



Clinical Trial Registration and Results Reporting: ClinicalTrials.gov and FDAAA

by Tony Tse, Ph.D., and Deborah A. Zarin, M.D.

There have been a growing number of calls for public registration and results reporting of clinical trials as a method for addressing scientific and ethical concerns.¹ ClinicalTrials.gov (<http://clinicaltrials.gov/>), the largest international clinical trials registry, is operated by the National Institutes of Health (NIH).² Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801)³ expands the ClinicalTrials.gov registry and adds a results database. Although other policies address various aspects of clinical trial registration (e.g., medical journal editors and World Health Organization (WHO)), FDAAA 801 provides a comprehensive framework with potentially far-reaching consequences for clinical research, medicine, and the public. This article focuses on some key issues and experiences encountered during the implementation of the expanded registry and results database provisions over the past year.

Historical Context

ClinicalTrials.gov, a federally-funded and operated clinical trial registry, was launched in February 2000 by the National Library of Medicine (NLM), a component of the NIH. Section 113 of the FDA Modernization Act of 1997 (FDAMA 113)⁴ required the public posting of summary information about publicly and privately funded clinical trials that study the efficacy of investigational new drugs (and biological products) for serious or life-threatening diseases and conditions. From its inception, ClinicalTrials.gov has also accepted voluntary registration of a wide range of health-related clinical studies not mandated by FDAMA 113, including studies of devices, surgical procedures, and behavioral interventions, and observational studies, for any disease or condition. Such a broad scope allowed ClinicalTrials.gov to serve a number of different policy needs and a broad range of user groups (Figure 1).

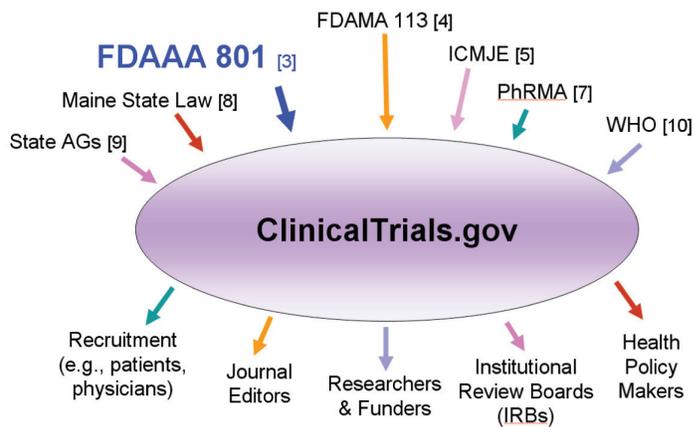


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Figure 1. Policies and Users Supported by ClinicalTrials.gov



For example, in 2004, the International Committee of Medical Journal Editors (ICMJE), a group of editors from leading medical journals, issued the first of several statements requiring the prospective registration of clinical trials (i.e., prior to enrollment of the first patient) by September 2005 as a condition for study results to be considered for publication.⁵ Subsequently, several data elements (e.g., primary and secondary outcome measures) were added to ClinicalTrials.gov to accommodate registrants who wanted to comply with the ICMJE policy. Largely as a result of this policy, the total number of registrations at ClinicalTrials.gov increased by 73 percent between May and October 2005.⁶ Other policies include the Joint Position on the Disclosure of Clinical Trial Information issued by four pharmaceutical industry associations worldwide, including the Pharmaceutical Research and Manufacturers of America (PhRMA), committing their members to register all “confirmatory” and “exploratory efficacy” (in general, phase II-IV) trials and to publicly disclose results for all such trials of “a medicinal product that has been approved for marketing and is commercially available. . . , regardless of outcome;”⁷ a Maine state law mandating the registration and public reporting of results of trials of drugs

marketed in Maine⁸ and several settlements between State Attorneys General and individual companies requiring public registration and results reporting for specified clinical studies (e.g., Pfizer for Bextra and Celebrex.⁹) In 2006, the WHO issued its 20-item minimum trial registration data requirements, which has since become a standard for registries worldwide.¹⁰ FDAAA 801, enacted on September 27, 2007, mandates registration for a broader set of trials than under FDAMA 113 with required items that roughly correspond to the WHO minimum registration requirements. FDAAA 801 also requires the reporting of results and sets stringent enforcement policies for non-compliance.

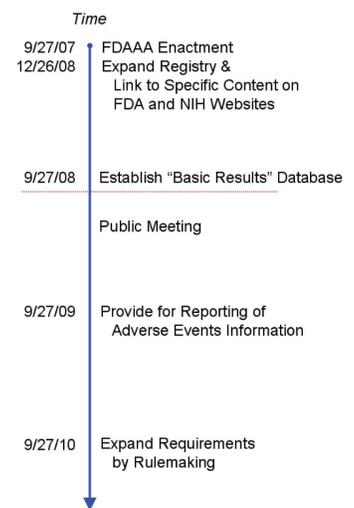
Implementation Timeframe

Overall, FDAAA 801 provides for several incremental implementation milestones that build upon previous ClinicalTrials.gov requirements and culminate in expansion of the registry and results database by rulemaking (Figure 2.) The first milestone required the expansion of ClinicalTrials.gov beyond FDAMA 113, within 90 days after enactment, including accepting and displaying registration of a greater number of required data elements (“clinical trial information.”) In addition, study

sponsors or designated principal investigators (“responsible party”) are required to submit more types of clinical trials (“applicable clinical trial”),¹¹ including device studies and studies of any disease or condition.

Also within the first 90 days, FDAAA 801 required Web-based links to be made to certain existing results information available at the FDA and NLM Websites (e.g., action packages for approval from Drugs@FDA¹² and structured product labels at DailyMed,¹³ respectively.) The next milestone required the addition of a “basic results” database within one year of enactment for the submission and posting of summary results information for certain applicable clinical trials of FDA-approved, licensed, or cleared drugs, biological products, and devices. Generally, the responsible party is required to submit “basic results” within one year of the date when final data collection for the primary outcome measure is completed (“completion date.”)¹⁴ Future implementation milestones include mandatory submission of adverse events information by September 27, 2009, and further modifications to ClinicalTrials.gov through rulemaking. Other FDAAA 801

Figure 2. Implementation Timeframe



provisions not discussed in this article include, among other things, developing certifications of compliance to accompany certain (1) grant and progress reports to specified federal agencies and (2) drug, biological product, and device submissions to FDA; conducting an NIH-FDA pilot quality control project; and posting public notices of violations and other enforcement mechanisms.

Expanding the Registry

When FDAAA 801 was enacted, ClinicalTrials.gov was a well-established registry that had been operational for over seven years and contained nearly 45,000 registered interventional and observational study records for a variety of interventions with study locations in 150 countries. Because most of the data elements explicitly enumerated by FDAAA 801 either overlapped with those developed under FDAMA 113 or had been implemented as “optional” data elements, the technical implementation of the expanded registry was achieved by the statutory deadline. Several data elements were added to support statutory requirements, like contact information of the responsible party (<http://prsinfo.clinicaltrials.gov/definitions.html>).

One substantial process change was the implementation of a delayed posting mechanism for applicable clinical trials of devices not previously cleared or approved by the FDA. Under FDAAA 801, clinical trial information for such trials must be submitted to ClinicalTrials.gov within the usual time frame (i.e., no later

than 21 days after enrollment of the first participant), but cannot be posted publicly until device clearance or approval. Prior to FDAAA 801, all registrations had been publicly posted upon submission. Thus, a new data element, “Delayed Posting? (Y/N),” was implemented to allow responsible parties to indicate whether an applicable device clinical trial is covered by the delayed posting provision.

The expanded registry requirements resulted in an increase in new registrations and modifications of registrations for ongoing studies. The average number of new registrations per week increased by more than 40 percent from about 250 (from December 2006 to November 2007) to 360 (from December 2007 to September 2008); modifications of registered records increased by 300 percent on average for those periods. Further, there was a 40 percent increase in the number of requests per week to create an account to register trials using the Web-based data entry system (<http://prsinfo.clinicaltrials.gov/>).

Adding a “Basic Results” Database

The “basic results” database had to be implemented *de novo*, as it did not exist at the time of enactment. The database was required to be operational within one year of enactment. Building on the existing technical infrastructure used to develop ClinicalTrials.gov, the “basic results” reporting component was integrated into the data entry system for data submission and ClinicalTrials.gov

for public display by September 2008.¹⁵ The “basic results” database is designed to provide flexibility in specifying a wide range of study designs, data types and measures, and other study-specific results information while presenting a consistent display to the public.

Based on discussions with numerous experts including the NLM-sponsored Meeting on Public Results Database Feasibility Study, various presentations to stakeholder groups, meetings of the NIH-FDA Working Group on Results, and the February 2008 meeting of the NLM Board of Regents Working Group on Clinical Trials, which was open to the public,¹⁶ key challenges and objectives were identified and formed the basis for determining requirements (Table 1).

Following the requirements analysis period, a series of mockups and interactive systems were developed and made available to elicit comments from stakeholders, as announced in a Federal Register notice (73 FR 29525, May 21, 2008.)¹⁷ The database uses a tabular format to collect and display “basic results” data. Data providers construct tables by defining rows (e.g., study-specific measures or categories), columns (e.g., arms or comparison groups) and data types (e.g., mean and standard deviation) where appropriate, before entering actual values. The “basic results” data elements are clustered into three modules (i.e., Participant Flow, Baseline Characteristics, and Outcome Measures and Statistical Analyses.) Administrative data elements (i.e., Results Point of Contact, Certain Agreements, and Overall Limitations and Caveats) are also included (see the Draft “Basic Results” Data Element Definitions at http://prsinfo.clinicaltrials.gov/definitions_results.html.) An “adverse events” module was developed and is optional until September 27, 2009.

Overall, the feedback from stakeholders was positive; many suggestions were adopted to improve the system.

Table 1. Summary of High-Level Requirements for the “Basic Results” Database

Key Challenges	Key Objectives
<ul style="list-style-type: none"> ▪ Accommodation of a wide range of study designs and data types ▪ Optimization of data quality and search capabilities using the database structure ▪ Accommodation of varying resources and reporting capabilities, ranging from sponsors of large multi-national studies to individual investigators ▪ Promotion of “good reporting practices” while accommodating actual practices in the field 	<ul style="list-style-type: none"> ▪ Streamlined data submission process <ul style="list-style-type: none"> ○ Develop tables similar to those used in journal articles ○ Use controlled vocabularies and data standards, as appropriate ○ Allow for interactive data entry and batch upload of data files ▪ Report accurate and objective information <ul style="list-style-type: none"> ○ Provide clear displays of results data that can be understood without significant narrative ○ Provide a consistent layout and format to facilitate comparisons across studies ○ Link to authoritative sources for more information pertaining to study topic or interpretation

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As of December 1, 2008, “basic results” for 25 clinical trials have been posted on ClinicalTrials.gov.¹⁸ As these trials have

ranged widely in study design and conditions evaluated, the database appears to accommodate variety and complexity while illustrating key features of the trials reported. It is apparent, however, that the preparation and submission of “basic

results” requires scientific knowledge and has a steeper learning curve than that for registration. Part of the issue is that summarizing results data is generally a more complex cognitive task that requires familiarity with the study, knowledge of biostatistics, and experience with expressing results clearly in a tabular format, similar to the process used to prepare data tables for publication. Because results are displayed without narrative text, the tables themselves must be sufficiently informative to allow people not familiar with the study to interpret the data (e.g., descriptive row and column labels.) In working with data providers during the first few months, the ClinicalTrials.gov staff identified a number of “Common Errors,” which have been compiled and posted online to assist others when submitting “basic results” (see the “Basic Results’ Database” section at <http://prsinfo.clinicaltrials.gov/fdaaa.html>.) It is anticipated that as data providers gain familiarity with the results reporting mechanism, they

U.S. Pharmacopeia (USP) is pleased to welcome Matthew B. Van Hook as Assistant General Counsel Compensial Sciences. In this role, Van Hook will be responsible for food and drug regulatory and compendial matters. He will report to Susan de Mars, chief legal officer for USP. Van Hook is experienced in advising drug and biotechnology companies on the Food and Drug Administration (FDA) review and approval process, and maintaining the integrity of the drug distribution system. He has spoken and testified frequently on FDA-related matters including drug safety and pharmacovigilance, drug diversion and importation, pedigrees and the advent of electronic track and trace technology, and the debate over affordability and access, including the changing roles of the Centers for Medicare & Medicaid Services (CMS) and FDA.

Hogan & Hartson LLP announced today that Craig H. Smith, former General Counsel of one of the nation’s largest

Medicaid and health regulatory agencies, has rejoined the firm as a partner in the Florida health practice. Smith will spend a significant amount of time in Miami and in Tallahassee where he has been actively involved in the state’s health care policy, regulatory oversight, and litigation matters.

BD (Becton, Dickinson and Company) has announced the appointment of Vincent A. Forlenza to the position of President, BD Biosciences, effective immediately. Mr. Forlenza, who joined BD in 1980, had served most recently as the Company’s Senior Vice President, Technology, Strategy and Development. He will succeed Deborah J. Neff, who is leaving BD to pursue other career opportunities. Mr. Forlenza holds a BS in Chemical Engineering from Lehigh University and a MBA from the Wharton Graduate School, University of Pennsylvania.

on the move

will find data submission to be easier, as has been the case for registration. This already appears to be the case as additional submissions by data providers demonstrate improvements. In addition, new features will likely be implemented in the data entry system in response to technical issues that may arise.

Looking Ahead

The next two years will see the implementation of additional statutory milestones (items below the horizontal line in Figure 2.) In addition, the lessons learned from operation of the expanded registry and “basic results” database will inform rulemaking. A Notice of Proposed Rulemaking (NPRM) is being prepared for the expanded registry. The proposed rule will provide operational definitions for key terms used in the statute such as “applicable clinical trial” and “responsible party” and will clarify registration requirements under FDAAA 801. It is anticipated that additional NPRMs will be issued for other components of the registration and results reporting requirements. In addition, as required by FDAAA 801, a public meeting will be held in early 2009 to inform expansion of the results database through rulemaking.

Conclusion

In the year since the enactment of FDAAA 801, NLM has implemented the expansion of the ClinicalTrials.gov registry and added a new “basic results” database. The new, broader scope of trial registration requirements has resulted in a steady increase in newly registered clinical studies and modifications of previously registered studies. With regard to the “basic results” database, considerable experience has been gained through interactions with data providers during the first two months following the launch of the database in late September 2008. To

date, the primary “lesson learned” is that reporting summary results appears to require knowledge similar to levels needed for journal manuscript preparation. The ClinicalTrials.gov quality assurance process currently reviews submissions for apparent validity, meaningful entries, logic and internal consistency, and formatting. Early experience suggests that the design of the results database allows sufficient flexibility to accommodate a wide variety of study designs.

It is anticipated that the new implementation of ClinicalTrials.gov will provide a more complete, holistic public view of the clinical research landscape from study inception to completion. Of course, considerable work is needed to fully implement FDAAA 801, including clarifying registration and results reporting requirements through rulemaking and public comment. The next few years will certainly be important ones for the implementation of clinical research registration and results reporting. ▲

- 1 Zarin DA, Tse T. Medicine. Moving toward transparency of clinical trials. *Science*. 2008 Mar 7;319(5868):1340-2.
- 2 As of December 1, 2008, ClinicalTrials.gov contains registration information for nearly 65,300 publicly and privately sponsored, active and closed, observational and interventional studies for a wide range of interventions and conditions with studies located in approximately 160 countries. Each month, the site receives over 40 million page views from approximately 800,000 unique visitors.
- 3 Public Law No. 110-85 § 801. http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110
- 4 Public Law No. 105-115 § 113. <http://www.fda.gov/cder/guidance/105-115.htm#SEC.%20113>
- 5 De Angelis C, Drazen JM, Frizelle FA, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *N Engl J Med*. 2004 Sep 16;351(12):1250-1. For additional information on the ICMJE clinical trial registration policy, see “ICMJE Editorials” at <http://icmje.org/>. The most recent statement, “Clinical Trial Registration: Looking Back and Moving Forward, was published in June 2008 and specifies that certain types of results reporting will not be considered “previous publication.”
- 6 Zarin DA, Tse T, Ide NC. Trial Registration at ClinicalTrials.gov between May and October 2008. *N Engl J Med*. 2005 Dec 29;353(26):2779-87.

- 7 European Federation of Pharmaceutical Industries and Associations (EFPIA), the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), the Japan Pharmaceutical Manufacturers Association (JPMA), and the Pharmaceutical Research and Manufacturers of America (PhRMA). Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases. 2008 Nov 18. http://www.ifpma.org/Documents/NR10990/Revised_Joint_Industry_Position_26Nov08.pdf. Note: Confirmatory clinical trials “serve to examine pre-stated questions (i.e., to test hypotheses) using statistically valid plans for data analysis and provide firm evidence of safety and/or efficacy to support product claims.” Exploratory efficacy clinical trials “serve primarily to explore therapeutic efficacy in patients ... [and] do not include ‘Phase 1 trials.’”
- 8 An Act Regarding Advertising by Drug Manufacturers and Disclosure of Clinical Trials, Maine State Law, 22 MRSA c605 § 2700-A. http://www.state.me.us/dhhs/boh/clinical_trials.htm.
- 9 Saul S. Pfizer to settle claims over Bextra and Celebrex. *The New York Times*. 2008 Oct 17. <http://www.nytimes.com/2008/10/18/business/18drug.htm>
- 10 Sim I, Chan AW, Gülmezoglu AM, Evans T, Pang T. Clinical trial registration: transparency is the watchword. *Lancet*. 2006 May 20;367(9523):1631-3.
- 11 In general, “applicable clinical trial” includes phase II-IV clinical trials of drugs and biological products regulated by the FDA and controlled clinical studies of medical devices regulated by the FDA that are not feasibility or pilots studies, including pediatric post-market surveillance under Section 522 of the Federal Food, Drug, and Cosmetic Act.
- 12 Drugs@FDA: FDA Approved Drug Products. <http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/>
- 13 DailyMed: Current Medication Information. <http://dailymed.nlm.nih.gov/dailymed/>
- 14 Delayed submission and extensions of the submission deadline for results reporting are permitted under certain circumstances, such as seeking approval for a new use for the drug or device.
- 15 National Library of Medicine. National Institutes of Health Launches ClinicalTrials.gov Results Database. 2008 Sept 26. http://www.nlm.nih.gov/news/expanded_clinicaltrials.html
- 16 National Library of Medicine. Board of Regents Working Group on Clinical Trials. Notice of Meetings. *Federal Register*. 2008 Jan 18; 73(13):3473. Meeting Minutes. 2008, Feb 11. http://www.nlm.nih.gov/od/bor/BoR_WG_CT_Minutes_11Feb08.pdf
- 17 Notice of Public Process for the Expansion of the ClinicalTrials.gov Registry and Availability for Public Comment of Preliminary Information Related to the Establishment of a Basic Results Database. *Federal Register*. 2008 May 21;73(99):29525-6. <http://edocket.access.gpo.gov/2008/E8-11042.htm>.
- 18 To view all posted study records with results, go to the ClinicalTrials.gov the advanced search page at <http://clinicaltrials.gov/ct2/search/advanced>, select “Studies With Results” from the Study Results dropdown menu, and click the Search button. Note that the items returned in the list of results are annotated with “Has Results.” Click on a study record title and then the “Study Results” tab to view the posted “basic results” for that study.