking of FDA reviews, by NCT number, to the records in ClinicalTrials.gov and to the published literature would be helpful to those seeking information about specific clinical trials. It must be noted, however, that only about 20% of Investigational New Drug applications result in approved drugs[68]; this means that most trials submitted to the FDA are not eligible for inclusion in Drugs@FDA.

Although data for marketed drugs might be considered the most relevant to the general public, there are instances in which data not in an approved New Drug Application could be important. For example, future trial participants and those charged with safeguarding trial participants need access to prior research results on similar (or identical) products to judge potential benefits and harms of a new clinical trial. In addition, clinical use of a drug, or drug class, may reasonably be influenced by knowledge of harms or benefits that were elucidated in prior research, even if that research did not lead to an FDA action. The NIH supports approximately 2000 clinical trials per year and is committed to expanding the dissemination of the study results. A number of options are being explored, including the possible development of a results database of NIH-funded studies, which could then inform the development of a database for trials from non-NIH sponsors.

Conclusion

The registration of clinical trials continues to expand for all types of trials throughout the world. Key scientific challenges warrant attention so that the system of registration can fully meet its goals. The desire for complete public reporting of results must be tempered with acknowledgment of the problems associated with bypassing independent scientific review and with attempting to convey complex results using simple, summary data.

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