Issues in the Registration of Clinical Trials

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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.7 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.8

Researchers have documented that up to 37% of clinical trials presented in abstracts never result in a full journal article;9 that even when published trial results exist, some prespecified outcome measures may be omitted;10 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

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.

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.15-18 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.17,18 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-
tant, unanticipated adverse effects may not be recognized due to relatively small sample sizes and incomplete publication of results from preapproval studies. 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 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 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*

<table>
<thead>
<tr>
<th>Policy Name</th>
<th>Policy Type</th>
<th>Intervention Type</th>
<th>Policy Scope</th>
<th>Inclusion of Provisions for Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDAMA, Section 113,26 1997</td>
<td>Federal law</td>
<td>Drugs and biologics</td>
<td>Efficacy trials for “serious or life-threatening diseases or conditions” regulated by the FDA</td>
<td>No</td>
</tr>
<tr>
<td>Fair Access to Clinical Trials (FACT) Act,29 2007</td>
<td>Bill introduced in US Senate by Senator Dodd (Conn)</td>
<td>Drugs, biologics, and devices</td>
<td>Ongoing trials for “serious and life-threatening diseases and conditions” regulated by the FDA</td>
<td>Yes</td>
</tr>
<tr>
<td>Enhancing Drug Safety and Innovation Act,30 2007</td>
<td>Bill introduced in US House of Representatives by Representative Waxman (Calif)</td>
<td>Drugs, biologics, and devices</td>
<td>Most “safety or effectiveness” trials for approved and unapproved products</td>
<td>Yes</td>
</tr>
<tr>
<td>Food and Drug Administration Revitalization Act,27 2007</td>
<td>Bill introduced in US Senate by Senator Kennedy (Mass)</td>
<td>Drugs, biologics, and devices</td>
<td>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</td>
<td>Yes</td>
</tr>
<tr>
<td>ICMJE Statement,18 2005</td>
<td>Publication policy</td>
<td>Any†</td>
<td>Interventional controlled trials; defines criteria for “acceptable registries”</td>
<td>No</td>
</tr>
<tr>
<td>WHO ICTRP,25 2006</td>
<td>WHO policy</td>
<td>Any</td>
<td>*All medical studies that test treatments on patients or healthy volunteers</td>
<td>Yes</td>
</tr>
<tr>
<td>Centers for Medicare &amp; Medicaid (CMS): Proposed Clinical Research Policy,25 2007</td>
<td>Proposed CMS Medicare policy</td>
<td>Any</td>
<td>All “qualified” research for which Medicare covers routine care costs</td>
<td>Yes</td>
</tr>
<tr>
<td>PhRMA Clinical Trial Registry Proposal,31 2004</td>
<td>Recommendation</td>
<td>Drugs and biologics</td>
<td>*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</td>
<td>Yes</td>
</tr>
<tr>
<td>Ottawa Group,32 2005</td>
<td>Recommendation</td>
<td>Any</td>
<td>*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”</td>
<td>Yes</td>
</tr>
<tr>
<td>AAMC Principles,31 2006</td>
<td>Recommendation</td>
<td>Any</td>
<td><em>All trials meeting the ICMJE requirements</em></td>
<td>Yes</td>
</tr>
<tr>
<td>IOM Report:Drug Safety,32 2006</td>
<td>Recommendation</td>
<td>Drugs only</td>
<td><em>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</em></td>
<td>Yes</td>
</tr>
<tr>
<td>Maine State Law,33 2005</td>
<td>State law</td>
<td>Drugs and biologics</td>
<td>Trials of “prescription drugs in this State” (of Maine); includes “biological products”</td>
<td>Yes</td>
</tr>
<tr>
<td>Prescription Drug Right-to-Know Act, New Jersey State Bill,34 2006</td>
<td>Bill before state legislature</td>
<td>Drugs and biologics</td>
<td>“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)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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. 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.

The registries currently accepted by the ICMJE are listed in Table 2. 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.

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. 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 3,646 organizational accounts, including 1,288 from industry, 93 from US federal agencies (including the National Institutes of Health [NIH]), and 2,265 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. 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>
<thead>
<tr>
<th>Registry Name</th>
<th>URL</th>
<th>Auspices/Funding</th>
<th>No. of Trials (As of 1/17/07)</th>
<th>Is Recruitment Status Recorded and Updated?</th>
<th>Can Users Search for “Open” Trials?</th>
</tr>
</thead>
<tbody>
<tr>
<td>ClinicalTrials.gov</td>
<td><a href="http://clinicaltrials.gov">http://clinicaltrials.gov</a></td>
<td>US Federal Government (National Library of Medicine at the NIH)</td>
<td>36,657</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>ISRCTN</td>
<td><a href="http://isrctn.org">http://isrctn.org</a></td>
<td>Not-for-profit entity administered by Current Controlled Trials Ltd fees collected from registrants</td>
<td>5,281</td>
<td>No (anticipated closure date is recorded)</td>
<td>Not currently</td>
</tr>
<tr>
<td>Australian Clinical Trials Registry</td>
<td><a href="http://www.actr.org.au">http://www.actr.org.au</a></td>
<td>Grant from Australian National Health and Medical Research Council (University of Sydney)</td>
<td>1,350</td>
<td>Recorded (plans to allow for updates by mid 2007)</td>
<td>No (planned by mid 2007)</td>
</tr>
<tr>
<td>Netherlands Trial Registry</td>
<td><a href="http://www.trialregister.nl">http://www.trialregister.nl</a></td>
<td>Grant from Dutch Ministry of Health (Dutch Cochrane Center)</td>
<td>797</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>UMIN Clinical Trials Registry</td>
<td><a href="http://www.umin.ac.jp/ctr/">http://www.umin.ac.jp/ctr/</a></td>
<td>Grant from Japanese Ministry of Education</td>
<td>534</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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. 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. 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.

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. 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. Approximately 47% of ClinicalTrials.gov trials are currently formatted and searchable.

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>January 2005</th>
<th>January 2006</th>
<th>January 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observational</td>
<td>2077 (17)</td>
<td>3684 (15)</td>
<td>5286 (15)</td>
</tr>
<tr>
<td>Intervventional</td>
<td>10 110 (83)</td>
<td>21 511 (85)</td>
<td>30 963 (86)</td>
</tr>
<tr>
<td>Type of intervention trial (data provider category)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>National Institutes of Health</td>
<td>7904 (78)</td>
<td>9415 (44)</td>
<td>10 828 (35)</td>
</tr>
<tr>
<td>University†</td>
<td>196 (2)</td>
<td>5696 (26)</td>
<td>10 007 (32)</td>
</tr>
<tr>
<td>Industry</td>
<td>1715 (17)</td>
<td>5714 (26)</td>
<td>9273 (30)</td>
</tr>
<tr>
<td>Other US federal</td>
<td>295 (3)</td>
<td>686 (3)</td>
<td>855 (3)</td>
</tr>
<tr>
<td>Intervention category‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>8711 (86)</td>
<td>16 682 (78)</td>
<td>23 367 (75)</td>
</tr>
<tr>
<td>Procedure</td>
<td>5028 (50)</td>
<td>6996 (33)</td>
<td>8923 (29)</td>
</tr>
<tr>
<td>Behavior</td>
<td>505 (5)</td>
<td>1819 (8)</td>
<td>2622 (8)</td>
</tr>
<tr>
<td>Device</td>
<td>121 (1)</td>
<td>890 (4)</td>
<td>1631 (5)</td>
</tr>
<tr>
<td>Vaccine</td>
<td>241 (2)</td>
<td>667 (3)</td>
<td>1075 (3)</td>
</tr>
<tr>
<td>Interventional study location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only in the United States</td>
<td>7203 (71)</td>
<td>12 265 (57)</td>
<td>16 397 (53)</td>
</tr>
<tr>
<td>Not in the United States</td>
<td>734 (7)</td>
<td>5064 (24)</td>
<td>8918 (29)</td>
</tr>
<tr>
<td>United States and other country</td>
<td>1399 (14)</td>
<td>2205 (10)</td>
<td>2928 (9)</td>
</tr>
<tr>
<td>Missing§</td>
<td>774 (8)</td>
<td>1977 (9)</td>
<td>2720 (9)</td>
</tr>
</tbody>
</table>

*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.
ISSUES IN THE REGISTRATION OF CLINICAL TRIALS

Table 4. Features of Search Engine in ClinicalTrials.gov

<table>
<thead>
<tr>
<th>Search Engine Feature</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identify and limit search to recruiting (open) studies</td>
<td>Potential trial participants would want to search only open trials</td>
</tr>
<tr>
<td>Spelling correction and relaxation of search terms</td>
<td>Misspelled words prompt a query; eg, a search for “Alzheimer’s disease” would prompt a query about “Alzheimer’s disease”</td>
</tr>
<tr>
<td>Use of synonymy from UMLS</td>
<td>A search for “heart attack” would find trials that list other terms, such as “myocardial infarction” or “cardiac syndrome”</td>
</tr>
<tr>
<td>Ability to search within a specific field</td>
<td>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</td>
</tr>
<tr>
<td>Use of hierarchy from MeSH</td>
<td>A search for “inflammatory bowel disease” would find trials of specific types of inflammatory bowel disease, such as Crohn’s disease.</td>
</tr>
<tr>
<td>Relevancy ranking</td>
<td>Trials that are most related to the user’s query are listed first</td>
</tr>
</tbody>
</table>

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

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. 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. 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. 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-
The system of human subjects protection requires that investigators, IRB members, and, eventually, potential participants know about relevant safety information. This system is under-
tained to the extent that prior re-
search 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 re-
search.30 However, without knowing 
the identity of this agent, it would not 
be possible to warn investigators, IRB 
memories, or potential participants 
about possible relationships to other 
agents being studied. An approach to 
resolving this problem is to have an ex-
ternal agency track company serial 
numbers in a system that would event-
ually require full disclosure.

Although marketed vaccines and 
other biologic products have unique 
names, they may not have publicly ac-
cessible premarket identifiers and can-
not always be unambiguously de-
scribed by chemical structure, as with 
active drug compounds. It is not clear 
how to ensure meaningful names that 
allow for differentiation between dif-
ferent versions of a biologic product (eg, 
pneumococcal vaccine). Currently in 
ClinicalTrials.gov, entries vary from 
“experimental HIV vaccine” to “me-
ingococcal ACWY conjugate vac-
cine” and “rgpl20/HIV-1 SF-2.”

The identification of specific medical 
devices is complicated by a single de-
vice having several components and by 
each component changing increment-
ally without a concomitant change in 
the device name. The issue becomes 
ev en more complex when combina-
tions of drugs or devices are consid-
ered. While nomenclatures have been 
developed (eg, Universal Medical De-
vice Nomenclature System, Global Medi-
cal Device Nomenclature),51-53 none pro-
vides for a unique listing of different 
versions of a device or its components. 
Naming problems also exist with pro-
cedures (eg, a new method of remov-
ing 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 cri-
tera, and researchers must navigate 

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

<table>
<thead>
<tr>
<th>Trial Registry Unique Identifier</th>
<th>Trial Description</th>
<th>NCT00399199</th>
<th>NCT00086684</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duplicate Trials With Different Trial Descriptions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Title</strong></td>
<td>An Effectiveness and Safety Study of Pentosan Polysulfate Sodium for the Treatment of Interstitial Cystitis</td>
<td>Efficacy and Tolerability of ELMIRON</td>
<td></td>
</tr>
<tr>
<td><strong>Official title</strong></td>
<td>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</td>
<td>Multi-Center, Randomized, Double-Blind, PBO-Controlled Parallel Evaluation of the Efficacy and Tolerability of ELMIRON</td>
<td></td>
</tr>
<tr>
<td><strong>Condition under study</strong></td>
<td>Interstitial cystitis</td>
<td>Interstitial cystitis</td>
<td></td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Pentosan polysulfate sodium</td>
<td>ELMIRON</td>
<td></td>
</tr>
<tr>
<td><strong>Sponsors</strong></td>
<td>McNeil Consumer &amp; Specialty Pharmaceuticals, a Division of McNeil-PPC Inc</td>
<td>Johnson &amp; Johnson Pharmaceutical Research &amp; Development LLC; McNeil Consumer &amp; Specialty Pharmaceuticals, a Division of McNeil-PPC Inc; Ortho-McNeil Pharmaceutical</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NCT00168298</th>
<th>NCT00168324</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonduplicate Trials With Identical Trial Descriptions</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Title</strong></td>
<td>A Study of the Safety and Efficacy of a New Treatment for Macular Edema Resulting From Retinal Vein Occlusion</td>
</tr>
<tr>
<td><strong>Condition Under Study</strong></td>
<td>Macular edema associated with retinal vein occlusion</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Dexamethasone</td>
</tr>
<tr>
<td><strong>Sponsors</strong></td>
<td>Allergan</td>
</tr>
</tbody>
</table>

*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. Other rudimentary search mechanisms already exist, including the ability in Google to search from a customized list of sites. 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. 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, 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 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 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. 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. Reports of these FDA reviews for some, but not all, approved drugs are available at Drugs@FDA. 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 have found that when conclusions were listed in these database, 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 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. 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 and the International Conference on Harmonisation E3 Guideline are possible frameworks for a results database, 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. 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.cochrane.org/resources/handbook/). Finally, the development of treatment recommendations involves other considerations, such as the risks and benefits of treatment alternatives.16,61 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. Turner10 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,38 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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Dr Harlan reports that he has past or current consultancies with the National Institutes of Mental Health, Office of Dietary Supplements, and the National Library of Medicine. Dr West reports that she is a consultant to the National Library of Medicine and is employed by the American Psychiatric Institute for Research and Education, which receives research support from the National Institute of Mental Health, the Agency for Healthcare Research and Quality, the Substance Abuse and Mental Health Services Administration, the US Food and Drug Administration, and the American Psychiatric Foundation (APF). The APF receives financial support from a consortium of pharmaceutical industry supporters including AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forrest, Janssen, Pfizer, Sanofi-Aventis, and Wyeth. No other financial disclosures were reported.

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ISSE IN THE REGISTRATION OF CLINICAL TRIALS