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ClinicalTrials.gov and Related Projects: Improving Access to Information about Clinical Studies

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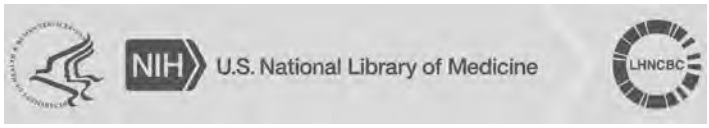

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1. Background

The National Library of Medicine (NLM) launched ClinicalTrials.gov in February 2000 in response to Section 113 of the Food and Drug Administration (FDA) Modernization Act of 1997 (FDAMA 113).[1] Since then, the database has been expanded to accommodate certain scientific goals as well as key international registration policies including the International Committee of Medical Journal Editors (ICMJE) Obligation to Register Clinical Trials, which requires prospective registration in an acceptable public database as a condition of publication.[2] Most recently, the ClinicalTrials.gov registry requirements were expanded, and a results database was developed and added, in response to Section 801 of the FDA Amendments Act of 2007 (FDAAA 801).[3]

Prospective registration and systematic results reporting provide for public access to key information about clinical research in humans. Public disclosure (1) allows people to find information on participation in research, (2) meets ethical and scientific obligations to ensure that research contributes to the medical evidence base, (3) promotes scientific integrity, and (4) provides summary information for exploring ethical, legal, and scientific aspects of the clinical research enterprise.

The ClinicalTrials.gov Web site (http://ClinicalTrials.gov/) receives over 95 million page views and approximately 900,000 unique visitors per month. Data are submitted to ClinicalTrials.gov through a Web-based Protocol Registration System (PRS) by over 12,000 sponsors including the U.S. federal government, pharmaceutical and device companies, academic, and international organizations. As of early March 2013, ClinicalTrials.gov listed nearly 142,000 interventional and observational studies with locations in all 50 states and in 182 countries. Approximately one-third of the studies are (or will be) open to recruitment, and the remaining two-thirds are closed to recruitment or completed. The number of registered studies has increased nearly 10-fold since May 2005, the last review by the Board of Scientific Counselors (BoSC) [see Table 1]. Since the launch of the results database in September 2008, over 8,320 of the registered studies include summary results tables.

This report summarizes the changes and updates to the ClinicalTrials.gov and Related Projects program since the May 2005 BoSC report.[4] In particular, we focus in more detail on three key areas of development during the past 8 years:

1. Developing and implementing a *de novo* ClinicalTrials.gov "basic" results database [see *Key Accomplishment 2* under section 4. *Methods and Procedures*]]
2. Developing and implementing quality assurance (QA) criteria, a review process, and a system within the PRS to evaluate results submissions prior to public posting on ClinicalTrials.gov [See *Key Accomplishment 3* under section 4. *Methods and Procedures*]
3. Using aggregate data from the ClinicalTrials.gov registry and results database to assess the overall state of the clinical research enterprise [see *Utilization* under section 5. *Evaluation Plan*]

Table 1: Comparison of the Number of Records Posted at ClinicalTrials.gov in April 2005 and March 2013.

	Number of Records	
	As of 4/14/05[4]	**As of 3/7/13**
Total	12,926 (100%)	141,696 (100%)
Study Type		
Observational Studies	2,107 (16%)	26,200 (18%)
Interventional Studies	10,819 (84%)	114,853 (81%)
Intervention Type*		
Drug or Biologic	9,542	77,283
Behavioral, other	627	28,081
Surgical procedure	3,896	12,926
Medical device	151	9,912
Recruitment Status		
Open	4,566 (35%)	45,002 (32%)
Closed	8,360 (65%)	96,694 (68%)
Lead Sponsor Class**		
NIH	6,492 (50%)	10,103 (7%)
University/Other	3,302 (26%)	84,642 (60%)
Industry	2,746 (21%)	44,722 (32%)
Federal, not NIH	411 (3%)	2,229 (1%)

*Because a study may include more than one type of intervention, the sum of counts by type of intervention does not equal the total number of interventional studies.
**Data as of 4/15/05 (N = 12,950); because the definition of "Sponsor" changed after enactment of FDAAA 801, these data cannot be compared.

2. Project Objectives

The primary objective of our program is to provide an accessible and authoritative resource that allows the public to seek and view structured information about clinical trials and summary results.

Secondary objectives include:

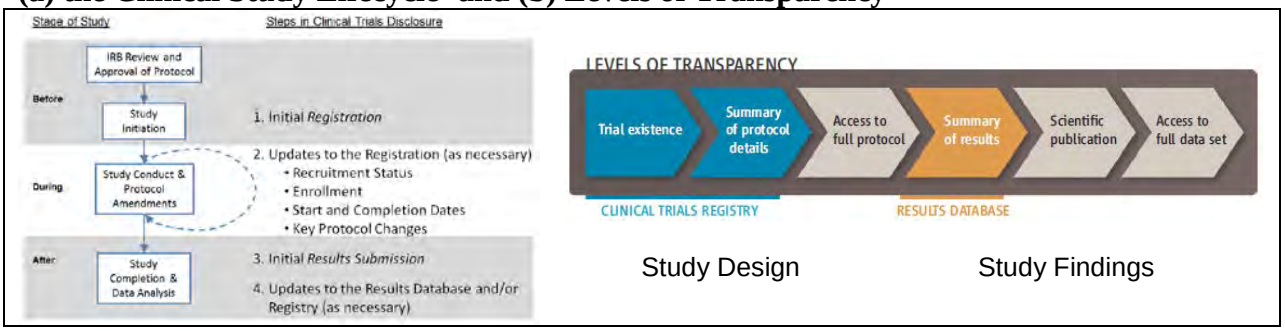
- To accommodate a broad range of clinical research disclosure policies, allowing ClinicalTrials.gov to become a central repository for summary information about clinical studies conducted around the globe.
- To promote the use of ClinicalTrials.gov and increase public understanding of the importance of transparency in the conduct and reporting of clinical research.
- To provide researchers, decision-makers, and other members of the public with structured data for analyses of the clinical research enterprise.
- To characterize and investigate the clinical research enterprise and to conduct iterative, evaluation for implementing procedural and system-wide enhancements to ClinicalTrials.gov.
- To improve and enhance the quality of reporting summary information about study design and results, in general, and to ClinicalTrials.gov, in particular.

3. Project Significance

A. Ethical and Scientific Rationale for Clinical Trial Disclosure

Clinical trial registration and *results submission* refer to the process of submitting and updating summary protocol and results information to a structured, Web-based registry and results database, respectively. Registration occurs at trial initiation and results submission occurs after the trial completes or is terminated. These two processes parallel the life-cycle of clinical trials and form part of the continuum in levels of transparency in clinical research [see Figure 1].

Figure 1: Registration and Results Reporting in Relation to (a) the Clinical Study Lifecycle[5] and (b) Levels of Transparency[6]



The initial need for clinical trial registration was driven by the desire to provide people with serious and life-threatening conditions access to information about ongoing research for potential participation. Over time, however, additional purposes and benefits of trial registration have been identified and realized. A number of high-profile cases, along with documentation of selective or incomplete publication, gave rise to awareness that the medical literature provided a skewed view about the safety or effectiveness of medical interventions.[5] This problem has become widely known in the literature as *publication bias.* Other cases led to the discovery that results described in the published literature were not always consistent with what was planned in the protocol (e.g., *selective reporting bias*) [see Table 2].[7,8] As a consequence, trial registries became a key tool for addressing publication and reporting bias by ensuring that the existence of a trial and its main features were documented publicly before the start date.

Table 2: Selected Examples of Distortion of the Evidence Base[5]

Issue	Description	Examples
Selective publication of studies	Publication limited to studies with favorable results (i.e., studies with unfavorable results not published)	Antidepressants,[9] Paxil (paroxetine) studies in children[10,11]
Selective reporting of outcomes	Publication limited to the most favorable prespecified outcomes; other less-favorable prespecified outcomes not acknowledged or reported	Cyclooxygenase-2 (COX-2) inhibitors[12,13]
Modification of prespecified outcome measures	Publication of outcome measures that differ from those prespecified in the protocol	Vytorin (ezetimibe + simvastatin),[14] Neurontin (gabapentin)[15]

Clinical trial registration and results submission today fulfills a broad range of scientific and ethical functions in the clinical research enterprise [see Table 3].

Table 3: Ethical and Scientific Rationale for Trial Disclosure[5]

Category	Reason
Human subjects protection	• Allows potential participants to find studies • Assists ethical review boards and others to determine appropriateness of studies being reviewed (e.g., harms, benefits, redundancy) • Promotes fulfillment of ethical responsibility to human volunteers—research contributes to medical knowledge
Research integrity	• Facilitates tracking of protocol changes • Enhances transparency of research enterprise
Evidence-based medicine	• Facilitates tracking of studies and outcome measures • Allows more complete identification of relevant studies
Allocation of resources	• Promotes more efficient allocation of resources (e.g., investigators, institutional review boards [IRBs], volunteers, funders)

B. Policy Landscape

In recognition of the ethical and scientific rationale for trial disclosure, policies and laws have been implemented around the world to promote the practice. The three major policies that we discuss are: (1) the ICMJE registration policy that applies the World Health Organization (WHO) standards, (2) U.S. federal law (FDAAA 801), and (3) regulations in the European Union (EU) implemented by the European Medicines Agency (EMA).

ICMJE and WHO

In 2004, the ICMJE, a group of medical journal editors, issued a statement requiring registration of clinical trials before the enrollment of the first participant to document publicly the prespecified study design, and to allow for the tracking of any changes to the protocol.[16] Implementation of the policy in 2005 led to a dramatic increase in the number of studies registered in ClinicalTrials.gov, from approximately 30 new records per week to 250 new records per week. This obligation to register is now part of the ICMJE Uniform Requirements for Manuscripts (URM), which is followed by over 1,000 journals from around the world.[17] The WHO has been involved in trial registration since 2004.[18] It developed a standard set of minimal registration items called the Trial Registration Data Set (TRDS)[19] and operates the International Clinical Trials Registry Platform Search Portal.[20] The ICMJE adopted the WHO TRDS as its minimum requirements for registration.

One goal of the ICMJE policy was to provide access to the total number of relevant trials for a given topic, whether published or unpublished (i.e., the "denominator"). Since the ICMJE policy was implemented, the landscape for trial registration has evolved. For example, the number of trial registries that are designated as "primary registries" in the WHO Registry Network, and thus accepted by the ICMJE, has increased from 4 in 2005 to 14 in 2013. The growth of trial registries has created challenges in study disclosure and identifying the total number of relevant trials. For

example, it is often difficult to identify single studies registered in multiple registries (i.e., "duplicate registration") [see Figure 2].[21] Duplicate records distort trial registry search results by returning more hits than actual trials. The ability to count the number of distinct open and completed clinical studies is critical to assessing the evidence base.

Figure 2: Challenges in Identifying Duplicate Records, Even Within ClinicalTrials.gov: (1) Pair of Records with Different Descriptions that Actually Represent the Same Trial (Top) and (2) Pair of Records with Identical Descriptions that Actually Represent Two Different Trials (Bottom)

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

Trial Description	Trial Registry Unique Identifier	
	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.

FDAAA 801

FDAAA 801 expands the ClinicalTrials.gov registry beyond the scope established in the previous federal law (FDAMA 113) by including more information about different types of trials (e.g., medical device trials) and adding a results database.[3] It requires the study sponsor or a designated principal investigator who controls the study data (called the "Responsible Party" in the law) to submit information to ClinicalTrials.gov for certain clinical trials of FDA-regulated drugs, biologics, and devices (called "Applicable Clinical Trials" in the law). Other provisions specify what clinical trial information is required to be submitted, when it is to be posted publicly, and the timeline for updating information. Enforcement provisions for noncompliance include civil monetary penalties and withholding of federal grant funding. The registration requirements of FDAAA 801 and the ICMJE policy are similar and Table 4 provides a comparison of their key provisions.

Table 4: Comparison of Key Registration Requirements from Two Disclosure Policies

	ICMJE[2]	FDAAA 801[3]
Which Studies?	Interventional Studies • All Intervention Types • All Phases	Interventional Studies • Drugs, Biologics, Devices • Not Phase 1/Feasibility
Who?	Author(s)	Sponsor or designated Principal Investigator who controls the data
When to Register?	Prior to enrollment of first participant	Within 21 days of enrollment of first participant
What to Register?	The WHO Trial Registration Data Set (TRDS)	TRDS plus other mandatory data elements
Where to Register?	ClinicalTrials.gov or a WHO Primary Registry	ClinicalTrials.gov
When to Submit Results?	Not Applicable • Policy restricted to registration	Within 12 months of final data collection for the primary outcome for certain trials of approved products
Penalty?	May not be eligible for journal publication	May involve civil monetary penalties and withholding of federal grant funding

FDAAA 801 also extends ClinicalTrials.gov by adding a "basic" results database. In general, Responsible Parties for certain clinical trials of FDA-approved drugs, biologics, or devices are required to submit summary data not later than one year after the date that the last participant in a clinical study was examined or received an intervention and that data for the primary outcome measure were collected (called "Completion Date" in the law and "Primary Completion Date" in ClinicalTrials.gov). Submission of information about all serious adverse events and other (non-serious) adverse events to the results database became required in September 2009. Summary results are displayed at ClinicalTrials.gov in a standard, tabular format without discussions or conclusions and consist of four scientific modules [see Figure 3] and other administrative information (e.g., results point of contact, description of any sponsor-imposed restrictions on results disclosure). In addition, FDAAA 801 calls for the expansion of the "basic" results database through rulemaking "to provide more complete results information" and requires the consideration of certain issues, including (1) results reporting for trials of drugs and devices not approved by the FDA, (2) non-technical and technical narrative summaries, and (3) the submission of full study protocols.[22]

The breadth of the scope for results submission to a public database under FDAAA 801 is unprecedented. When FDAAA 801 was enacted, the results reporting landscape included the GSK Clinical Study Register with result summaries (http://www.gsk-clinicalstudyregister.com/result_compounds.jsp), which was mandated by the 2004 settlement between the New York State Attorney General's Office and GlaxoSmithKline; other voluntary industry databases (e.g., the now-defunct ClinicalStudyResults.org Web site which was supported by the Pharmaceutical Research and Manufacturers of America (PhRMA)[23]) and the Maine state law passed in 2005 requiring results reporting, but repealed in 2011.

Figure 3: Summary Description of the ClinicalTrials.gov Results Database Modules[24]

Basic Results Module	Summary Description	Overview of Minimum Required Information
Participant flow	Description of the No. of research participants starting and completing the study, including exclusions and dropouts, for each arm or comparison group (frequently reported as a CONSORT diagram in a journal article)	No. of participants who entered study; and No. of participants who completed study
Baseline characteristics	Demographic and baseline data for the study population and each arm or comparison group (frequently reported as "Table 1" in a journal article)	Overall No. of participants analyzed; age; gender; for all other measures reported: name (and description); unit of measurement; and summary data, total and by arm
Outcome measures and statistical analyses	Table of outcome measure values for each arm/comparison group, including appropriate statistical analyses	For all prespecified primary and secondary outcome measures: name and description; unit of measurement; time frame; analysis population; and summary data, total and by arm
Adverse events (optional prior to September 2009)	Number and frequency of all serious adverse events and other adverse events exceeding a specified frequency threshold in each arm/group, grouped by organ system	For all adverse events reported: adverse event term; organ system; type of assessment (spontaneous vs systematic); and No. of participants affected, No. of participants at risk, and total No. affected, by arm

EMA

Since the passage of FDAAA 801, the international landscape for results reporting has continued to evolve. In early 2011, the EMA launched the EU Clinical Trials Register (EU CTR at https://www.clinicaltrialsregister.eu/ctr-search/), which provides public access to registration information submitted to the European Union Drug Regulating Authorities Clinical Trials database (EudraCT). As of March 2013, the public EU CTR described nearly 20,000 drug clinical trials. Subsequent EU regulations require that results-related information for certain EMA-regulated clinical trials be made available publicly, regardless of drug marketing approval status. To meet this results-reporting requirement, EMA has been developing its own results database, modeled on the ClinicalTrials.gov results database [See *Key Accomplishment 2*]. When the EU results database becomes operational, it is intended to be largely compatible to the ClinicalTrials.gov results database, thereby forming a *de facto* results reporting standard. The European Commission Guideline states that "[t]he content of the [EU results database] data fields [will be] kept identical with the U.S.-database 'clinicaltrials.gov,' with limited exceptions… (p. C 302/8)."[25]

4. Methods and Procedures

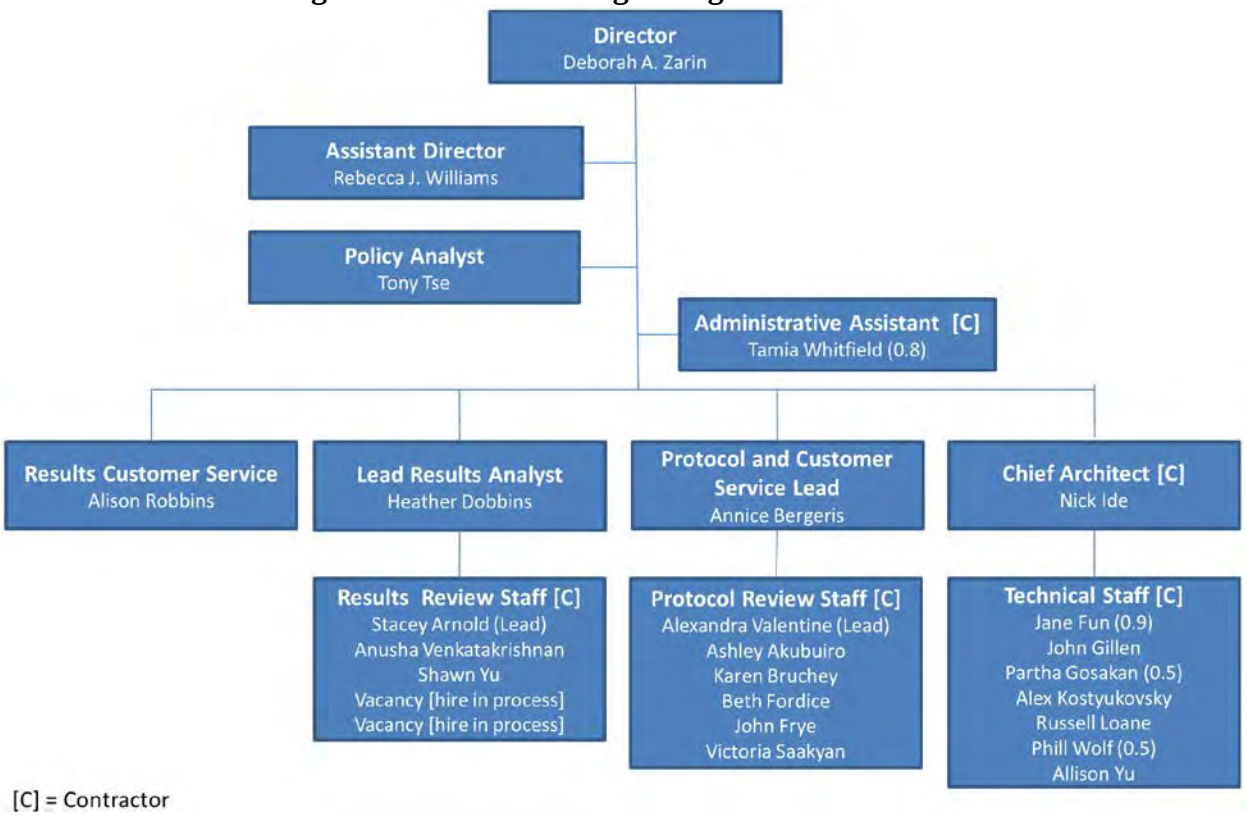
We have taken a multifaceted approach to meet the program's objectives. In this report, we describe new methods and provide updates on procedures reported in 2005.[4] In general, these methods and procedures are distributed into the following areas, although the estimated percentage of effort varies by person and time period:

- **Daily Operations for Managing Information Flow** (50%) – reviewing all registry and results submissions and supporting system users and other stakeholders.
- **Technical Development and Maintenance—Web Site and PRS** (25%) – enhancing the registry and creating the results database; updating and maintaining the PRS; maintaining the Essie backend tool and other tools for generating reports; and supporting Web site operations.

- **Outreach and Training** (10%) – creating and giving presentations; hosting workshops, webinars, and providing training on submitting data; updating both the content and appearance of the public Web site; and developing online and print materials.
- **Science Policy and Regulatory Activities** (10%) – drafting the Notice of Proposed Rulemaking (NPRM); participating in Trans-NIH and other working groups; assisting other initiatives (e.g., NIH Comparative Effectiveness Research Coordinating Council (CER-CC) and the Agency for Healthcare Research & Quality's (AHRQ) Registry of Patient Registries (RoPR)); and maintaining awareness of relevant policy issues.
- **Research** (5%) – conducting analyses; communicating research findings through presentations and publications; and undertaking other scientific activities (e.g., serving on committees; journal peer review).

To carry out our Project Objectives, ClinicalTrials.gov currently consists of 26 staff positions. These include the Director, six project area specialists, and 17 staff members and positions for conducting QA review and programming activities [see Figure 4].

Figure 4: ClinicalTrials.gov Organizational Chart



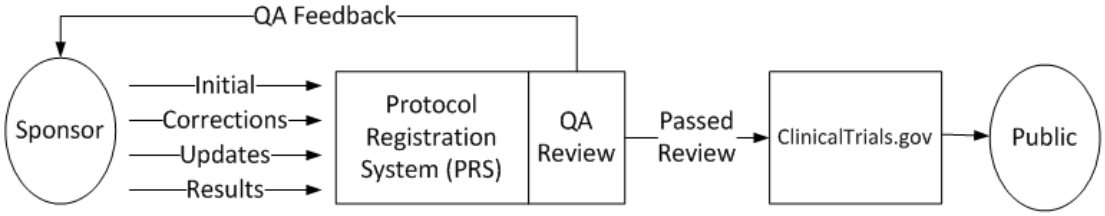
A. Daily Operations for Managing Information Flow

Daily operations at ClinicalTrials.gov generally involve interactions with two key systems [see Figure 5]:

1. **PRS**: A Web-based data entry system designed for (1) data providers to submit, edit, and update information about clinical studies and (2) ClinicalTrials.gov staff members to review submissions and conduct other administrative tasks (e.g., create new accounts).

2. **ClinicalTrials.gov**: The Web site designed for members of the public; includes basic and advanced search tools for finding clinical studies and provides resources on various topics such as help for using the site, information on registration and results submission processes, and how to download content for analysis.

Figure 5 : Data Flow from Sponsor at PRS to the Public User at ClinicalTrials.gov



Account Management

The PRS is organized into accounts. All investigators from a company, university, or medical center are encouraged to use a single organizational PRS account to manage their records. Persons using a PRS account are assigned to one of two roles or access levels: Administrator or User. Administrators manage accounts, such as creating login IDs for new Users, and have access to view, edit, and change the status for all study records in the organization's account. In contrast, Users only have access to study records that they create or for which they are granted access. Currently, the PRS contains over 12,000 accounts. In 2012, we processed an average of 460 new account requests per month, of which only some are granted; most requests are submitted by individuals from organizations with existing PRS accounts.

Record Management

Information entered into the PRS by a data provider is subject to a two-step quality control process prior to being posted on the public ClinicalTrials.gov Web site:

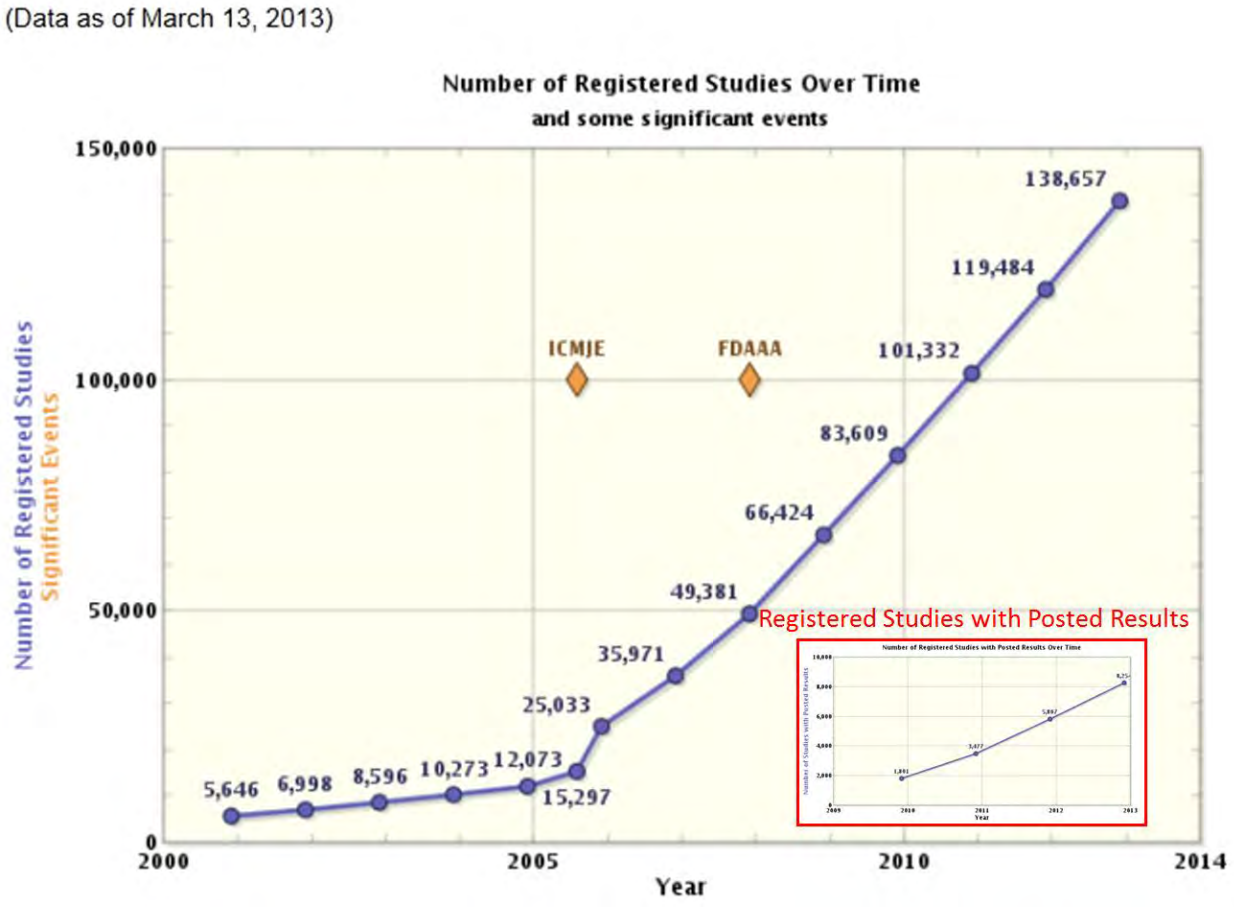
1. **Automated Validation.** A record must first pass automated validation rules before it can be submitted to ClinicalTrials.gov for processing. These rules produce messages that are categorized into three levels of severity: **ERROR**, **WARNING**, or **NOTE**. Error messages must be resolved before a record can be submitted. All other messages raise issues to be evaluated for possible correction, but do not prohibit record submission.

2. **Manual Quality Assurance Review.** The record must then pass manual review based on specified criteria.[26,27] Overall, the criteria focus on apparent validity, meaningful entries,

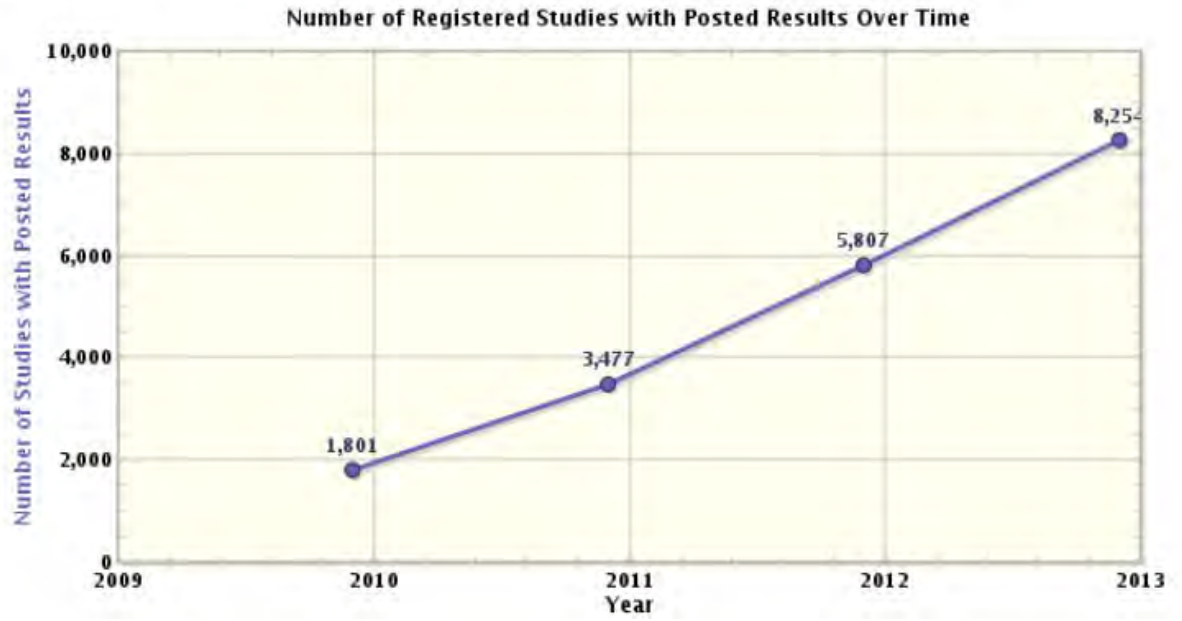
logic and internal consistency, and formatting. All substantive issues identified by ClinicalTrials.gov staff must be addressed before the record can be posted on the ClinicalTrials.gov Web site. All issues are documented in the record for the data provider as Review Comments and returned for correction and resubmission.

Registration records (summary protocol information) are generally processed within three days of submission. In 2012, approximately 400 new records and 2,500 modified records were reviewed and posted weekly. The staff responded to 1,500 general and protocol-related inquiries monthly. Records with results are generally processed within 30 days of receipt. In 2012, 265 records with results were reviewed weekly and approximately 125 were posted weekly. In general, approximately 36% of results submission could be posted on the first submission. The staff responded to nearly 300 results-related inquires monthly and held about 15 teleconferences per month to provide technical assistance to submitters on complex reporting issues. The results quality review process is described in more detail later in this report as part of Key Accomplishment 3. Over time, submission rates have grown rapidly [see Figure 6].

Figure 6: (a) Number of Registered Studies over Time and (b) Number of Registered Studies with Posted Results over Time



(Data as of March 13, 2013)



B. Technical Development and Maintenance—Web Site and PRS

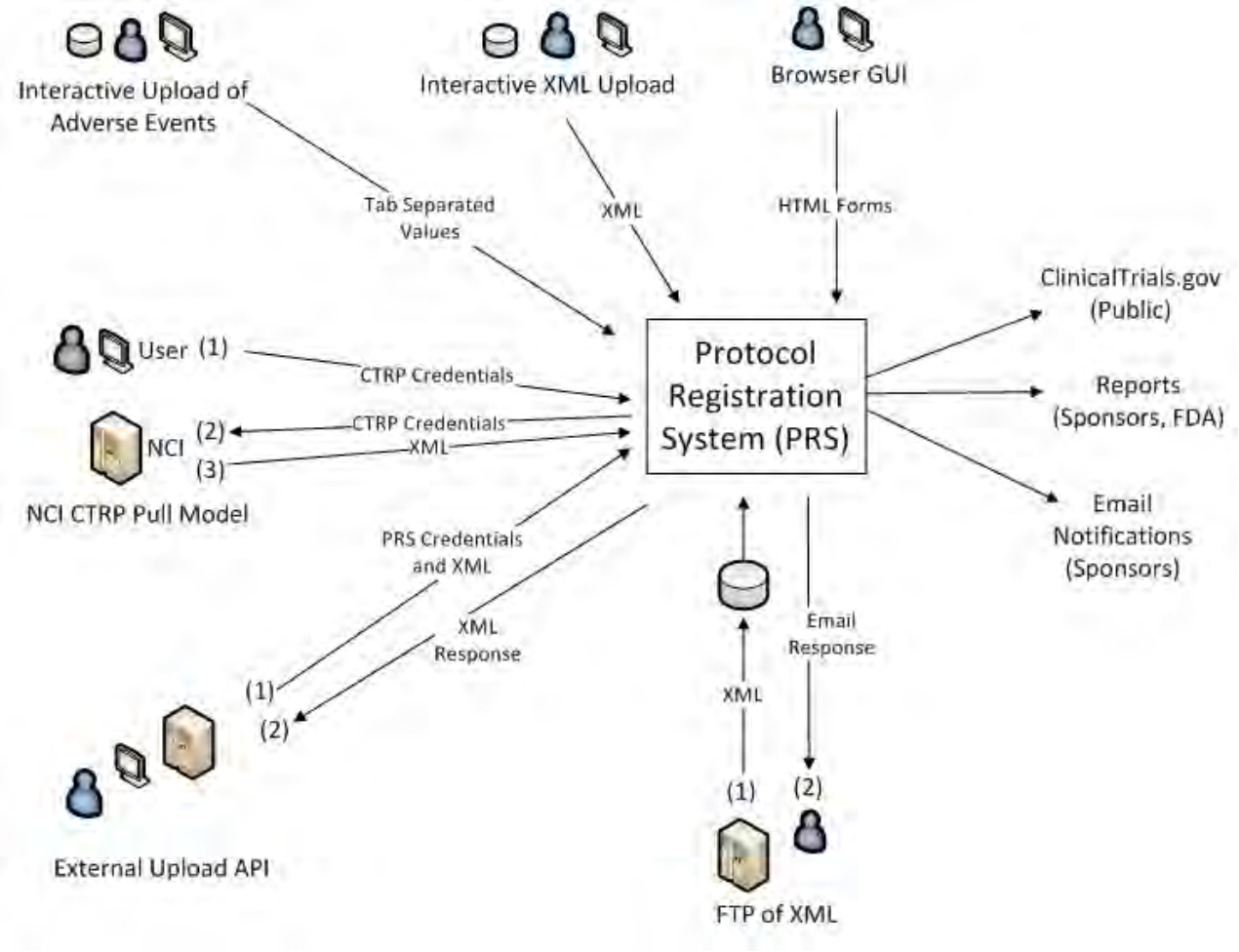
Since the launch of the ClinicalTrials.gov Web site in 2000[28] and the PRS in 2003[29], each component has constantly undergone assessment and system development to enhance usability as well as to expand functionality. For instance, to accommodate a growing number of visitors and new audiences (e.g., journal editors), we have updated the public Web site multiple times, including two major redesigns in 2007[30] and 2012[31] [see Figure 7].

Figure 7: Evolution of the ClinicalTrials.gov Home Page: 2000, 2007, and 2012

The three data submission mechanisms in 2005 were (1) interactive Web-based HTML forms via a Web browser GUI, (2) interactive XML upload, and (3) FTP of an XML file. Over time, we have added options to support data transfer from other clinical trial information systems. In 2011, the NCI Clinical Trial Reporting Program (CTRP) "pull model" was launched to pull information from the NCI CTRP database directly into the PRS. In 2012, we developed the external upload API 2012 as a general solution for pulling information from other databases,

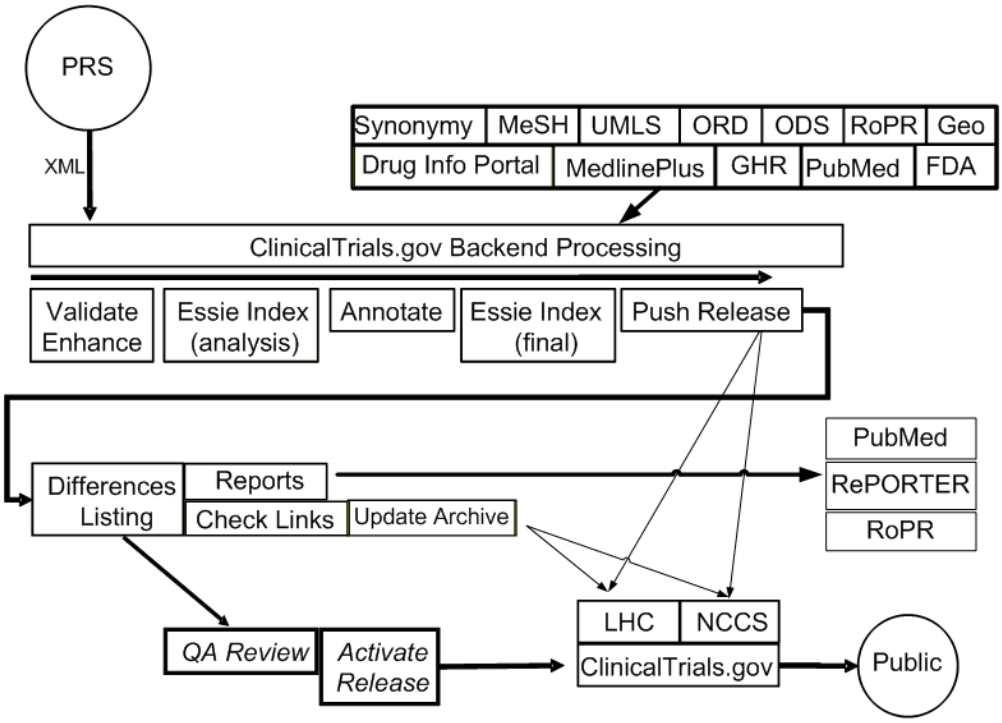
including the NIH Intramural Research Biomedical Translational Research Information System (BTRIS). We also added a way to upload adverse event information using a tab-separated values format (e.g., Excel spreadsheet file) [see Figure 8].

Figure 8: Interaction Use Cases for the PRS



After a study record is submitted by any of the mechanisms (e.g., GUI, XML, API) and passes QA review, it undergoes backend processing. The system uses a variety of NIH- and NLM-developed informatics tools and services, which have expanded and been refined over time. For example, the Unified Medical Language System (UMLS)® Metathesaurus® is used to identify synonyms for conditions and interventions to support synonym expansion during search. The UMLS is also used to map terms contained in submitted records to related MeSH terms for linking to other resources, such as MedlinePlus®. NCT Numbers indexed by MEDLINE® are used to automatically link ClinicalTrials.gov records to PubMed records of peer-reviewed journal articles about those trials. Drug names are used to match records to records in the Drug Information Portal. After processing, information is output to several different places, including the Archive, a hot backup site (offsite), and ultimately, the ClinicalTrials.gov public Web site [see Figure 9].

Figure 9: ClinicalTrials.gov Public Web Site Data Flow



Key changes to the Web site and PRS since 2005 are summarized in Table 5.

Table 5: Key Technical Milestones at ClinicalTrials.gov by Category, 2005-2012

Category	Description of Technical Milestone
Requirements/ Features	**FDAAA 801** • 2010: Designed and implemented software to gather information about records within the PRS and send out email messages advising data providers of possible problems with their records and potential FDAAA 801 issues (i.e., missing FDAAA-required data elements, appears to be overdue for results) • 2009 o Implemented a set of data elements in the PRS to allow sponsors to submit certifications and requests for extension, as specified by FDAAA 801 o Implemented required data elements in the Adverse Events module, as specified by FDAAA 801 • 2008 o Conducted extensive analyses, design, and development work to prototype the ClinicalTrials.gov results database o Designed and launched the ClinicalTrials.gov "basic" results database[32] as required by federal law, which included the data entry[24] and QA review screens in the PRS as well as the record display and search features on the public site[33] • 2007: Updated the ClinicalTrials.gov registry, as specified by FDAAA 801[34] **Maine State Regulation** • 2007: Added several data elements to accommodate the Maine state registration and results reporting regulation (repealed in 2011)

	ICMJE Policy
	• 2005
	  o Expanded the scope of ClinicalTrials.gov to support international studies and added/modified data elements to support the ICMJE/WHO Trial Registration Data Set[35]
	  o Added hardware resources and adapted software to respond to the dramatic increase in new registrations in response to the ICMJE registration policy
	BPCA
	• 2006: Added expanded access data elements, as specified in the Best Pharmaceuticals for Children Act of 2002 (BPCA)

Infrastructure	• 2012
	  o Deployed API for XML transfer to PRS; Updated production database infrastructure: new hardware and RAID 10
	  o Provided support for IPV6; Implemented performance enhancements for Archive site
	  o Added mechanism for linking to FDA documents (with FDA)
	• 2011: Underwent security audit and penetration testing
	• 2010: Began providing a regular data feed to the NIH Research Portfolio Online Reporting Tools (RePORTER) that allows pages on their Website to link to specific ClinicalTrials.gov records (in collaboration with NIH)
	• 2008: Updated the system infrastructure to 64-bit Linux
	• 2007: Implemented software to (1) locate NCT Numbers indexed in MEDLINE records (cited in journal publications) and (2) add links to the appropriate ClinicalTrials.gov records automatically
	• 2006
	  o Migrated the software development platform and production configuration from Sun/Solaris to x86/Linux, resulting in increased performance and reduced hardware/licensing costs
	  o Implemented a compartmentalized network, a new firewall, and a load bearing device to enhance security
	  o Developed a new version of Essie, the ClinicalTrials.gov search system[36] (presented at the September 2006 BoSC meeting)

PRS Functionality	• 2012
	  o Configured ClinicalTrials.gov to interact with the NIH Biomedical Translational Research Information System (BTRIS) (in collaboration with the NIH Clinical Center)
	  o Implemented upload of adverse events to the results database using a spreadsheet format
	• 2011
	  o Designed and implemented an interface within the PRS that allows users to pull data from the database used by NCI Clinical Trials Reporting Program (CTRP) (with NCI)
	  o Designed the interface linking the PRS to the RoPR data entry system (in collaboration with AHRQ) (see Table 10)
	  o Added a reporting interface to the backend of the PRS to assist in the management of the database
	  o Developed and implemented greater structure and more validation rules for the Responsible Party data element and sub-elements
	  o Implemented multiple user access to a study record
	• 2010: Developed and deployed the “results wizard mode” in the PRS, an online data entry usability enhancement for submitting results information
	• 2009
	  o Updated the PRS to allow QA staff to embed review comments in the record itself, rather than sending comments by email and PDF

	○ Added the ID Type sub-element to the implementation of the Secondary IDs data element, which allows ClinicalTrials.gov to identify legitimate NIH grant numbers and provide linkages to the NIH RePORTER database
ClinicalTrials.gov Public Web site	• 2012 ○ Implemented second ClinicalTrials.gov public Web site redesign[31] ○ Implemented the ClinicalTrials.gov components of the Registry of Patient Registries (RoPR) (in collaboration with AHRQ) (see Table 10) • 2010: Enhanced the public site with an option to include summary results for download in XML • 2007 ○ Implemented first ClinicalTrials.gov public Web site redesign: e.g., introduced the "Tabular View" for study records, Advanced Search fields, "Display Options" in the List Results page, and search "Results by Map"[30] ○ Incorporated design-specific data elements for the registration of observational studies[37] • 2006: Developed and deployed the ClinicalTrials.gov Archive, which provides access to all previously posted versions of study records

The key milestones summarized in Table 5 include three especially significant system development projects, which are highlighted and expanded upon below.

1. Key Accomplishment 1: Expanding the ClinicalTrials.gov Registry under FDAAA 801

Although ClinicalTrials.gov was a well-established trial registry at the time that FDAAA 801 was enacted, the law mandated new registration requirements to be implemented *within 90 days*. The majority of the required data elements explicitly enumerated by FDAAA 801 either overlapped with those already required under FDAMA 113 or existed as optional data elements. However, several new FDAAA 801-specific data elements were added (e.g., Responsible Party) and the PRS was substantially changed to implement a delayed posting mechanism for certain trials of devices. FDAAA 801 requires registration information to be submitted within 21 days of participant enrollment for trials of FDA-regulated drugs, biologics and medical devices. However, FDAAA 801 also requires that the posting of information on the ClinicalTrials.gov public Web site be delayed for trials that include devices that have not been cleared or approved by the FDA (i.e., a "lock box" for registrations of trials of unapproved devices). Information about such trials may only be posted after clearance or approval of such devices. Thus, we created a mechanism to delay the posting of registration information for such trials.

2. Key Accomplishment 2: Developing a *De Novo* "Basic" Results Database

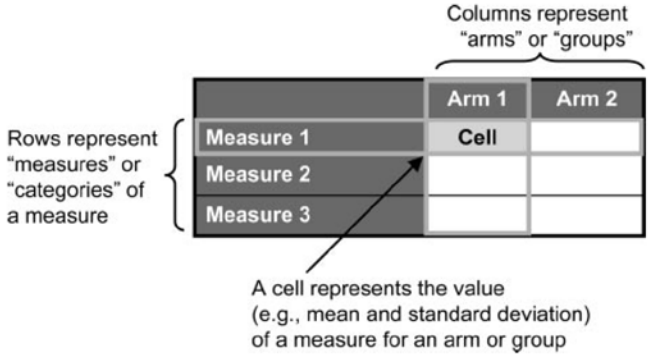
FDAAA 801 mandated that the mechanism for submitting, displaying, and searching summary results be implemented in ClinicalTrials.gov within *one year* of enactment. In contrast to expanding the registry, the "basic" results database had not existed at the time of enactment and there were no similar databases in the public domain. By building upon the existing registry infrastructure, we successfully met the one year deadline for developing a structured results database.

The law specified that specific "basic" results elements are to be presented in a tabular format with little to no narrative text. In evaluating these requirements, we first identified key objectives and challenges [See Table 6]. For example, the results database would need to provide flexibility for accommodating a wide range of study designs, data types and measures, and other study-specific results information, while also maintaining uniformity across studies in the public display. Data providers would need to construct tables specific to their study design by defining rows (e.g., study-specific measures or categories) and columns (e.g., arms or comparison groups) before entering actual values [See Figure 10].

Table 6: Summary of High-Level Requirements for the ClinicalTrials.gov Results Database[38]

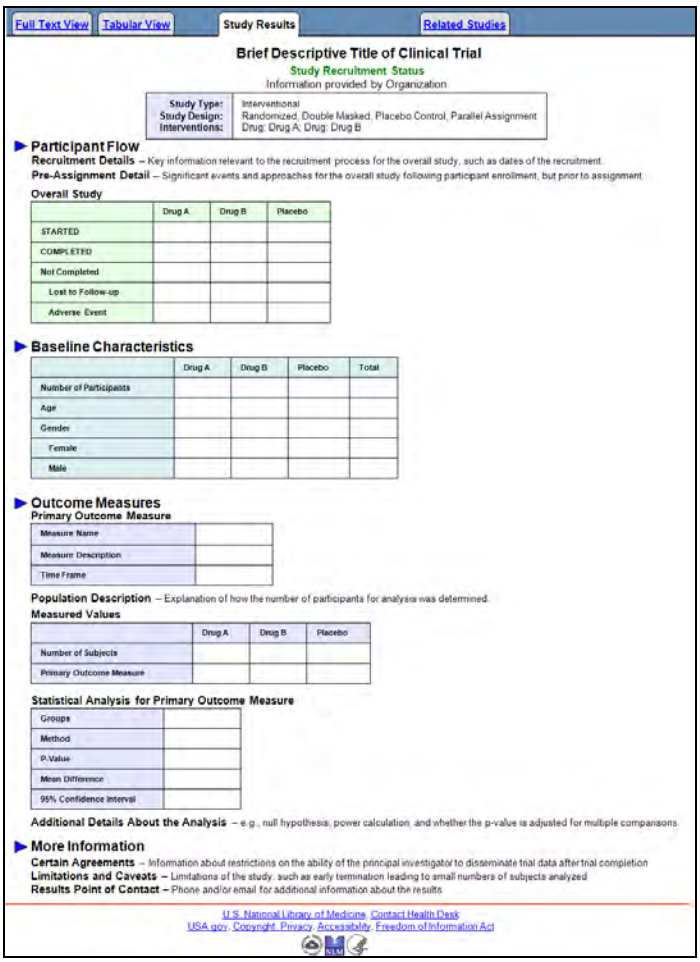
Key Objectives	Key Challenges
▪ Streamlined data submission process o Develop tables similar to those used in journal articles o Use controlled vocabularies and data standards, as possible o Allow for interactive data entry and batch upload of data files ▪ Report accurate and objective information o Provide clear displays of results data that can be understood without significant narrative o Provide a consistent layout and format to facilitate comparisons across studies o Link to authoritative sources for more information pertaining to study topic or interpretation	▪ 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

Figure 10: General Structure of a Results Data Table



The structure of the results display, which tracks the legally specified requirements, includes four scientific modules (Participant Flow, Baseline Characteristics, Outcome Measures and Statistical Analyses, and Adverse Events) and administrative data elements [See Figure 11]. Each module contains required data elements that were determined to be authorized by FDAAA 801 and optional data elements intended to promote understanding of the study design and analysis. The structure of the modules was informed by current evidence and best practices in the reporting of biomedical information and designed to accommodate a diverse range of study designs, from simple to complex.

Figure 11: Schematic Illustrating the Tabular and Modular Nature of the Results Display
(NOTE: Details have been omitted for simplicity and the Adverse Events Module is not shown)

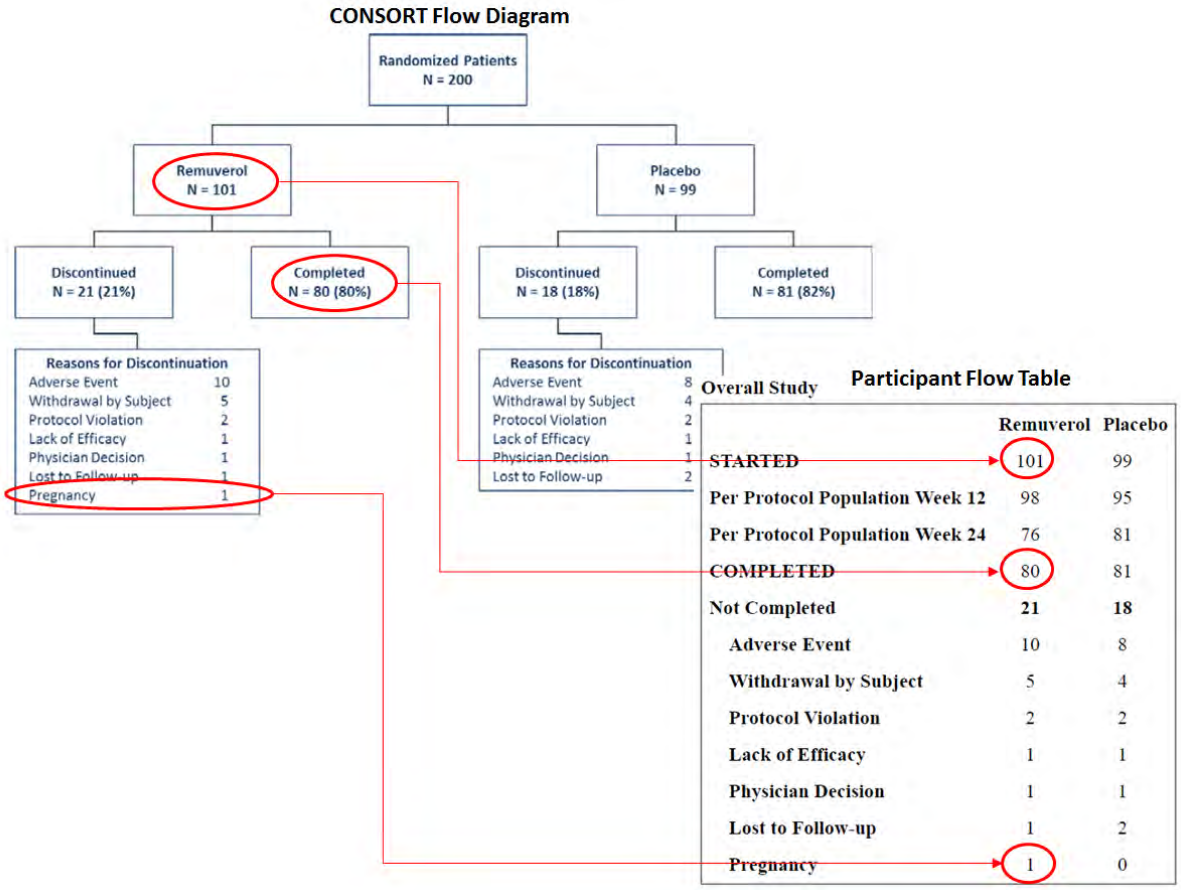


Overall, the design of the results database was informed by critical reviews of existing pharmaceutical industry results databases, an NLM-hosted workshop on determining the feasibility of a results database in May 2007, and an iterative design process involving expert and stakeholder input. For instance, we posted a set of mockups and interactive prototypes to elicit stakeholder comments in 2008.[39] The first public government-operated clinical trial results database in the world was launched in September 2008.[32] A brief description of each module and some of the key design aspects are described in each of the following sections.

Participant Flow Module

The purpose of the Participant Flow module is to depict the initial allocation of participants to study arms to track their progress through each stage of a study, from study start to completion. The tables in this module are modeled on the Consolidated Standards of Reporting Trials (or CONSORT) flow diagram (typically "Figure 1" in a journal article)[40] [see Figure 12]. The CONSORT flow diagram provides a mechanism for understanding the study design and tracking the number of participants who did not complete the study.

Figure 12: Depiction of Equivalent Information Displayed as a CONSORT Flow Diagram and as a ClinicalTrials.gov Participant Flow Module Table



In ClinicalTrials.gov, data providers are required to provide the number of participants who started and completed a study by "arm." The number of participants who did not complete the study in each arm is calculated using the entered values. Optional data elements allow for the specification of different Periods or stages of the study (e.g., washout, follow-up), Milestones within a period (e.g., participants who received intervention), and Reasons for Non-completion from a list of standard terms adapted from CDISC[41] (e.g., Lost to Follow-up, Withdrawal by Subject). Optional free text fields may be used to provide information about the recruitment setting (Recruitment Details) and any significant events that may have occurred prior to randomization (Pre-Assignment Details). The required and optional data elements for the Participant Flow Module are shown in the template in Figure 13. Templates for all of the modules can be viewed at http://clinicaltrials.gov/ct2/manage-recs/how-report#ScientificInformation.

Figure 13: Participant Flow Template Depicting Required* and Optional Data Elements.

More details available in the "Basic Results" Data Element Definitions. Sept 11, 2012

Participant Flow Template ***ClinicalTrials.gov***

Recruitment Details	
Pre-assignment Details	

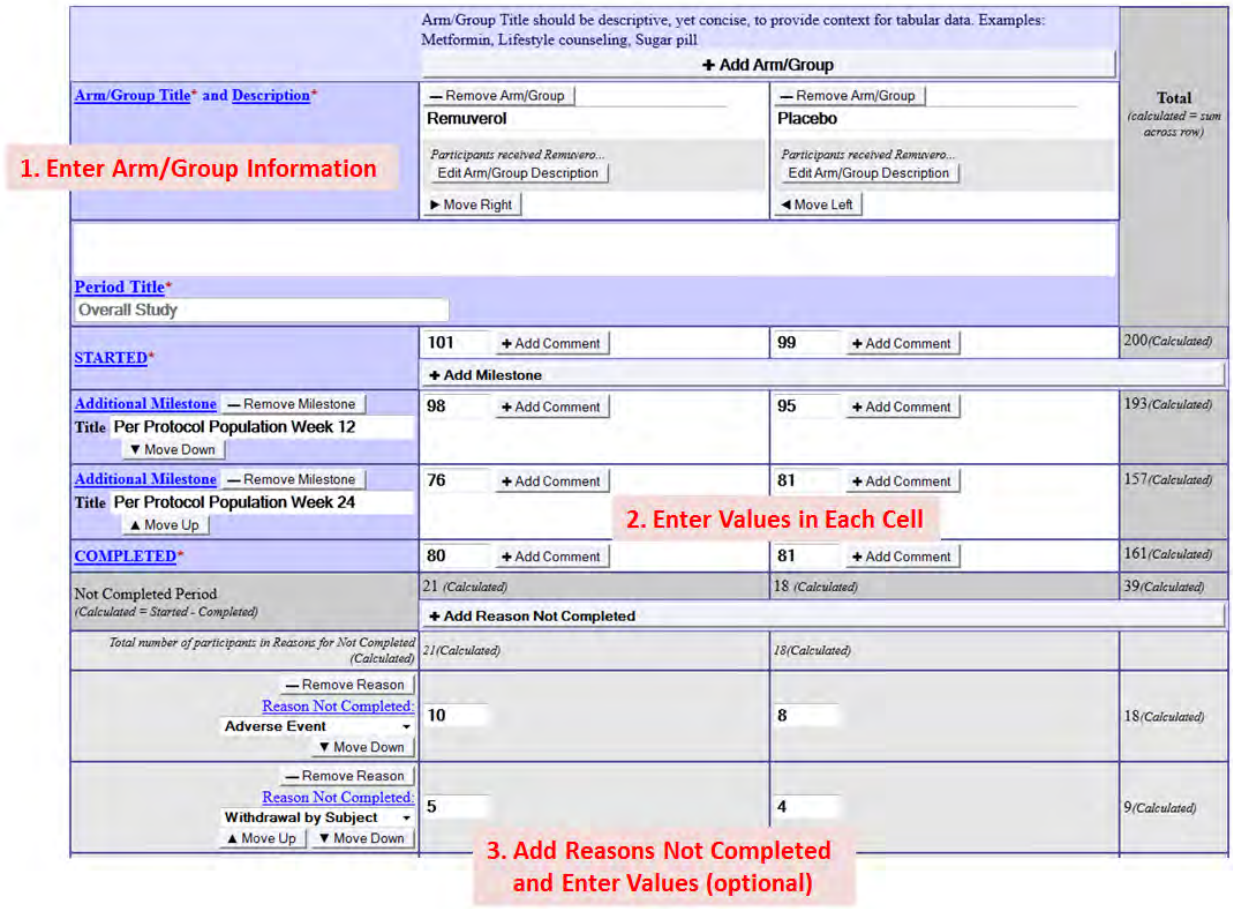
Period ① Title: Overall Study

Arm/Group Title *		*	*	*
Arm/Group Description ②				
		Number of Participants *	Number of Participants *	Number of Participants *
STARTED *		*	*	*
Milestone Title ③	[*]	[*]	[*]	[*]
Milestone Title ③	[*]	[*]	[*]	[*]
Milestone Title ③	[*]	[*]	[*]	[*]
COMPLETED *		*	*	*
Reason Not Completed				
Adverse Event		[*]	[*]	[*]
Death		[*]	[*]	[*]
Lack of Efficacy		[*]	[*]	[*]
Lost to Follow-up		[*]	[*]	[*]
Physician Decision		[*]	[*]	[*]
Pregnancy		[*]	[*]	[*]
Protocol Violation		[*]	[*]	[*]
Withdrawal by Subject		[*]	[*]	[*]
Other Reason ③	[*]	[*]	[*]	[*]
Other Reason ③	[*]	[*]	[*]	[*]
Other Reason ③	[*]	[*]	[*]	[*]

* Required by ClinicalTrials.gov
[*] Conditionally required by ClinicalTrials.gov
① Complete a Period table for each Period you wish to report. Provide a descriptive Title for each reported Period.
② Arm/Group Description describes details about the interventions administered (e.g., dosage, dosage form, frequency of administration) or groups evaluated.
③ [Optional] Add as many Milestone Title or Other Reason Not Completed rows as needed. A descriptive title for each row is required.

The PRS interactive data entry mode for the Participant Flow module builds on the information already provided as part of the protocol registration information in the Arms and Interventions data elements by allowing the user to copy that information directly into the Participant Flow module (and edit as needed). Figure 14 provides a view of the online data entry form for Participant Flow. Each of the results modules uses similar data entry templates and forms.

Figure 14: Screenshot of the Participant Flow Data Form for Interactive Data Entry in the PRS



Baseline Characteristics Module

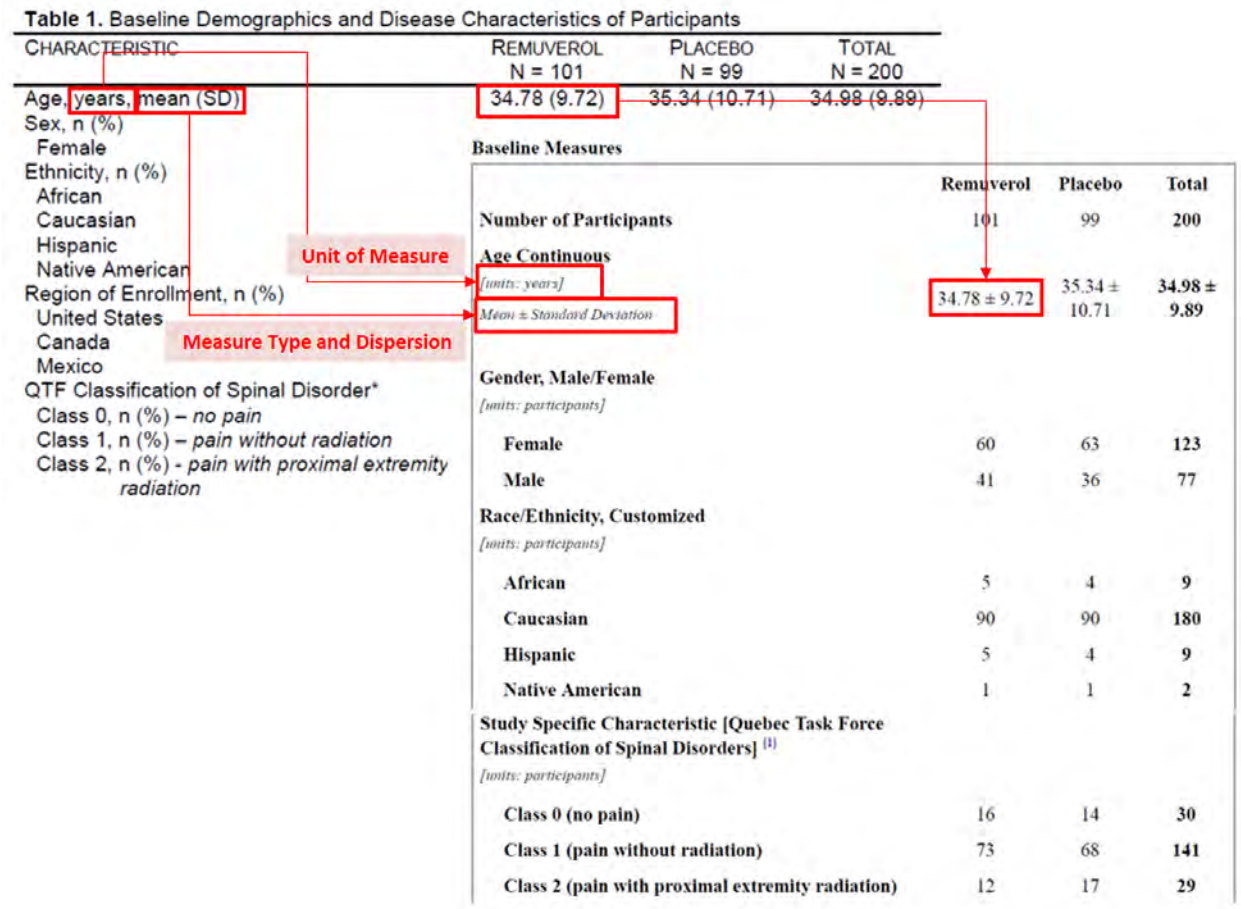
The Baseline Characteristics module is a table of demographic and baseline characteristics for all participants in the study sample and within each arm or comparison group (typically "Table 1" in journal articles). It displays information about participants in each arm and provides a way to assess the degree of bias across groups and the external relevance of the study findings.

To determine the minimum requirements for this module, we reviewed 100 published articles of randomized controlled trials to identify variables that were uniformly reported. The number of participants assessed at baseline by age and gender were the only common elements reported consistently across these articles. Thus, age and gender are the only two baseline characteristics required by ClinicalTrials.gov. After reviewing reporting standards (e.g., CONSORT[40]) and obtaining feedback from stakeholders, we provided structured templates to facilitate and

encourage reporting of other common and useful baseline characteristics: Race and Ethnicity (using the standard NIH and U.S. Office of Management and Budget Classification Categories) and Region of Enrollment. Location information, which is submitted as protocol information, is used to pre-populate the Region of Enrollment measure and can be edited as appropriate for the study. In addition, any number of "study-specific" baseline measures such as important clinical characteristics may be added by the data provider.

In addition to specific baseline measures, we determined what information would be necessary to understand the data reported for each described measure. Each measure is characterized by Units of Measure (e.g., "participants" or "mm Hg" for blood pressure) and the data are described as either "categorical" (discrete) or "continuous." CONSORT and other reporting standards indicate that all continuous measures should be accompanied by a measure of the variability of the data (e.g., a "standard deviation" would accompany a "mean"). Therefore, for each Baseline Measure that is a continuous variable, the Measure Type and an appropriate Measure of Dispersion must be provided [see Figure 15]. After consulting with experts, we developed a standardized list of Measure Types that addressed both types of data.

Figure 15: Depiction of Equivalent Information Displayed as a Table in a Journal Article and as a ClinicalTrials.gov Baseline Characteristics Module Table



Outcome Measures and Statistical Analyses Module

The prespecified Primary and Secondary Outcomes of a study, which represent the key findings in the study, are summarized by arm or comparison group in the Outcome Measures module. The concepts related to measures described in the Baseline Characteristics module also apply to this module. A complete Outcome Measure consists of a description of the measure and details about the data including Units of Measure, Measure Type, and Measure of Dispersion or Precision. Each Outcome Measure also includes a data element for describing the Time Frame of assessment. After outcome measure data are summarized in a table, information about any statistical analyses derived from the summary data (e.g., t-Test) can be described as part of an associated statistical analysis form. This form is designed to capture specific, objective features of the statistical analysis: the arms compared by the analysis, the hypothesis being tested, power calculation, and the specific tests. The information may be entered by the data provider with a combination of check boxes, pull-down menus and free text fields. Figure 16 compares outcome information presented in a journal article and displayed at ClinicalTrials.gov.

Figure 16: Depiction of Equivalent Information Displayed as a Table in a Journal Article and as a ClinicalTrials.gov Outcome Measure Module Table

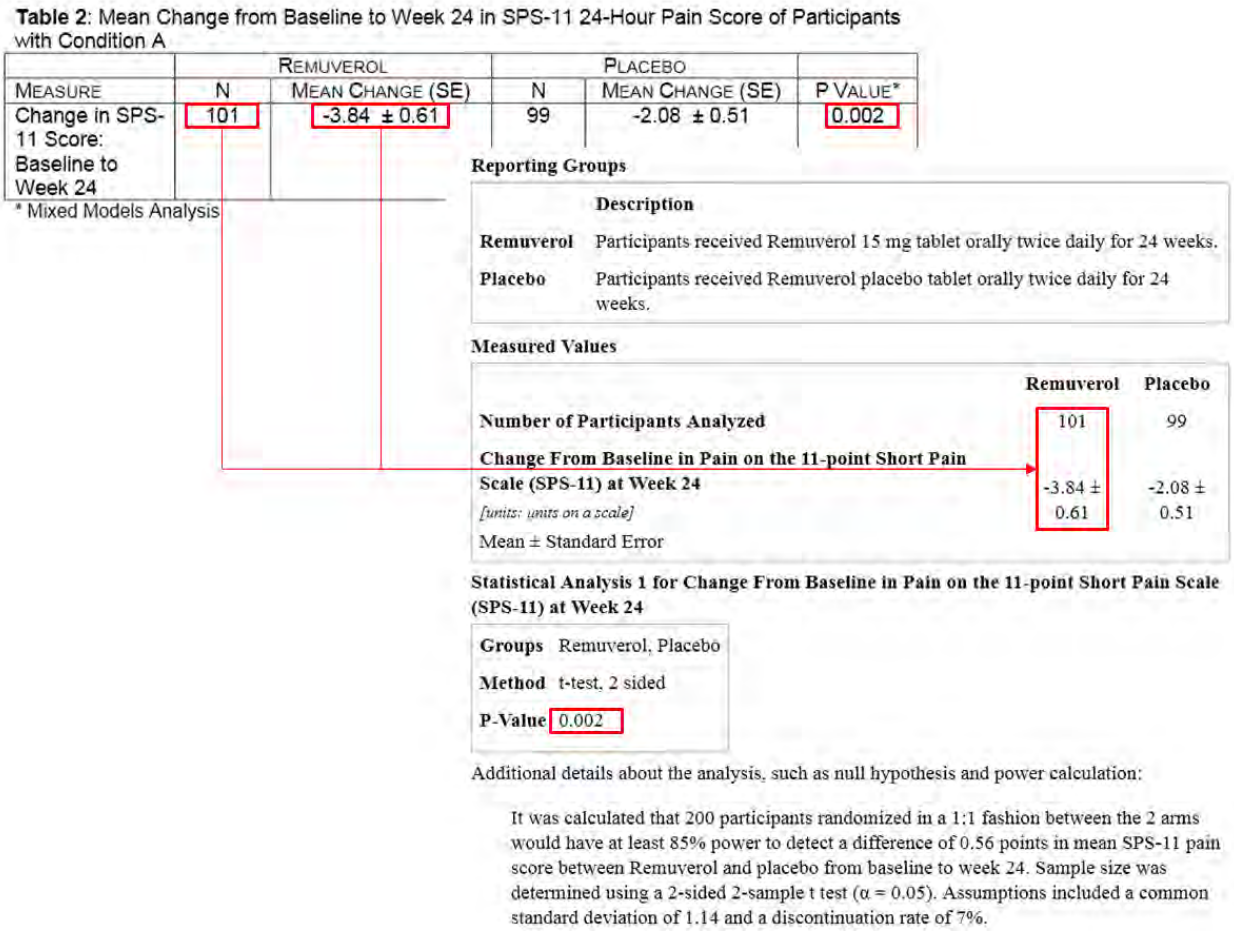


Table 2: Mean Change from Baseline to Week 24 in SPS-11 24-Hour Pain Score of Participants with Condition A

	Remuverol		Placebo		
Measure	N	Mean Change (SE)	N	Mean Change (SE)	P Value*
Change in SPS-11 Score: Baseline to Week 24	101	-3.84 ± 0.61	99	-2.08 ± 0.51	0.002

* Mixed Models Analysis

Reporting Groups

	Description
Remuverol	Participants received Remuverol 15 mg tablet orally twice daily for 24 weeks.
Placebo	Participants received Remuverol placebo tablet orally twice daily for 24 weeks.

Measured Values

	Remuverol	Placebo
Number of Participants Analyzed	101	99
Change From Baseline in Pain on the 11-point Short Pain Scale (SPS-11) at Week 24 *[units: units on a scale]* Mean ± Standard Error	-3.84 ± 0.61	-2.08 ± 0.51

Statistical Analysis 1 for Change From Baseline in Pain on the 11-point Short Pain Scale (SPS-11) at Week 24

Groups	Remuverol, Placebo
Method	t-test, 2 sided
P-Value	0.002

Additional details about the analysis, such as null hypothesis and power calculation:

It was calculated that 200 participants randomized in a 1:1 fashion between the 2 arms would have at least 85% power to detect a difference of 0.56 points in mean SPS-11 pain score between Remuverol and placebo from baseline to week 24. Sample size was determined using a 2-sided 2-sample t test ($\alpha = 0.05$). Assumptions included a common standard deviation of 1.14 and a discontinuation rate of 7%.

The Outcome Measures module in the PRS is pre-populated with the Outcome Measure information submitted during registration. Edits may be made to the Outcome Measure Title, Description, and Time Frame at the time of results data entry. The Outcome Measure can

incorporate the same Arms/Groups that were used in previous modules or they can be modified to accommodate groups unique to the outcome assessment and analysis. Data for "Other pre-specified" (e.g., tertiary or exploratory) and "*Post hoc*" outcome measures can also be reported.

Adverse Events Module

This module consists of two tables: (1) all Serious Adverse Events and (2) Other (not serious) Adverse Events. Under FDAAA 801, if requirements for the adverse events module were not established by rulemaking, then specified default requirements would become mandatory in September 2009, one year after the other results module requirements became effective. We initially implemented the default requirements as an optional module in September 2008 (1) to allow for balanced results information and (2) to gain additional experience with adverse event data submission. During that time, we collected feedback from users, NIH and FDA (including legal counsel), and external experts in the reporting of harms and risk communication. We also received feedback at the statutorily mandated public meeting in April 2009. Based on this input, we implemented the adverse events module in September 2009 as required by the default requirements and designed it to be consistent with good reporting practices, existing federal policies, and definitions related to adverse events.

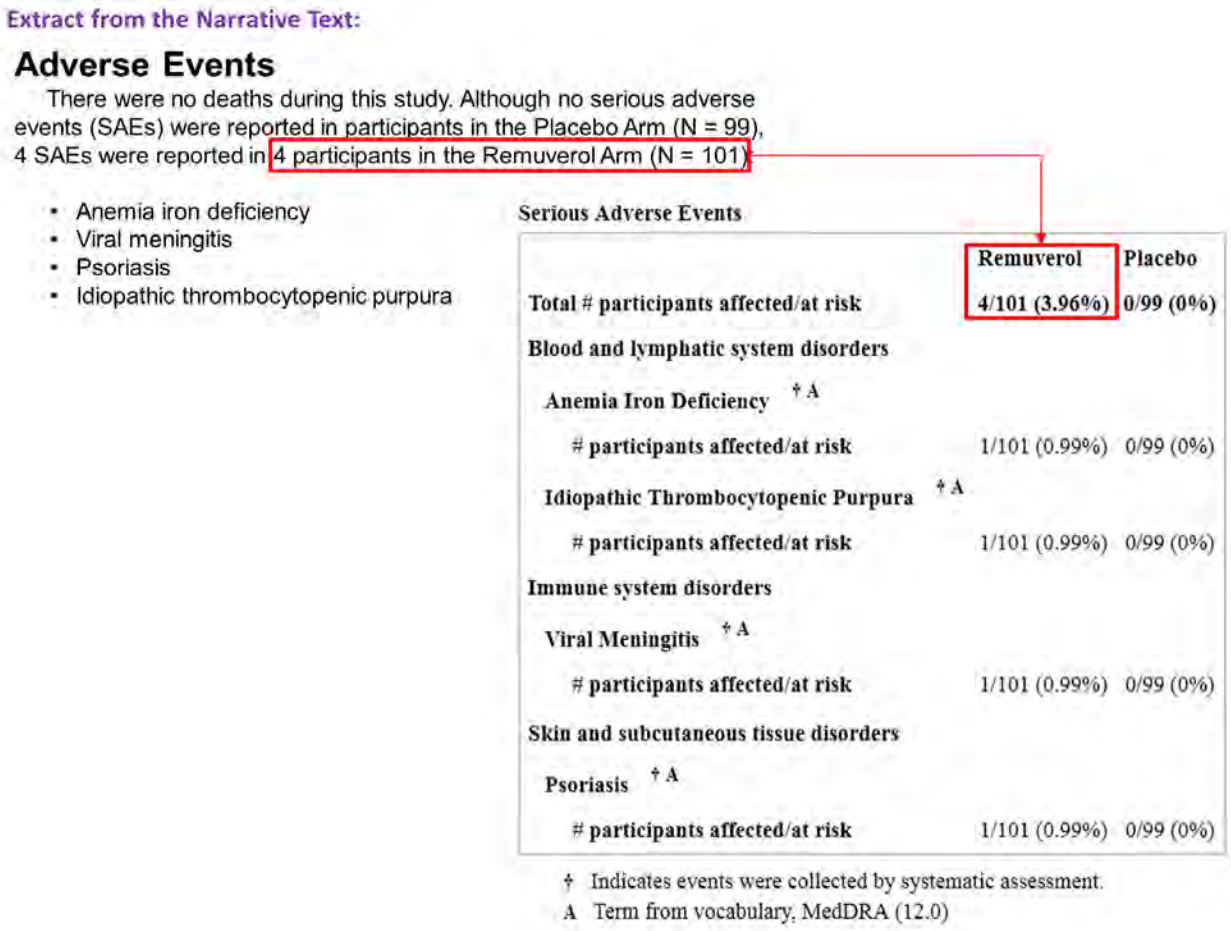
Each adverse event table is similar in structure and provides a summary of adverse event data by Arm/Group: the overall number of participants affected by (1) all adverse events and (2) each adverse event, organized by system organ class. For each adverse event, both the Number of Participants Affected (numerator) and at Risk (denominator) are required; the total number of occurrences of the event is optional. Any necessary elaboration may be provided in a free-text data field for each adverse event term. Additional optional data elements, which permit the reporting of a more complete description of adverse event data, consistent with good reporting practices,[42] include the following:

- Time Frame for Adverse Event Reporting - period of adverse event data collection
- Adverse Event Reporting Additional Description – other relevant information about adverse event collection (e.g., methods described in protocol that differ from Adverse Event module requirements)
- Assessment Type – Systematic (e.g., structured questionnaire) or Non-Systematic Assessment of adverse events
- Source Vocabulary – name of the vocabulary used, if any, for adverse event terms (e.g., SNOMED CT, MedDRA 10.0)

The adverse event information available in ClinicalTrials.gov is generally more comprehensive than what is available in the published literature [see Figure 17].

In the PRS, data providers enter adverse events data by selecting the appropriate Arms/Groups from previous results modules, or by entering groups that are most appropriate for reporting of adverse events. In addition to the interactive data entry mode, we recently implemented a feature that allows for the upload of adverse event information from a tab-delimited (spreadsheet style) file into the PRS. There are also many data providers who upload adverse event information into the PRS using XML. For large studies with many adverse events, the tab-delimited file and XML upload mechanisms offer alternatives to time-consuming interactive data entry.

Figure 17: Depiction of Equivalent Information Displayed as Narrative Text in a Journal Article and as a ClinicalTrials.gov Adverse Events Module Table



Extract from the Narrative Text:

Adverse Events

There were no deaths during this study. Although no serious adverse events (SAEs) were reported in participants in the Placebo Arm (N = 99), 4 SAEs were reported in 4 participants in the Remuverol Arm (N = 101):

- Anemia iron deficiency
- Viral meningitis
- Psoriasis
- Idiopathic thrombocytopenic purpura

Serious Adverse Events

	Remuverol	Placebo
Total # participants affected/at risk	**4/101 (3.96%)**	**0/99 (0%)**
Blood and lymphatic system disorders		
Anemia Iron Deficiency †A		
# participants affected/at risk	1/101 (0.99%)	0/99 (0%)
Idiopathic Thrombocytopenic Purpura †A		
# participants affected/at risk	1/101 (0.99%)	0/99 (0%)
Immune system disorders		
Viral Meningitis †A		
# participants affected/at risk	1/101 (0.99%)	0/99 (0%)
Skin and subcutaneous tissue disorders		
Psoriasis †A		
# participants affected/at risk	1/101 (0.99%)	0/99 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (12.0)

3. Key Accomplishment 3: Developing and Refining the Quality Review System and Criteria

Prior to FDAAA 801, the PRS already had a QA system that incorporated automated and manual quality checks. The passage of FDAAA and the addition of the results database resulted in an expansion of this system.

Automated Quality Check

The use of automated, system-enforced rules during data entry and before record submission provide three main benefits: 1) real-time feedback to data providers, so that they can address the issues immediately; 2) more complete submissions, which improve the chances that a record will pass manual quality review, thereby reducing burdens on data providers and reviewers; and 3) resolution of more "straightforward" issues, which allows reviewers to focus on substantive issues during the manual quality review process.

Data entry format requirements and data entry rules restrict the types of data that can be entered in the spaces provided (e.g., a number, controlled terms using a pick list). Automated validation rules are used to check consistency between values in separate data elements. When a rule is triggered, the PRS displays a validation message at one of three levels of severity:

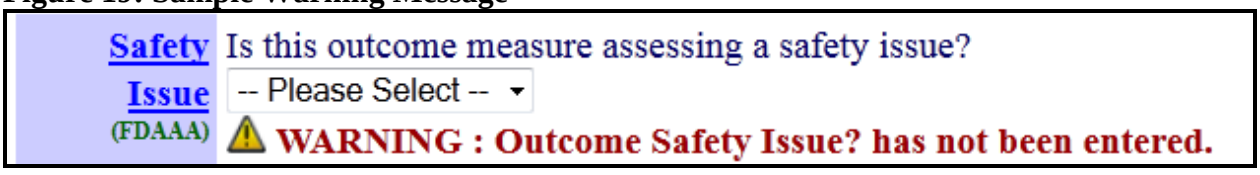
1. **ERROR:** An issue that MUST be addressed before the record can be submitted
2. **WARNING:** FDAAA-related issue that should be addressed
3. **NOTE:** Helpful hints indicating there may be an issue in the record, but may not apply in all cases

Only messages at the most severe level (ERROR) prevents a data provider from submitting the record. For example, in the Participant Flow module, the number of participants completing a period cannot be greater than the number of participants starting that period [see Figure 18]. Only rules that are valid across all records can be implemented as Error messages, as even a relatively rare exception to a rule (e.g., one in 1000 records) would create a problem for data providers and ClinicalTrials.gov staff.

Figure 18: Sample Error Message

The second type of validation message (WARNING) is displayed when a data element that is or may be required by FDAAA 801 has not been entered. For example, according to the law, the database should be searchable by the safety issue being studied, if any. Thus, if a data provider does not include this information with an outcome measure, the PRS displays a Warning message [see Figure 19].

Figure 19: Sample Warning Message



The third type of validation message (NOTE) simply indicates that data should be verified because the information appears inconsistent with general results reporting principles. These types of messages are a method of using the automated system both to (1) spot problems prior to submission and (2) alert data providers and reviewers to potential problems. However, a tension faced in developing these messages is providing an optimal number of helpful automated messages without creating cognitive overload or fatigue in data providers such that they ignore all messages. We are continuously refining the automated validation rules based on lessons learned in evaluating results records.

Manual Quality Review

Review Criteria

When the results database was first launched, it was not clear that there would be many opportunities for quality review. We had thought that it would not be possible to know whether or not the entered data were correct without a clear reference standard. However, it quickly became clear that there were obviously erroneous or uninterpretable data in results submissions that violated general principles. These principles were consistent with the manual review criteria already in practice for protocol information: apparent validity, logic, meaningful entries, internal consistency, and formatting. Over time, based on our experience, we developed review criteria for results information (http://prsinfo.clinicaltrials.gov/ResultsDetailedReviewItems.pdf). These criteria and some specific examples and comments/explanations are described in Table 7.

Table 7: Summary of ClinicalTrials.gov Results Review Criteria[32]

Table 3. ClinicalTrials.gov Quality Review Criteria.

Quality Review Criterion	Description	Example	Comment
Lack of apparent validity	Data are not plausible on the basis of information provided	Outcome measure data: mean value of 263 hours of sleep per day	Measure of mean hours per day can have values only in the range of 0 to 24, so value of 263 is not valid
Meaningless entry	Information is too vague to permit interpretation of data	Outcome measure: description states "clinical evaluation of adverse events, laboratory parameters, and imaging"; data reported as 100 and 96 participants in each group	Data are uninformative; unclear what counts of 100 and 96 participants refer to; description of outcome measure not sufficient for an understanding of the specific outcome
Data mismatch	Data are not consistent with descriptive information	Outcome measure is described as "time to disease progression"; data reported as 42 and 21 participants in each group	A time-to-event measure requires a unit of time (e.g., days or months)
Internal inconsistency	Information in one section of record conflicts with or appears to be inconsistent with information in another section	Study type is "observational," but study title includes the word "randomized"	Randomized studies are interventional, not observational
Trial design unclear	Structure of tables and relevant group names and descriptions do not permit a reader to understand the overall trial design or do not accurately reflect the design	Results modules: participant flow and baseline characteristics entered as a two-group study with a total of 400 participants; outcomes entered for three comparison groups with 600 participants	If there is a third group, this should be reflected in the description of participant flow and baseline characteristics

Process Implementation

In addition to establishing results review criteria, we needed to develop internal processes and procedures by which the QA staff would apply these criteria. During this process, we used several approaches. First, we had to identify the appropriate personnel and skills required to be a successful results reviewer. We initially tried to train senior protocol reviewers, but learned that they did not have the requisite background knowledge or skill set. Even though QA review does not depend on having domain-specific knowledge (e.g., trials in oncology, rheumatology, and cardiology would all be evaluated by the same reviewers), results reviewers need to have advanced training in epidemiology, biostatistics, or a related scientific field, and possess excellent analytical and problem-solving skills, in order to understand, apply, and master the intricacies of the PRS, submission requirements, and review criteria.

After identifying the types of people who would be qualified to be results reviewers, we piloted different models for performing the work. First, we used on-site reviewers. We also piloted a program to supplement on-site staff with individuals employed by an academic medical center's evidence-based practice center. While these individuals had more than sufficient background to understand clinical study designs and health outcomes, it was challenging to instill a deep understanding of the PRS and submission requirements needed to perform a comprehensive review. In addition, because they were only doing this work on a part-time basis, it was difficult for them to become fully immersed in the results review culture and processes. Based on this pilot, we learned that having all necessary staff on-site and working full-time is preferable.

The final aspect of developing the review process focused on finding the most efficient balance between attention to detail in the review and total record throughput. In the initial stages, all initial results submissions were evaluated by two reviewers, and the commenting process included minor issues (e.g., typos, spelling mistakes). This detailed, double-review process could not be maintained as the rate of results submissions increased. Thus, reviewers currently focus on major issues that affect the ability of a general reader of the medical literature to understand the data. We have provided additional guidelines and tools online for data providers to assist with the detection of minor issues. In addition, each record is routinely reviewed by only one QA staff member, but a reviewer may request a second review (e.g., complicated submissions). Major policy issues are reviewed and adjudicated by senior federal staff.

The efficiencies gained by having a single reviewer conduct a review independently created new challenges in ensuring that reviewers are calibrated with respect to the way that review criteria are applied. We developed a multifaceted approach to this challenge. First, we documented the review criteria and implemented standard operating procedures. Second, although members of the review team discussed issues with each other verbally and electronically on a daily basis, weekly meetings with the entire results review team were established to discuss significant or unique issues encountered during their reviews. Third, when previously rejected records are resubmitted with updates, it is assigned randomly to a reviewer, allowing for a cross-check within the process. This ensures that all reviewers see comments provided by all other reviewers, as well as their own comments over time. Finally, each month, two senior staff members pick a random sample of record reviews from each QA staff member to perform a quality check and provide feedback to individual reviewers.

The software development team provided significant support to the manual review process by implementing new PRS features as review needs were identified. The most significant was the addition of a tool for commenting on records. This tool allows comments to be entered by a reviewer in the relevant sections of the record. Comments are then stored with the record in the PRS and the data provider is notified by email that comments have been recorded and are available for review. In addition, a new section of the record visible only to QA review staff was added to accommodate internal documentation associated with a review, and to record any relevant communications with the data provider regarding a specific record.

To date, the quality review process is continuing to evolve and adapt based on our growing experience. The ClinicalTrials.gov staff monitoring emails and reviewing records are constantly looking for opportunities to improve the system and to provide guidance to data providers.

Whenever possible, new automated validation rules are added. Although there has not yet been a study design that the PRS has not been able to accommodate, some study designs have been more challenging and required creative solutions. We pay particular attention to these complicated cases and attempt to identify ways to make submission of such trials easier and more intuitive. When we encounter an issue frequently, we adapt the PRS to accommodate it. For example, we modified the Outcome Measures module to allow for specification of units of analysis that are other than participants (e.g., number of hips).We also continue to encourage data providers to report issues to us as such issues are encountered, so that we may determine if there is a solution that we can implement as part of the PRS, the review process, or help documentation. We continue to work to optimize the review process in order to make the most efficient use of staff and data provider resources.

C. Outreach and Training

In parallel to technical system development and maintenance activities, our outreach and training activities aim to inform the public about the ClinicalTrials.gov Web site, the laws and policies that require registration and results submission, and to provide assistance to data providers in meeting these requirements. We reach a broad audience through presentations at professional society meetings and ongoing relationships with various groups, organizations, and entities that work in related clinical, technical, or policy areas.

For members of the public, our activities have focused on developing Web-based resources. The online American Customer Satisfaction Index (ACSI) survey at ClinicalTrials.gov indicates that patients, family members, and friends (40%) are the largest user group of the site [see Table 8]. To address the needs of this group, the 2012 Web site redesign enhanced the Help information for finding studies on ClinicalTrials.gov. Existing resources were updated with improved explanations of clinical research concepts and terms used on the Web site.[31] The NLM Division of Library Operations developed brief, online tutorials on using ClinicalTrials.gov for the general public (http://www.nlm.nih.gov/bsd/viewlet/ct/). We also added reference pages for researchers, study record managers, and the media during the redesign.

Table 8: Visitors to ClinicalTrials.gov by Self-Described Role Based on the ACSI Online Consumer Survey, 4th Quarter 2012

Role	Response (N = 2,216)
Patient	28%
Scientist/Researcher	18%
Family/Friend	14%
Health Care Provider	8%
Other	7%
Clinical Trial Staff	6%
Clinical Research Support	5%
Student/Educator	4%
Medical Communications	3%
Librarian/Information Professional	2%
IRB or Ethics	<1%

Another key aspect of our outreach and training efforts, especially after the enactment of FDAAA 801, has been providing directed personal assistance to sponsors, principal investigators, and others responsible for submitting data. The types of Web-based information we have made available range from explaining the purpose of registration and results submission and relevant laws and policies to how to submit and maintain data at ClinicalTrials.gov using the PRS. Initial activities focused on developing basic explanatory documents and later activities focused on making explanatory information easier to find and use as reference material. Concurrently, efforts to improve just-in-time help, add time-saving features, and other modifications are occurring within the PRS.

In March 2011, we developed eight online presentations to provide background on trial registration and results reporting, explain key features of FDAAA 801, describe the PRS and provide more details on results submission (http://clinicaltrials.gov/ct2/manage-recs/present#OnlinePresentations). With the 2012 Web site redesign, we integrated content formerly available at http://prsinfo.clinicaltrials.gov with the main ClinicalTrials.gov Web site under the section titled "Submit Studies" (http://www.clinicaltrials.gov/ct2/manage-recs), which provides specific content on explaining FDAAA 801 Requirements, How to Register a Study, How to Submit Results, Frequently Asked Questions, Training Materials, and a page that includes all Support Materials for easy referencing.

Also in 2011, we initiated a ClinicalTrials.gov Results Database Train-the-Trainer Workshop. We organized this workshop because academic organizations, which often have de-centralized models, were having less success with results than industry organizations, which typically have a centralized model. The workshop trains key personnel at institutions who are responsible for providing training and support to staff involved with data submission to ClinicalTrials.gov. The content of the curriculum was modeled on training developed internally for the NIH Intramural Quality Assurance Professionals Advisory Committee (QAPAC) and based on input from the Clinical Translational Science Awards (CTSA) Clinical Trials Registration Taskforce. The curriculum focuses on providing participants from CTSA institutions with background information on submission requirements and detailed instruction on the content, structure, and quality review criteria for results submission in the PRS. The format includes a mixture of traditional and interactive lecture styles as well as hands-on tutorial style learning. Since 2011, we have hosted three workshops at NIH and have trained 51 people from 33 CTSA Institutions, representing more than half of all CTSA Institutions. There are currently two workshops planned for 2013 in which we will expand the class size and the institutions targeted. We have posted materials from the most recent workshop on our Web site on the "Training Materials" page under "Submit Studies" (http://clinicaltrials.gov/ct2/manage-recs/present#ResultsTrainTrainer).

A third component of our outreach effort is presentations at professional society meetings, visits to major research institutions, NIH grantee seminars, and other similar activities. Table 9 summarizes some of the organizations that we have reached since 2005. We also participate in routine liaison (e.g., monthly teleconferences) with organizations that represent a large number of stakeholders and users:

- Drug Information Association (DIA) Clinical Trial Disclosure Community
- CTSA Clinical Trials Registration Task Force

- Clinical Data Interchange Standards Consortium (CDISC) and HL7 Working Groups for developing Clinical Trial Registration (CTR) standards
- The WHO ICTRP Advisory Group

In addition to these activities, a committee was established within the National Network of Libraries of Medicine (NN/LM) to develop educational materials to train medical librarians on the ClinicalTrials.gov results database. A pilot training course has been developed by the group, with input from ClinicalTrials.gov, and is currently being revised.

Table 9: Examples of Key Organizations, By Category

Professional Organizations
Advanced Medical Technology Association (AdvaMed)
American Academy of Child & Adolescent Psychiatry (AACAP)
American Academy of Medical Colleges (AAMC)
American Association for the Advancement of Science (AAAS)
American College of Neuropsychopharmacology (ACNP)
American Colleges of Clinical Pharmacy (ACCP)
American Heart Association (AHA)
American Medical Informatics Association (AMIA)
American Public Health Association (APHA)
American Society of Clinical Oncology (ASCO)
Association for Clinical and Translational Science (ACTS)
Association for Clinical Research Training (ACRT)
Association for Research in Vision and Ophthalmology (ARVO)
Association of Clinical Research Professionals (ACRP)
Biotechnology Industry Organization (BIO)
Clinical Translational Science Award (CTSA)
Clinical Trials Transformation Initiative (CTTI)
Drug Information Association (DIA)
EU-USA International Rare Diseases Research Consortium (IRDiRC)
Health Level Seven International (HL7)
Institute of Medicine (IOM)
International Committee of Medical Journal Editors (ICMJE)
International Society for Medical Publication Professionals (ISMPP)
Medical Library Association (MLA)
Public Responsibility in Medicine and Research (PRIM&R)
Regulatory Affairs Professionals Society (RAPS)
Society for Clinical Translational Science (SCTS)
Society for Clinical Trials (SCT)
Society of Clinical Research Associates (SoCRA)
Universities and Medical Centers
Brigham and Women's Hospital
Duke University
Georgetown University
Harvard School of Public Health
Massachusetts General Hospital
Mayo Clinic
Northwestern University
Partners Healthcare
Stanford University
Tufts Evidence-Based Practice Center
University of California - San Francisco

University of Illinois-Chicago
Yale University
Federal Agencies and Other Government Entities
Centers for Medicare and Medicaid Services (CMS)
European Medicines Agency (EMA)
Food and Drug Administration (FDA)
Health Resources and Services Administration (HRSA)
National Network of Libraries of Medicine (NN/LM)
Pan American Health Organization (PAHO)
Patient-Centered Outcomes Research Institute (PCORI)
Secretary's Advisory Committee on Human Research Protections (SACHRP)
US Army Medical Materiel Development Activity (USAMMDA)
States Attorneys General
Walter Reed Army Medical Center
World Health Organization (WHO)

D. Science Policy and Regulatory Activities

ClinicalTrials.gov staff provides technical assistance and data to support science policy issues and projects that are consistent with our program objectives [see Table 10]. A key project since 2007 has been supporting NLM (the lead IC) in drafting a proposed rule to implement FDAAA 801.

Table 10: Key Projects that Utilize ClinicalTrials.gov

Project	Description	Relation to ClinicalTrials.gov
AHRQ Registry of Patient Registries (RoPR) https://patientregistry.ahrq.gov/	RoPR is a Web site that "contains [patient] registry specific information intended to promote collaboration, reduce redundancy, and improve transparency among registry holders." It was funded by the American Recovery and Reinvestment Act of 2009 (ARRA).	ClinicalTrials.gov supports the registration of observational studies that are also patient registries. Data providers can submit additional optional information about patient registries at RoPR.
HHS Comparative Effectiveness Research (CER) Inventory http://www.cerinventory.com/About	The CER Inventory is intended to provide "access to CER findings, ongoing CER, CER methods, and related data resources." It was funded by the American Recovery and Reinvestment Act of 2009 (ARRA).	ClinicalTrials.gov is one of six resources used by the CER Inventory.
WHO International Clinical Trials Registry Platform (ICTRP) Search Portal http://apps.who.int/trialsearch/	The Search Portal provides access to a central database containing the trial registration data sets provided by 15 trial registries worldwide.	ClinicalTrials.gov is a data provider to the WHO Search Portal.

Clinical Trials Transformation Initiative (CTTI) State of Clinical Trials Project https://www.ctti-clinicaltrials.org/project-topics/clinical-trials.gov	An FDA-funded project to investigate the state of the clinical trial enterprise in a number of medical specialties. Its Aggregate Analysis of ClinicalTrials.gov (AACT) database uses information extracted from ClinicalTrials.gov.	ClinicalTrials.gov provided technical assistance in the development of the AACT.
European Medicines Agency (EMA) – *Draft Implementing Technical Guidance*. June 2010. http://ec.europa.eu/health/files/clinicaltrials/technical_guidance_en.pdf and *Technical Guidance on the Format of the Data Fields of Result-Related Information on Clinical Trials.* Jan 2013. http://ec.europa.eu/health/files/eudralex/vol-10/2013_01_22_tg_en.pdf	EMA is required to develop, by regulation, a results database for disclosing findings from the drug trials that it regulates (generally, those conducted in the EU).	EMA has been consulting with ClinicalTrials.gov since 2009 "to ensure that a common set of data elements can be used for reporting results to both" the EU and ClinicalTrials.gov results databases. [43]
Presidential Commission for the Study of Bioethical Issues. *Moral Science: Protecting Participants in Human Subjects Research*. December 2011. http://bioethics.gov/cms/sites/default/files/Moral%20Science%20June%202012.pdf	The Commission serves as an advisory panel to the President "on bioethical issues arising from advances in biomedicine and related areas of science and technology."[1] In 2010, the President requested the Commission to review the current policies related to the protection of human subjects participating in federally-funded research.	ClinicalTrials.gov provided technical advice regarding mechanisms for assessing federally funded studies in humans. In its final report, *Moral Science*, the Commission endorsed "registration and reporting results of all human clinical research including early phase studies and all privately funded research (p. 52)"[44] and cited ClinicalTrials.gov as an exemplar.

Since the enactment of FDAAA 801 in September 2007, science policy operations have included understanding requirements specified by the statute and responding to questions from data providers. While many basic requirements are specified in the law (e.g., registration no later than 21 days after enrollment of the first participant, and submission of results no later than 1 year after the Primary Completion Date), others are not and are therefore subject to interpretation (e.g., what is the Primary Completion Date when a study has more than one Primary Outcome?). For the latter we have consulted with the NIH Office of the General Counsel, the NIH Office of Science Policy, and their counterparts at FDA. Whenever possible, we have made information on the Agency's current thinking available, such as the key statutory terms, "responsible party" and "applicable clinical trial" (http://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf). These and documents have been collected, organized, and made publicly available on the FDAAA 801 Requirements page at http://clinicaltrials.gov/ct2/manage-recs/FDAAA 801. As issues arise, we add items to the Frequently Asked Questions page (http://clinicaltrials.gov/ct2/manage-recs/faq).

[1] http://bioethics.gov/cms/about

Resolution of some requirements will require promulgation of final regulations. We continue to support and participate in the decision-making process related to key elements in the implementation of FDAAA 801.

We also provide data and technical input to organizations based on our experience with the registry and results database. We have long-standing relationships with organizations such as the ICMJE and the WHO International Clinical Trials Registry Platform (ICTRP). Since 2009, we have also been working with the EMA to provide them with technical feedback on developing a results database for drug clinical trials in the EU that is compatible with ClinicalTrials.gov.

In addition, ClinicalTrials.gov staff continues to provide support for researchers and organizations interested in using ClinicalTrials.gov to answer specific questions and/or to capture specific types of studies (e.g., comparative effectiveness research (CER) studies for Patient-Centered Outcomes Research Institute (PCORI)). We have also provided technical assistance for others who are building registries or related databases (e.g., AHRQs Systematic Review Electronic Data Repository (SRDR) and Registry of Patient Registries (RoPR) systems; Germany and Japan).

E. Research

In addition to the above responsibilities, we conduct primary research. Our research efforts have focused on two broad areas:

(1) Advancing best practices in registration and results reporting based on first-hand experiences with ClinicalTrials.gov and
(2) New ways of using data available from ClinicalTrials.gov to inform improvements in the clinical research enterprise and trial reporting.

Since 2005, the ClinicalTrials.gov staff has published over 20 peer-reviewed articles, participated in a number of invited-committees and workshops, and established many productive collaborations.

See Appendix A for annotated lists of the following:

1. Publications since 2005
2. Selected presentations at invited committees and workshops
3. Selected Collaborations

5. Project Status

ClinicalTrials.gov has been operational for over 12 years and is well-known as the largest public registry and results database in the world. The system as well as individual records (uniquely identified by the ClinicalTrials.gov identifier or NCT Number[28]) are cited by in the peer-reviewed biomedical literature, the U.S. Congress (e.g., Committee on Energy and Commerce letter to Chairmen of Schering-Plough and Merck & Co regarding the ENHANCE trial, 2007) and federal regulators (e.g., Devices@FDA), researchers and study sponsors (e.g., press releases), professional societies (e.g., The Association for Research in Vision and Ophthalmology (ARVO) requires registration for submitted abstracts in Guidelines on Clinical

Trials Registration, 2008), patients and advocacy groups (BreastCancerTrials.org at https://www.breastcancertrials.org/), and the popular media among others. Although it is mandated by federal law (FDAAA 801 and FDAMA 113), ClinicalTrials.gov accommodates international, national, and other clinical research disclosure policies to advance public health policy. As the largest single repository of information about ongoing and completed clinical studies since 2000, with increasing public awareness, its data are being used with increasing frequency for research.

Examples of ongoing scientific issues include:

- Specifying the parameters for identifying a single study
- Examining the implications of using the registry and results database for studies other than clinical trials (e.g., observational studies, patient registries)
- Investigating ways to structure data elements for describing the study designs/methods and their conduct precisely and accurately (without ambiguity) (e.g., levels of specification in reporting outcome measures; adequate descriptions of device and biologics as interventions)
- Examining the implications of when and what to prespecify in a study protocol/registration (e.g., statistical analysis plan, level of specificity for outcome measures)
- Developing and evaluating the results database
- Developing a mechanism for citing ClinicalTrials.gov results database entries so they can be cited uniformly and widely in references lists, including clinical investigators' CVs.
- Investigating ways to mitigate duplicate registration across various international registries (e.g., determining an accurate "denominator" for trials conducted worldwide)

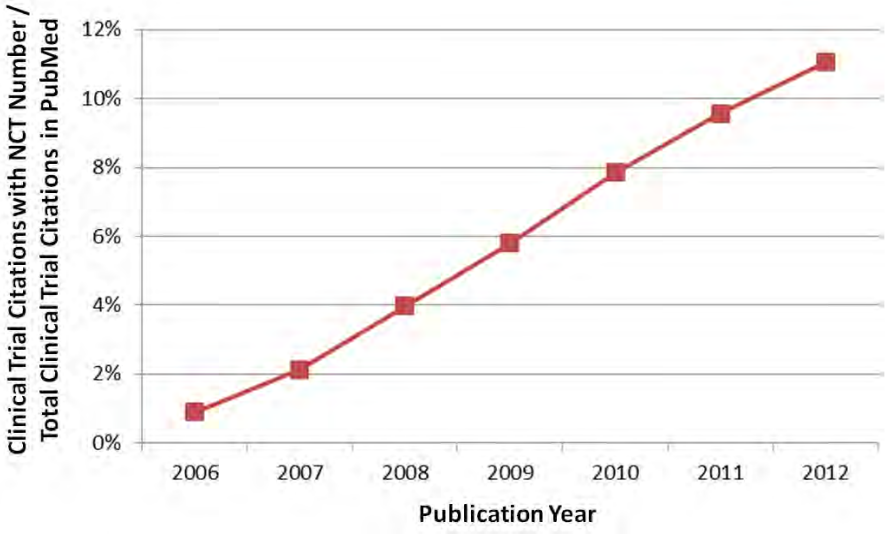
6. Evaluation Plan

Registration and results reporting at ClinicalTrials.gov is still in its infancy and may be considered a public health experiment. As such, we continually look for evidence of the impact of ClinicalTrials.gov in various areas and of the achievement of various scientific and ethical goals. Three specific types of evaluation are described below: (1) utilization, (2) user-centered evaluation, and (3) an evaluative framework for the results database.

A. Utilization

Because a goal of transparency is to make information accessible to the public, one metric we have used to informally evaluate the impact of ClinicalTrials.gov is Web site utilization. ClinicalTrials.gov currently receives over 95 million page views and approximately 900,000 unique visitors per month. A rough indicator of the rate of adoption of the ICMJE policy is the number of MEDLINE citations that have been indexed with at least one NCT Number, a practice that began in 2005.[45] As of January 7, 2013, 16,664 citations in PubMed have been indexed with NCT Numbers in the Secondary Source Index field. These include multiple Publication Types (e.g., "Clinical Trial," "Review," "Editorial") [see Figure 20].

Figure 20: Percentage of Clinical Trials Citations Indexed by ClinicalTrials.gov Identifier (NCT Number) by Publication Year



Another rough indicator of utilization is the number of research papers that use ClinicalTrials.gov as a data source. Since 2011, we have been noting such publications and have observed that the topics of analysis generally fall into one of several categories [see Table 11].

Table 11: Selected Categories and Examples of Research Involving Analysis of Data from ClinicalTrials.gov

Research Area	Example – Statement of the Objective from the Abstract
Quality of Registration/ Consistency with Policies	• To assess "the adequacy of randomized controlled trial (RCT) registration, changes to registration data and reporting completeness for articles in ICMJE journals."[46] • "We examine the extent to which ClinicalTrials.gov is meeting its goal of providing oversight and transparency of clinical trials with human subjects. We analyzed the ClinicalTrials.gov database contents as of June 2011, comparing interventions, medical conditions, and trial characteristics by sponsor type. We also conducted a detailed analysis of incomplete data."[47] • "To determine whether two specific criteria in Uniform Requirements for Manuscripts (URM) created by the International Committee of Medical Journal Editors (ICMJE)—namely, including the trial ID registration within manuscripts and timely registration of trials, are being followed."[48]
Quality of Results Submission/ Consistency with Policies	• "To examine compliance with mandatory reporting of summary clinical trial results (within one year of completion of trial) on ClinicalTrials.gov for studies that fall under

	the recent Food and Drug Administration Amendments Act (FDAAA) legislation."[49] • "We studied the longer-term impact of the federal mandate on the registration and reporting of results for drug and biological trials in ClinicalTrials.gov."[50] • "To examine (1) how often and how numbers of deaths are reported in ClinicalTrials.gov records; (2) how often total deaths can be determined per arm within a ClinicalTrials.gov results record and its corresponding publication and (3) whether counts may be discordant."[51]
Identification of Research Gaps in a Domain (e.g., Geographical Area, Medical Specialty)	• "[t]o quantify and describe current cancer clinical trial activity in Australia and help guide future trials research." [52] • "to measure the prevalence of pediatric studies among clinical drug trials and compare trial characteristics and quality indicators between pediatric and adult drug trials"[53]
Characterization of Comparative Effectiveness Research	"an observational study of clinical trials addressing priority research topics defined by the Institute of Medicine and conducted in the US between 2007 and 2010"[54]
Estimation of Condition-Specific Results Across Studies	"We sought to answer: what are the characteristics of pain trials; how frequently are these trials stopped and why; what is the magnitude of attrition due to lack of efficacy or adverse events; and whether the withdrawal rates depend on pain syndrome. To facilitate this and subsequent studies, we have developed a system called Sherlock that automatically downloads data from ClinicalTrials.gov into a relational database. We included pain interventional trials."[55]
Systematic Review and Meta-Analysis	"to identify any adverse event (AE) associated with LCM [lacosamide] treatment by conducting a systematic review and meta-analysis of all available randomized controlled trials (RCTs)."[56]
Publication Bias/ Selective Reporting of Outcomes	"To assess the proportion of registered trials with results recently published in journals with high impact factors; to compare the primary outcomes specified in trial registries with those reported in the published articles; and to determine whether primary outcome reporting bias favored significant outcomes."[57]
Assessment of the Clinical Research Enterprise	"We undertook a survey of the current capability in the United States to conduct controlled clinical trials. The intention was to use the results as a foundation for understanding how to create a controlled clinical trial capability sufficient to meet future needs of US health care."[58]

An indicator of the degree to which ClinicalTrials.gov is utilized to register studies conducted internationally is the relative number of registrations in ClinicalTrials.gov with at least one site

in a country/region compared to individual national/regional registries. The WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/) recognizes 14 primary registries in their Registry Network. Table 12 compares the numbers of registered studies in each WHO Primary Registry with those in ClinicalTrials.gov that are being conducted in a comparable region as of January 7, 2013. Note that ClinicalTrials.gov appears to contain more records that list at least one location in a country or region than 8 of 14 (57%) primary registries in the same country or region.

Table 12: Number of Studies Registered in WHO ICTRP Primary Registries Compared to ClinicalTrials.gov, for a Country or Comparable Region

WHO Primary Registry	Number of Studies	ClinicalTrials.gov by Location	Number of Studies
1. Australian New Zealand Clinical Trials Registry (ANZCTR)	7,287	Australia, New Zealand	3,821
2. Brazilian Clinical Trials Registry (ReBec)	197	**Brazil**	**3,152**
3. Chinese Clinical Trial Registry (ChiCTR)	2,954	**China**	**3,512**
4. Clinical Research Information Service (CRiS), Republic of Korea	618	**Republic of Korea**	**3,941**
5. Clinical Trials Registry - India (CTRI)	3,287	India	2,146
6. Cuban Public Registry of Clinical Trials (RPCEC)	139	Cuba	35
7. EU Clinical Trials Register (EU-CTR)	19,665	**Europe**	**37,128**
8. German Clinical Trials Register (DRKS)	1,573	**Germany**	**9,687**
9. Iranian Registry of Clinical Trials (IRCT)	3,605	Iran	499
10. ISRCTN.org - limited to United Kingdom	6,473	**United Kingdom**	**7,320**
11. Japan Primary Registries Network (JPRN)	10,829	Japan	2,575
12. The Netherlands National Trial Register (NTR)	3,593	**Netherlands**	**4,413**
13. Pan African Clinical Trial Registry (PACTR)	150	**Africa**	**3,108**
14. Sri Lanka Clinical Trials Registry (SLCTR)	82	Sri Lanka	28

B. User-Centered Evaluation

As the scope of registration and results reporting policies expands, the numbers of different audiences with specific needs also increases. To understand who the audience is and what they are looking for at ClinicalTrials.gov, we have implemented several levels of user-centered evaluation strategies.

- American Customer Satisfaction Index (ACSI). In 2007, we ran the ACSI survey (including a number of customized questions) on ClinicalTrials.gov for a year. The results of the evaluation informed the planning for the first redesign of the Web site.

Since 2011, we have been running the ACSI survey continuously and regularly review the responses. The average monthly satisfaction score at ClinicalTrials.gov is 73, which is also the average monthly score across all participating federal government sites. In late 2012, we also designed and launched a second ACSI survey within the PRS in advance of conducting usability studies.

- Usability Studies. We have conducted several usability studies with users representing specific audiences and experience levels. These results were used to inform the two Web site redesigns in 2007 and 2012. As of early 2013, usability studies of the new Web site and the PRS are in progress.

C. Evaluative Framework for the Results Database

We have proposed a framework for evaluating the results database. This framework was adapted from the Fryback/Thornbury hierarchical model for diagnostic tests[59] and includes the following three levels:

1. Is the results database feasible?
    a. Can it accommodate a wide range of trial types and designs?
    b. Can data providers use it to submit data that meet the review criteria (e.g., complete, internally consistent, face valid, and logical)?
    c. Do data providers submit accurate data?
2. Is the results database usable and useful?
    a. Can summary results be easily found and used?
    b. Do the data tables provide "necessary and sufficient" information for use in research to support evidence-based medicine (EBM)?
    c. How are individual summary results entries used?
    d. How are aggregated summary results across entries used?
3. What is the potential impact of the results database in relation to various resources?
    a. Peer-reviewed literature
    b. Grey literature (e.g., scientific abstracts, press releases)
    c. Individual participant-level data (IPD)

We plan to conduct ongoing, iterative evaluation to make optimal use of this public health experiment and to develop new reporting tools for researchers wishing to analyze data from the results database.

7. Project Schedule and Resources

Daily operations are conducted by on-site program personnel [see Figure 4]. Personnel consist of six Federal staff and 20 Contractors (for a total of 17.8 Full-time equivalents). PRS and Web site development is primarily carried out by staff programmers, supplemented as needed by external experts such as project managers, usability specialists, Web designers, and copy editors. For domain-related issues, we have access to a wide range of experts, including the NLM Board of Regents Working Group on Clinical Trials, an internal NIH Institute and Center Subcommittee, NIH colleagues in the intramural and extramural programs, FDA, and experts at academic organizations with which we have professional services contracts. In conducting our science policy and regulatory activities, we work closely with the NLM Office of the Director, which

coordinates with the NIH Office of the Director, FDA, and other entities. Finally, our research projects typically involve collaborative efforts (e.g., Yale University Medical School, the Duke Clinical Research Institute, HHS Office for Human Research Protections (OHRP)).

8. Summary and Future Plan

As described in this report, the ClinicalTrials.gov and Related Projects program has made considerable advances toward reaching its project objectives since its BoSC review in May 2005. For example:

- In accommodating international disclosure policies (e.g., ICMJE/WHO), ClinicalTrials.gov has substantially expanded its scope (e.g., added a results database) and size (i.e., over 10-fold increase in registrations), becoming the largest public registry for a global community.
- Not only has the program contributed to increased public awareness of the importance of transparency to the clinical research enterprise through outreach, it has been— and continues to be— an active participant in a number of activities and forums that have resulted in new policies and standards promoting transparency (e.g., ICMJE, WHO, SPIRIT).
- Researchers and decision-makers increasingly use ClinicalTrials.gov as a reference for characterizing and studying the clinical research enterprise, as evidenced by the growing number of peer-reviewed articles using ClinicalTrials.gov data and references to ClinicalTrials.gov in reports, Congressional letters, and official documents.
- We have and continue to use a number of evaluation tools and techniques (e.g., usability studies, surveys, and user feedback) to assess ClinicalTrials.gov and to develop new features and other enhancements.
- The ongoing development of summary protocol and results review criteria, which is informed by expert guidelines, good reporting practices, and experience, contributes to the improvement and enhancement of the quality of reporting clinical research information.

Looking forward toward our second decade, we anticipate exciting developments in the transparency landscape and predict that trial disclosure will play an ever increasing role in building a more complete, accurate, and timely picture of the medical evidence base. In particular, we continue active monitoring of the rapidly evolving area of clinical research disclosure, provide technical advice and lessons learned from the ClinicalTrials.gov experience, and seek opportunities for synergy and collaboration. Following the redesign of the public Web site in September 2012, we are evaluating other aspects of the ClinicalTrials.gov system (e.g., study record format, PRS data entry system) and plan to further refine and/or implement new system features. We continue to develop new outreach and training materials to support different users and educate various audiences; two new Results Database Train-the-Trainer Workshops are scheduled in 2013. We continue to be engaged in the rulemaking process, other policy developments, and research intended to (1) inform best practices in reporting summary information or (2) characterize the clinical research enterprise.

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Appendix A: Research Publications, Talks, and Collaborations

1. Publications

Publications by ClinicalTrials.gov staff since 2005 and submitted papers are summarized in the following annotated bibliography, in reverse chronological order.

1. Ross JS, Mocanu M, Lampropulos JF, Tse T, Krumholz HM. Time to publication among completed clinical trials. *JAMA Intern Med*. 2013;():1-3. doi:10.1001/jamainternmed.2013.136.[60]

   Estimates the time between trial completion and publication using a sample of registered trials from ClinicalTrials.gov with associated MEDLINE-indexed peer-reviewed journal publications. Among the published trials in the sample, there was an average of 2 years between study completion and the publication date.

2. Zarin DA, Tse T. Unambiguous identification of obesity trials. *N Engl J Med*. 2013; 368:580-1.[61]

   Comments on the benefits of using ClinicalTrials.gov Identifiers (NCT Numbers) to identify clinical studies uniquely. The editors agreed, indicating that their policy is "to refer to clinical trials by their registration number. (p. 581)"

Table 1. Different Identifiers for the Same Clinical Studies.*

Drug, Identifier Used by Colman et al., and Identifier Used in References Cited by Colman et al.	Probable ClinicalTrials.gov Identifier	Publication (PubMed Identifier) Associated with Probable ClinicalTrials.gov Identifier
Belviq		
Studies 1 and 2 combined		
BLOOM	NCT00395135	Smith et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. N Engl J Med 2010; 363:245-56 (20647200)
BLOSSOM	NCT00603902	Fidler et al. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. J Clin Endocrinol Metab 2011; 96:3067-77 (21795446)
Study 3		
BLOOM-DM	NCT00603291	O'Neil et al. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. Obesity (Silver Spring) 2012;20:1426-36 (22421927)
Qsymia		
Study 1		
OB-302	NCT00554216	NA
Study 2		
OB-303	NCT00553787	Gadde et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomized, placebo-controlled, phase 3 trial. Lancet 2011;377:1341-52 (21481449)

* BLOOM denotes Behavioral Modification and Lorcaserin for Overweight and Obesity Management, BLOOM-DM Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus, BLOSSOM Behavioral Modification and Lorcaserin Second Study for Obesity Management, and NA not applicable.

3. Tse T, Zarin DA, Williams RJ, Ide NC. The role and importance of clinical trial registries and results databases. In: Gallin JI, Ognibene FP (eds), *Principles and Practice of Clinical Research*. 3rd ed. Amsterdam: Academic Press; 2012: 171-81.[5]

Chapter 15

The Role and Importance of Clinical Trial Registries and Results Databases

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Chapter Outline

4. Califf RM, Zarin DA, Kramer JM, Sherman RE, Aberle LH, Tasneem A. Characteristics of clinical trials registered in ClinicalTrials.gov, 2007-2010. *JAMA*. 2012;307(17):1838-47.[62]

Assesses the study design, funding source, enrollment size, and other fundamental attributes of clinical trials using aggregate data extracted from trials registered at ClinicalTrials.gov. Overall, this study found that "Clinical trials registered in ClinicalTrials.gov are dominated by small trials and contain significant heterogeneity in methodological approaches, including reported use of randomization, blinding, and DMCs [data monitoring committees]. (p. 1838)" The data also showed selected differences across trials in three therapeutic areas: oncology, cardiovascular, and mental health. For example, single group and non-randomized study designs were used more frequently to describe registered oncology trials than those in the other two specialties

Table 3. Trial Characteristics and Summary of Designs for All Interventional Trials, Registered October 2007–September 2010

	No./Total No. (%)			
	All Clinical Trials (n = 40 970)	Oncology (n = 8992)	Cardiovascular (n = 3437)	Mental Health (n = 3695)
Interventional group				
Single group	12 144/38 969 (31.2)	4822/7451 (64.7)	890/3394 (26.2)	754/3620 (20.8)
Parallel	21 782/38 969 (55.9)	2422/7451 (32.5)	2145/3394 (63.2)	2386/3620 (65.9)
Crossover	4351/38 969 (11.2)	140/7451 (1.9)	295/3394 (8.7)	353/3620 (9.8)
Factorial	692/38 969 (1.8)	67/7451 (0.9)	64/3394 (1.9)	127/3620 (3.5)
Missing	2001/40 970 (4.9)	1541/8992 (17.1)	43/3437 (1.3)	75/3695 (2.0)
Blinding				
Open	22 234/39 871 (55.8)	7342/8386 (87.6)	1731/3394 (51.0)	1451/3629 (40.0)
Single blind	4457/39 871 (11.2)	288/8386 (3.4)	484/3394 (14.3)	538/3629 (14.8)
Double blind	13 180/39 871 (33.1)	756/8386 (9.0)	1179/3394 (34.7)	1640/3629 (45.2)
Missing	1099/40 970 (2.7)	606/8992 (6.7)	43/3437 (1.3)	66/3695 (1.8)
Allocation				
Randomized	27 027/39 240 (68.9)	2919/8035 (36.3)	2481/3366 (73.7)	2893/3612 (80.1)
Nonrandomized	12 213/39 240 (31.1)	5116/8035 (63.7)	885/3366 (26.3)	719/3612 (19.9)
Missing	1730/40 970 (4.2)	957/8992 (10.6)	71/3437 (2.1)	83/3695 (2.2)

5. Wong E, Williams R. ClinicalTrials.gov: Requirements and implementation strategies. *Regulatory Focus*. 2012 May.[63]

Table 1. Sample Checklist for Identifying Potential Applicable Clinical Trials Subject to *FDAAA*

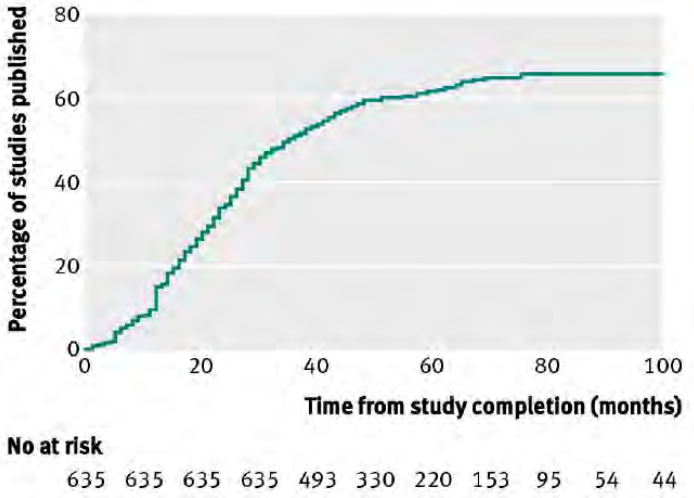
A study may be subject to the requirements of FDAAA*, if YES is answered to all 5 questions:	YES	NO
1. Was the study either a. initiated after 27 September 2007? b. initiated on or before 27 September 2007, and ongoing as of 26 December 2007?		
2. Is the study "interventional" (i.e., participants are assigned to interventions by protocol)?		
3. Does the study evaluate a "drug," "biological product" or "medical device" (whether or not approved for marketing in the United States)?		
4. Is the study **other than** either a a. "Phase 1" drug or biological product trial (e.g., it is a Phase 2 study)? b. "small feasibility" device trial (e.g., it is a pivotal study)?		
5. Does the study have at least one site located in the United States **or** is the study conducted under an IND or IDE?		

* For a complete definition and description of "applicable clinical trial", please see http://prsinfo.clinicaltrials.gov/fdaaa.html.(1,2)

6. Ross JS, Tse T, Zarin DA, Xu H, Zhou L, Krumholz HM. Publication of NIH funded trials registered in ClinicalTrials.gov: cross-sectional analysis. *BMJ*. 2012;344:d7292.[64]

Analyzes publication and publication time of NIH-funded clinical trials registered at ClinicalTrials.gov. Among a sample of trials that reached their completion dates in 2008, 46% (294/635) were published in MEDLINE-indexed journals within 30 months of completion. Even after a median of 51 months after completion, only 68% (432/635) of the trials had been published.

Fig 2 Cumulative percentage of studies published in a peer reviewed biomedical journal indexed by Medline during 100 months after trial completion among all NIH funded clinical trials registered within ClinicalTrials.gov



7. Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC. The ClinicalTrials.gov results database—update and key issues. *N Engl J Med*. 2011;364(9):852-60.[32]

Provides an overview of our experience with the results database and reports on specificity in entries for reporting outcome measure and apparent discrepancies in reported analysis populations.

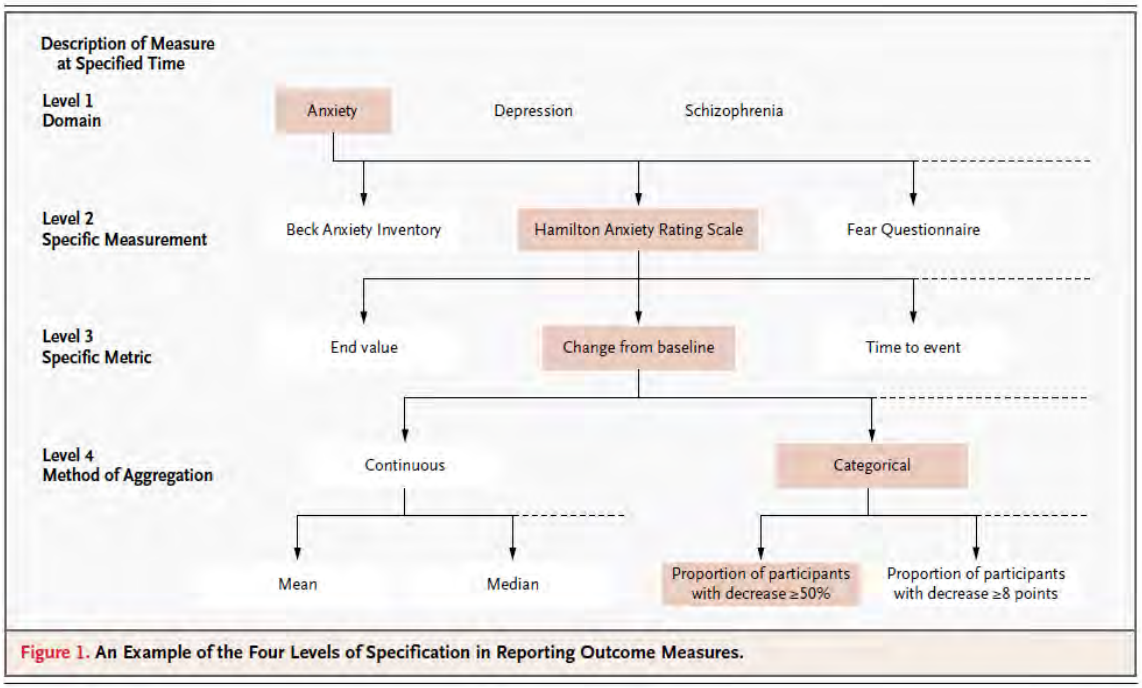
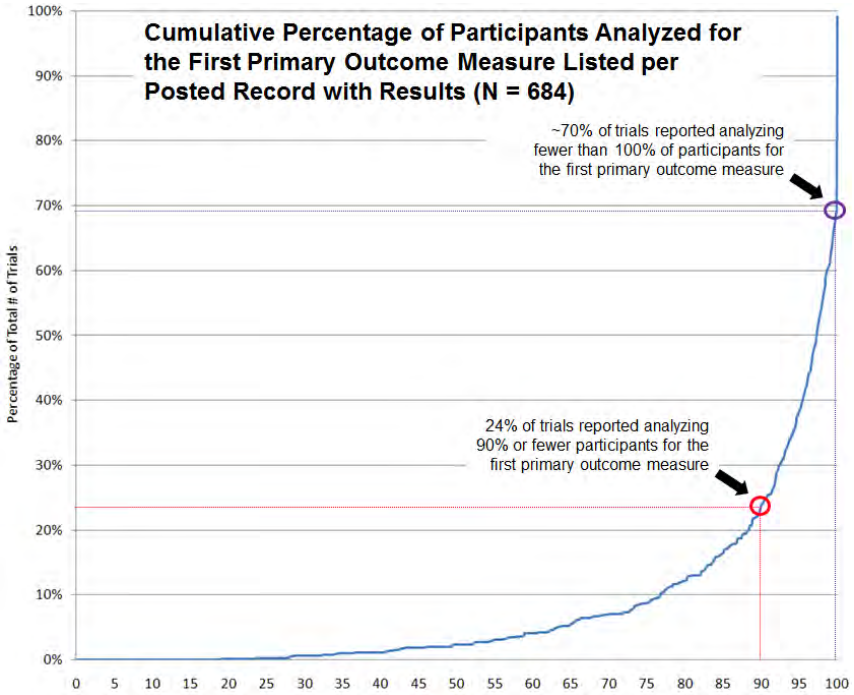


Figure 1. An Example of the Four Levels of Specification in Reporting Outcome Measures.



8. Zarin DA, Tse T. The effect of funding source on outcome reporting among drug trials [letter]. *Ann Intern Med*. 2011 Jan 18;154(2):137-8.[65]

9. Williams RJ, Tse T, Harlan WR, Zarin DA. Registration of observational studies: Is it time?. *CMAJ*. 2010;182(15):1638-42.[37]

   Evaluates and describes the evidence from the registration of observational studies at ClinicalTrials.gov to inform an ongoing question about the role of registering observational studies.

Appendix 2: Observational studies first received Nov. 1, 2007 through Mar. 26, 2010

		Time perspective*					
		Prospective	Cross-Sectional	Retrospective		Missing	Total
Study design†	Cohort	2 617	265	305		95	3 282
	Case only	995	191	140		39	1 365
	Case–Control	848	232	102		41	1 223
	Other†	136	78	25		14	253
	Missing	752	97	91		672	1 612
	Total	5 348	863	663		861	7 735

*Time perspective and study design (ClinicalTrials.gov data element – Observational Study Model) definitions available at: http://prsinfo.clinicaltrials.gov/definitions.html.
†Includes: case-crossover, ecologic or community, family based, and other.

10. Zarin DA, Califf R. Point Counterpoint: ClinicalTrials.gov: Bureaucratic nuisance or opportunity to improve the field? *APOR Newsletter*. 2010 Aug;6(2):3-5.[66]

    Responds to Raj SR. Point-Counterpoint: ClinicalTrials.Gov, a case of a dolphin caught in a fishnet? *APOR Newsletter*. 2010 Jan;6(1):2-3. "ClinicalTrials.gov has evolved through a complex but public debate about the obligations of those who perform experiments on human beings. While investigators who do Phase I studies are not required to register their studies or their results, we hope that the POR [patient-oriented research] community will embrace the spirit of transparency by voluntarily entering their studies with ClinicalTrials.gov. In doing so, they will help improve this important tool and, in turn, further accelerate the advancement of scientific methods and knowledge. (p. 5)"

11. Tse T, Williams RJ, Zarin DA. Reporting "Basic Results" in ClinicalTrials.gov. *Chest*. 2009;136(1):295-303.[24]

    Provides an overview of the results database and "tips for creating clear, understandable entries (p. 259)" for submission to the ClinicalTrials.gov results database, such as:
    - "…as in writing a manuscript for a journal, an individual familiar with the study design and data analysis (eg, a clinical investigator) will need to carefully consider ways to organize and annotate the results in order to optimize data presentation, especially for complex clinical study designs and results. (p. 296)"
    - "…it may be helpful to ask a colleague who is familiar with the overall research area but has not been involved in that particular trial to review the tables for comprehension and clarity. (p. 297)"
    - "Given that these summary data are displayed in a tabular format with minimal narrative, it is critical that the labels for the rows (representing measures and their units) and columns

(representing arms or comparison groups) be specified in a meaningful and precise manner to allow people not familiar with a study to interpret the data. (p. 303)"

12. Tse T, Williams RJ, Zarin DA. Update on registration of clinical trials in ClinicalTrials.gov. *Chest*. 2009;135:304-5.[34]

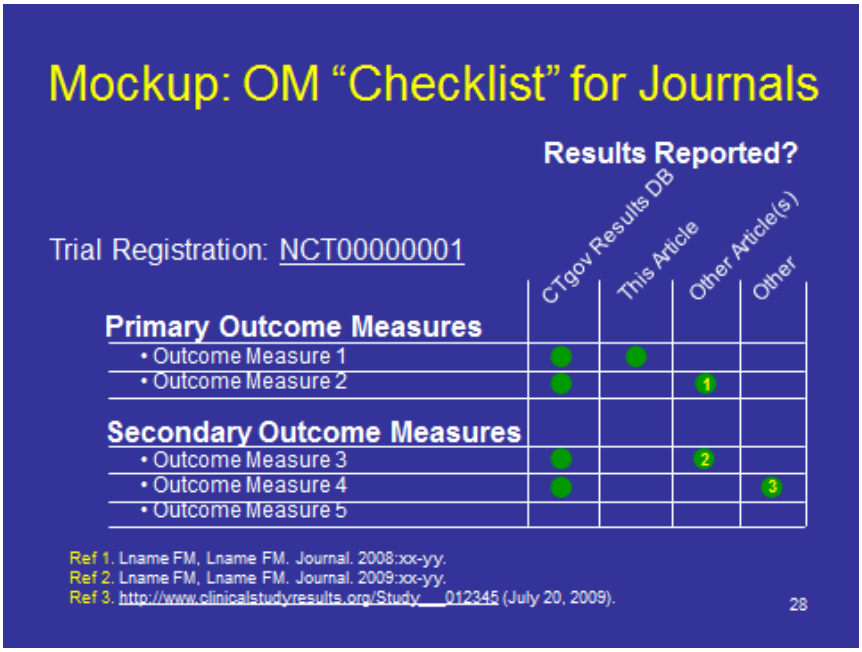
    Updates readers on the registration requirements under FDAAA 801.

13. Tse T, Zarin DA. Clinical trial registration and results reporting: ClinicalTrials.gov and FDAAA. *Food and Drug Law Institute Update*. 2009;1:18-22.[67]

    "...focuses on some key issues and experiences encountered during the implementation of the expanded registry and results database provisions over the past year (p. 28)" under FDAAA 801.

14. Zarin DA, Tse T, Williams RJ. Frequency and nature of changes in primary outcome measures. Presented at: *Sixth International Congress on Peer Review and Biomedical Publication*; September 2009; Vancouver, BC, Canada.[68]

    Explores ways to track and communicate important (vs. unimportant) changes to the specified primary outcome measure (i.e., notion of "principality") using current and archived ClinicalTrials.gov study records. In comparing Primary Outcome Measures reported in registration records and corresponding journal publications, discrepancies were found in 19% (19/100) of the pairs in the sample analyzed. Over 10% (18/150) of the registrations had substantive changes between the initial and updated Primary Outcome Measure information. A framework for assessing the level of specification in assessing Outcome Measures reported to ClinicalTrials.gov and a checklist or "score card" for identifying where each outcome measure had been published were proposed.



15. Williams RJ, Tse T, Zarin DA. Characterizing sponsor-imposed restrictions on disclosing results of clinical trials. Presented at: Sixth International Congress on Peer Review and Biomedical Publication; September 2009; Vancouver, BC, Canada.[69]

    Explores ways to categorize the Certain Agreements information in the ClinicalTrials.gov Results Database (e.g., providing more standardized options for describing restrictions on results disclosure imposed by sponsors).

Table 1. Schematic of Restrictions by Funder and Study Phase (8/17/09)

	PI Employed by Sponsor	PI Not Employed by Sponsor				Total
		No Disclosure Restrictions	Type of Disclosure Agreement			
			Embargo		"Other"*	
			≤60 Days	>60 & ≤180 Days		
All Results	81	98	35	72	308	594
Primary Sponsor						
Industry	52	31	27	72	306	488
Non-Industry	29	67	8	0	2	106
Study Type						
Observational	1	9	6	0	13	29
Interventional	80	89	29	72	295	565
Phase 1 – 2	16	24	12	28	110	190
Phase 3 – 4	47	42	16	44	177	326
N/A	17	23	1	0	8	49

* No descriptive text was provided for 9 "Other" Disclosure Agreement Types

Table 2. Analysis of "Other" Sponsor-Imposed Restrictions (8/17/09)

"Other" Restriction Areas	Number of Trials (N = 308)	Number of Sponsors (N = 57)*
After multi-site results disclosure	**153**	**22**
No time limit specified	65	8
Time limit specified, after study completion	88	15
12 months	60	8
18 months	22	3
24 months	7	4
Control of Content	**298**	**55**
PI not permitted to disclose**	59	6
Sponsor written consent/approval	19	15
Sponsor can change confidential information only or delay disclosure (e.g., patent pending)	103	20
Sponsor review & comment, including "Good faith"/"mutually agreeable" resolution of differences	60	20
Unspecified**	57	7
Embargoes with Content Restrictions	**182**	**46**
≤60 days	135	28
>60 and ≤180 days	16	9
Unspecified amount of time	31	18
Extended Embargo for Confidential Information	**62**	**15**

*Subcategories are not additive: a sponsor may have several types of agreements **Not associated with an embargo time period

16. Zarin DA, Tse T. Moving towards transparency of clinical trials. *Science*. 2008;319(5868):1340-42.[6]

    Discusses the need for promoting transparency in clinical trials and describes what recent registration and results reporting policies address and do not address using case studies to illustrate sample issues reflecting recent concerns.

CATEGORY OF PERCEIVED PROBLEM	SAMPLE ISSUES	RECENT EXAMPLES	ADDRESSED BY § 801?
Design, conduct, or analysis	• Appropriateness of comparator • Lack of data integrity/fraud • Insufficient informed consent	Arcoxia (*35*) Ketek (*34*) Trovan (*33*)	No
Lack of public information			
Clinical trial	• Suppression of trial existence and results	Paxil (*40*) Vioxx (*30*) Zetia (*31*)	Yes
Observational study	• Suppression of study existence and results withheld	Baycol (*39*) Trasylol (*36*)	No
Postmarket adverse event reports	• Failure to disseminate data	ICD* (*41*)	Pending†
Regulatory agency decision-making	• Delayed agency disclosure • Delayed agency action	Ketek (*34*) Avandia (*42*)	No

*Ventak Prizm 2 DR implantable cardioverter-defibrillator. †For example, postmarket surveillance is addressed in FDAAA, § 905.

Sample medical product safety concerns by category of perceived problems.

17. Drazen JM, Zarin DA. Salvation by registration [editorial]. *N Engl J Med*. 2007 Jan 11;356(2):184-5.[70]

    "The message should be clear to all investigators participating in clinical trials: before you enroll a patient in a study, be sure that there is a full and appropriate registration of the trial in a public database approved by the ICMJE (www.icmje.org). It could salvage a study report that otherwise would not be published. (p. 185)"

18. Zarin DA, Ide NC, Tse T, Harlan WR, West JC, Lindberg DA. Issues in the registration of clinical trials. *JAMA*. 2007;297(19):2112-20.[21]

    Discusses key challenges in registration, including the need to minimize inadvertent duplicate registrations, ensure that interventions have unambiguous names, and develop search engines that identify all trials that meet a user's specifications. It also proposes ways to coordinate trial registration internationally and explores challenges associated with developing a results database.

19. Zarin DA, Keselman A. Registering a clinical trial in ClinicalTrials.gov. *Chest*. 2007;131(3):909-12.[71]

    Provides tips and hints for submission of registration information to ClinicalTrials.gov, including:
    - "It is sometimes unclear whether a specific clinical study must be registered according to the law, or according to ICMJE or other policy mandates. As long as the study meets the

ClinicalTrials.gov requirements (human subjects with health or biomedical outcome measures), it is generally better to register it. (p. 911)"

- "A multisite study is generally regarded as a single study if the sites use the same protocol, and if the data are intended to be pooled for analysis. Each such study should be registered only once, regardless of the number of sites. (p. 911)"
- "Randomized controlled trials, or other trials with two or more arms, should list the interventions separately for each arm of the study. Drug interventions should be identified by a generic name if available; when there is not yet a generic name, the company serial number or the chemical name may be used. (p. 912)"

20. Ide NC, Loane RF, Demner-Fushman D. Essie: A concept-based search engine for structured biomedical text. *J Am Med Inform Assoc*. 2007;14(3):253-63.[36]

"**Abstract**. This paper describes the algorithms implemented in the Essie search engine that is currently serving several Web sites at the National Library of Medicine. Essie is a phrase-based search engine with term and concept query expansion and probabilistic relevancy ranking. Essie's design is motivated by an observation that query terms are often conceptually related to terms in a document, without actually occurring in the document text. Essie's performance was evaluated using data and standard evaluation methods from the 2003 and 2006 Text REtrieval Conference (TREC) Genomics track. Essie was the best-performing search engine in the 2003 TREC Genomics track and achieved results comparable to those of the highest-ranking systems on the 2006 TREC Genomics track task. Essie shows that a judicious combination of exploiting document structure, phrase searching, and concept based query expansion is a useful approach for information retrieval in the biomedical domain. (p. 253)"

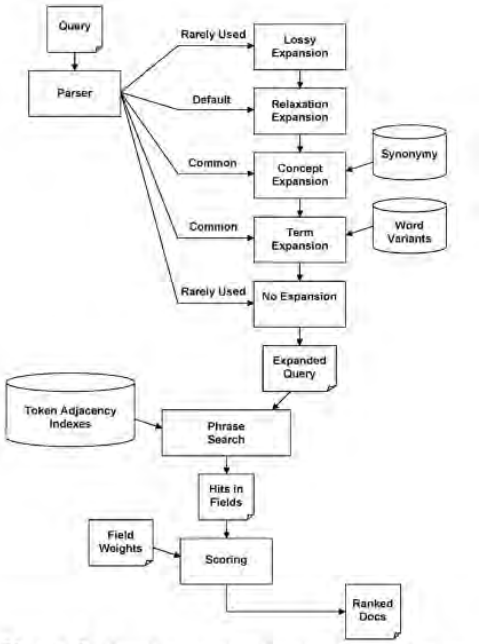


Figure 3. Search processing. Queries are parsed to extract search syntax and search texts. Syntax operators can control query expansion, but the default is relaxation expansion, which extends concept and term expansion. Expansion results in a large set of variations of the original search text, all of which are searched as phrases. Hits in the corpus are collected, and the documents containing them are scored, ranked, and returned.

21. Zarin DA, Tse T, Ide NC. Trial registration at ClinicalTrials.gov between May and October 2005. *N Engl J Med*. 2005 Dec 29;353(26):2779-87.[72]

Describes the impact of the ICMJE policy on the volume/rate of registration at ClinicalTrials.gov and identified a decrease in the use of nonspecific entries for Intervention Name. Overall, the number of registrations increased by 73% after the effective date of the ICMJE policy. While 76% of Industry-registered studies in the sample included information about the Primary Outcome Measure, 36% of the entries in a subsample were vague or non-specific.

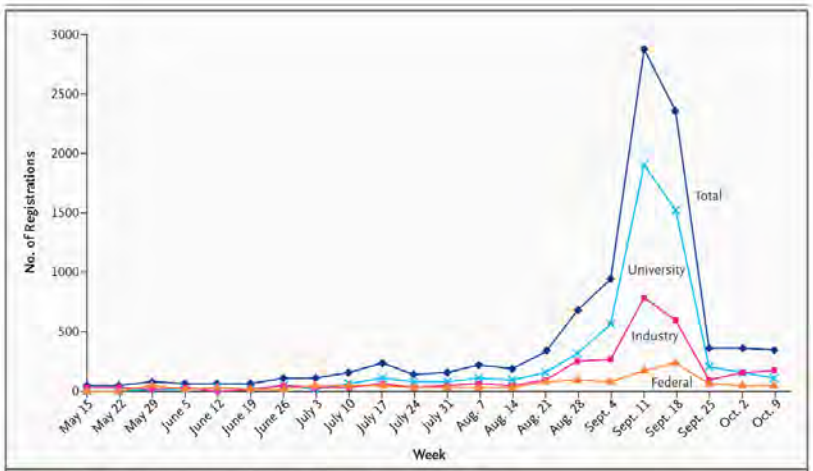


Figure 2. New Trials Registered in ClinicalTrials.gov, According to Week.

The figure shows the number of new registrations per week (beginning on the date indicated) from mid-May through early October 2005. The "Industry" category includes all commercial data providers; the "Federal" category includes the National Institutes of Health and other U.S. federal data providers; and the "University" category includes universities, foundations, and other providers.

N ENGL J MED 353;26 WWW.NEJM.ORG DECEMBER 29, 2005

Table 4. Attributes of Entries in "Primary Outcome Measure" Field.

Attribute	Frequency (N=657)*	Examples from ClinicalTrials.gov
	%	
Vague	17	Clinical response Tolerability
Domain without specific measure	19	Glucose regulation Severity of symptoms of schizophrenia
Specific measure without time frame	23	Intravenous glucose-tolerance test Structured clinical interview — positive and negative syndrome scale No. of hospitalizations
Time frame without specific measure	10	Tumor response at 3 mo Freedom from progression at 2 yr Improvement in glucose control over 16-wk period
Specific measure and time frame	31	Change in glycosylated hemoglobin from baseline to 6 mo Mortality from any cause at 30 days

* Frequencies are based on a review of 657 records from the top 10 drug companies, ranked according to data from IMS Health on the volume of U.S. sales.[21] Phase 2, 3, and 4 trials were included.

22. Hartung D, Zarin DA, Guise J-M, McDonagh M, Paynter R, Helfand M. Reporting discrepancies between the ClinicalTrials.gov results database and peer-reviewed publications. *Submitted*.

    In comparing entries in the ClinicalTrials.gov results database with results reported in the peer-reviewed literature, this study identifies and enumerates types of reporting discrepancies, such as description of prespecified primary outcome measures and the number of individuals with a serious adverse event.

23. Zarin DA, Tse T, Menikoff J. Scope of scientific and ethical review of clinical trials in the United States. *In progress*.

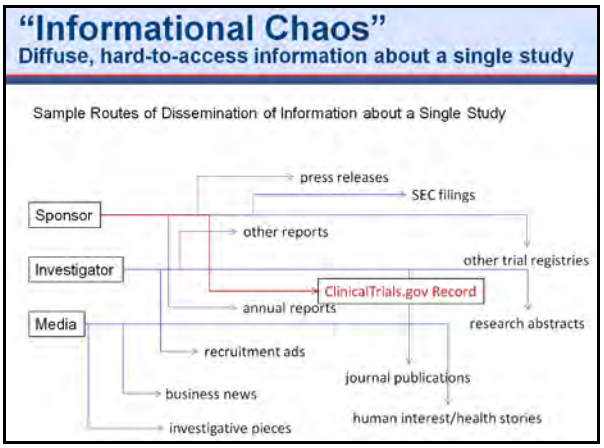
    Models and evaluates the pattern of coverage by two federal human subjects protection regulations (the Common Rule and FDA) across a sample of registered trials with at least one listed location in the U.S.

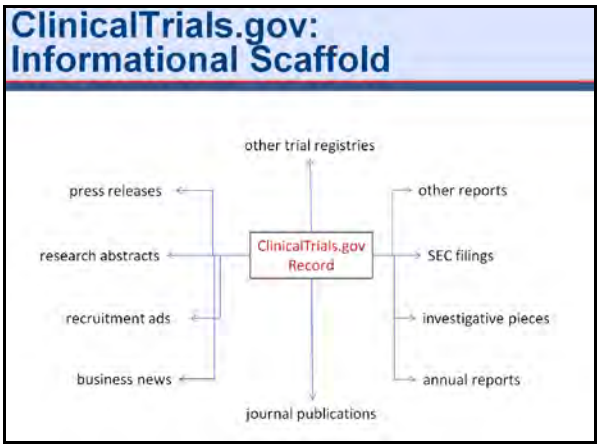
2. Selected Presentations at Invited Committees and Workshops

Selected presentations, with sample slides, are listed below in reverse chronological order.

1. **Editorial Board of the *New England Journal of Medicine*. Boston, MA. February 2013**.

The first slide depicts the current state of clinical trial information as "Informational Chaos" – diffuse and hard to access. The second slide depicts a conceptual model using ClinicalTrials.gov as an "informational scaffold," where each record links to all information about a single trial, even if scattered throughout the Web (e.g., linked by a unique NCT Number).





The next slides (1) illustrate the issues addressed by registration at ClinicalTrials.gov and (2) provide suggestions for ways that journal editors can use the registry to mitigate publication bias.

Goals of Trial Registration
Issues Addressed by ClinicalTrials.gov

- Helping potential participants find trials
- Addressing publication bias
  - By ensuring a publicly accessible denominator
- Allowing assessment of fidelity to the protocol and exposing selective publication of outcome measures

Publication Bias: What Can Journals Do?

- Continue to insist on trial registration
- Check the denominator
- At the time of publication, use generic name (along with code name) if possible

2. **Independent Data Monitoring Committee Training: Pilot Program and Think Tank. Durham, NC. January 2013**.

Slide showing an analysis of ClinicalTrials.gov registry data using responses to the optional "Has DMC?" data element.

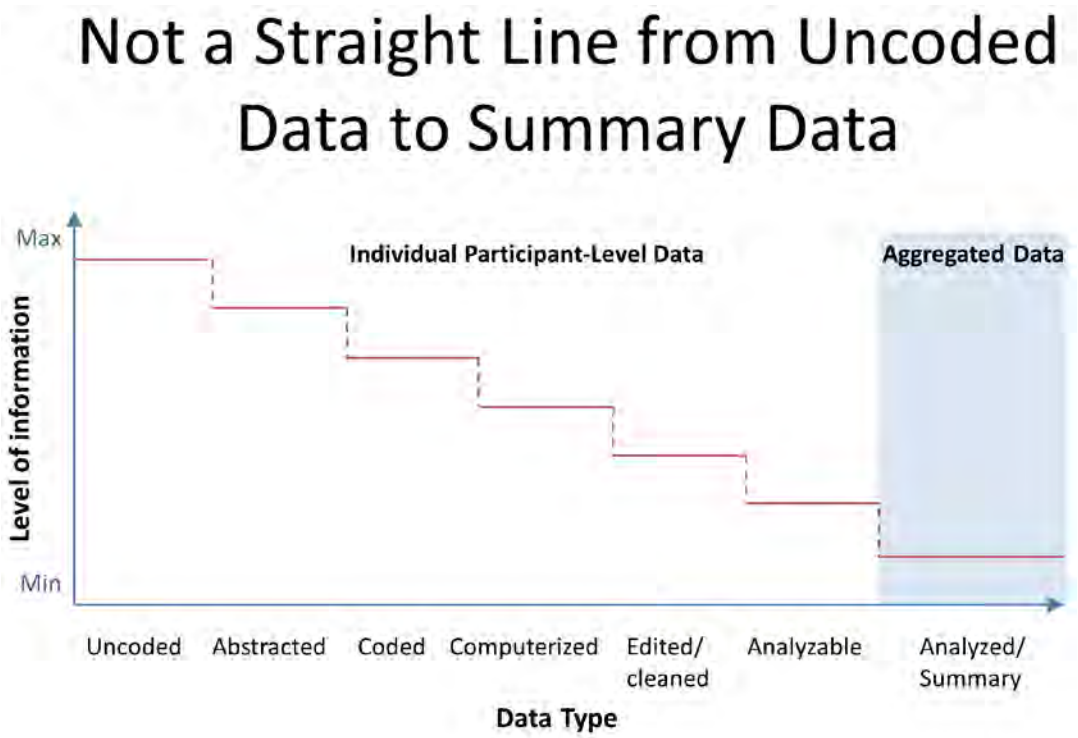
Has DMC? Status by "Large" Multisite RCTs*

Funding Class** (N = 4,518)	Has DMC = "Yes"	Has DMC = "No"	Has DMC = <Missing>
Industry (N = 2,729)	37%	47%	17%
NIH (N = 302)	68%	14%	18%
Other (N = 1,487)	53%	43%	3%

* Sample: Interventional studies first registered at ClinicalTrials.gov in 2011 and 2012 that indicate: Study Design Allocation = "Randomized" + No. of Arms > "1" + Enrollment > "50" + Number of Location > "1"
** Funding Class: "Industry" = at least 1 Industry Sponsor or Collaborator; "NIH" = at least 1 NIH (but NO Industry) Sponsor or Collaborator; "Other" = NO Industry or NIH Sponsor or Collaborator

3. **Sharing Clinical Research Data: A Workshop. Institute of Medicine. Washington, DC. October 2012**.

Dr. Zarin co-chaired Session 1: "Benefits of Sharing Clinical Research Data." She also presented a presentation in Session 2: "Design, Best Practices, and Lessons Learned." The title of her talk was, "The Limits of Summary Data Reporting: Lessons from ClinicalTrials.gov." The following slide depicts the "loss of information" that occurs through the clinical trial life cycle from data collection to data analysis – first within different types of individual participant-level data (e.g., uncoded vs. edited/cleaned data) and ultimately, aggregated data.

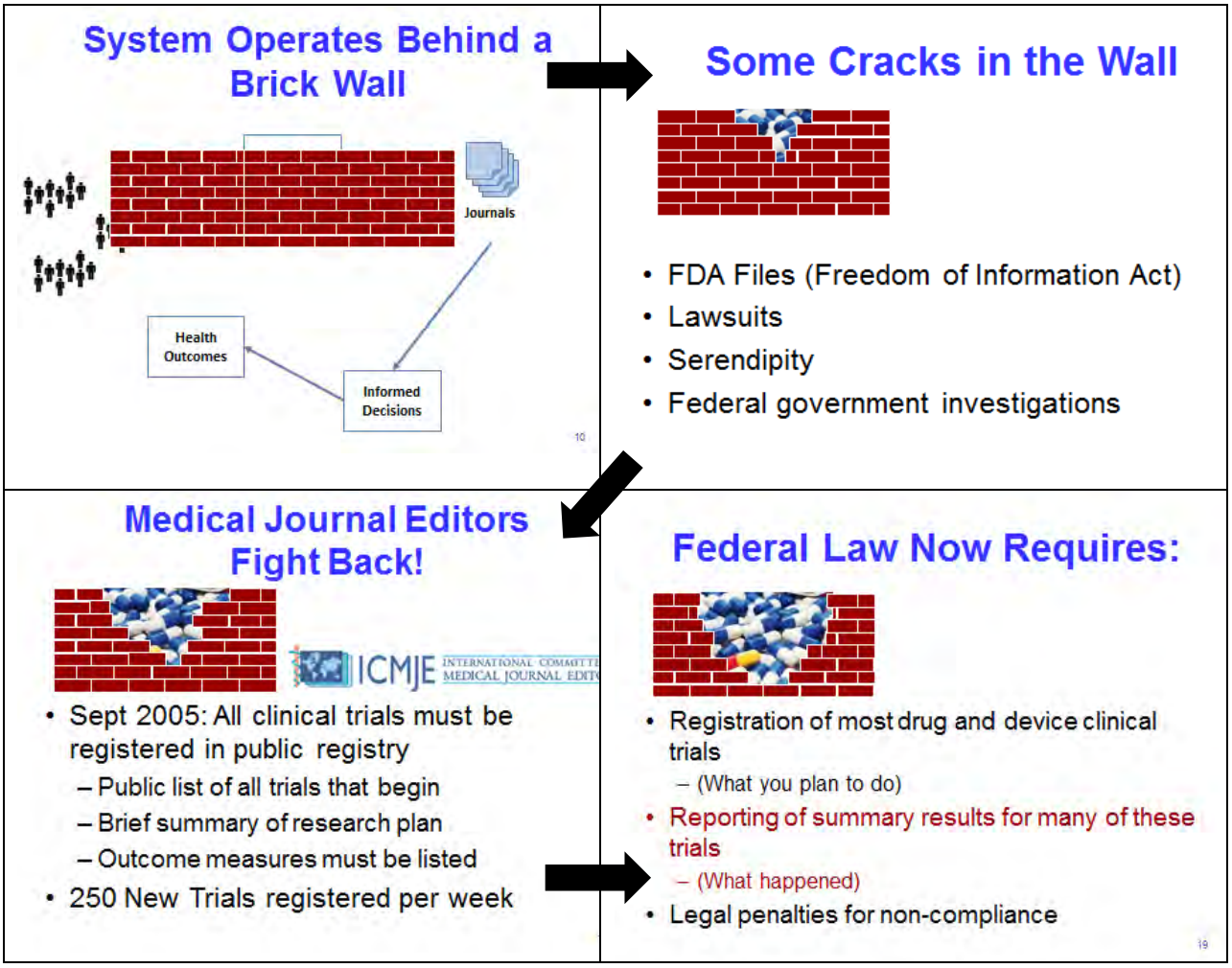


4. **The Program in Human Biology (HumBio) at Stanford University: 40th Reunion Presentation. Stanford, CA. October 2011**.

Dr. Zarin was a keynote speaker. In her presentation, "Clinical Trials & Evidence Based Medicine: What You Don't Know Might Hurt You," she explained the goals of evidence-based medicine and explained how results from all clinical trials are supposed to inform clinical practice. However, she noted that, "you can only receive evidence-based care IF:"

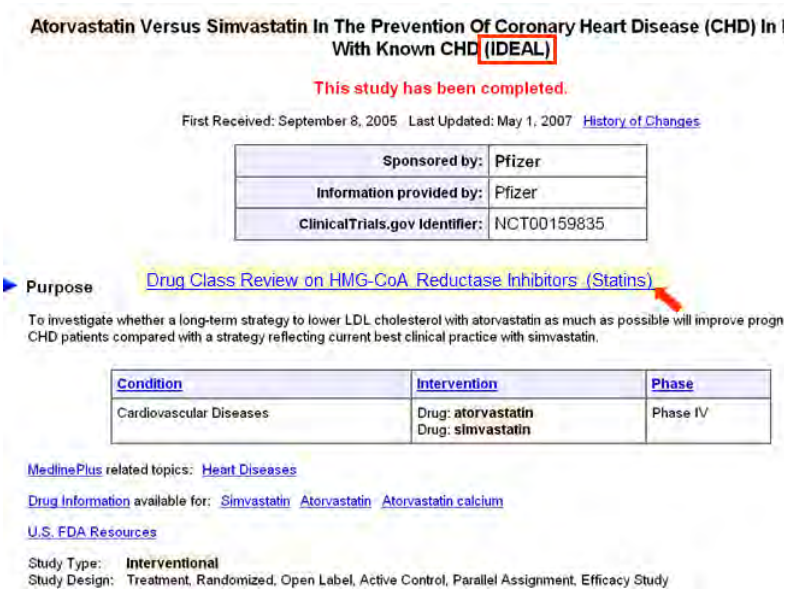
- **Other** people participate in clinical trials
- The results of those trials are **accurately** and **completely** reflected in medical journals.

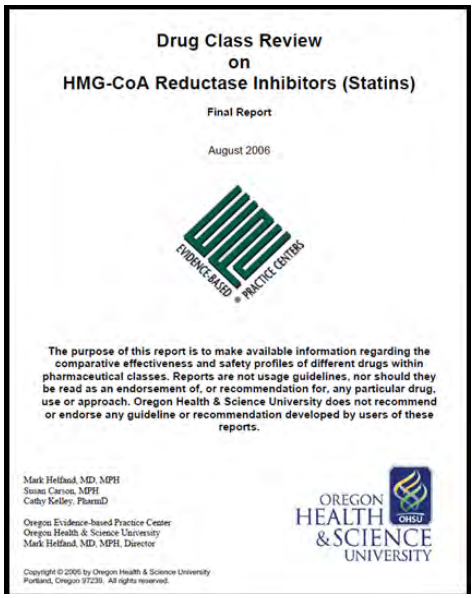
She also presented evidence from recent scandals that the "system operates behind a brick wall." Extending the metaphor, she explained how lawsuits, the journal editors' registration policy, and federal law are helping to tear down that wall through transparency.



5. **Health and Human Services (HHS) Secretary's Advisory Committee on Human Research Protection (SACHRP) Session on "Return of Aggregate Research Results." Washington, D.C. March 2011.**

Dr. Zarin briefed the committee on ClinicalTrials.gov results reporting at this public meeting. Among other enhancements to the system, she discussed the concept of linking ClinicalTrials.gov records to published systematic reviews, as appropriate. This would provide visitors to ClinicalTrials.gov with easy access to synthesized medical evidence selected from trials that have passed the "critical appraisal" process. For example, as shown in the slides, clicking on the link provided in a registered clinical trial comparing two statin drugs would open the most recent drug class review on statins from the Oregon Health and Science University (OHSU) Evidence-Based Practice Center.





6. **Forum on Drug Discovery, Development, and Translation. Institute of Medicine. Washington, DC. October 2010.**

In "A Random Walk Through the 'Sausage Factory'," Dr. Zarin highlighted three concerns about threats to the validity of reported trial data due to lack of transparency: (1) lack of key competencies among some who submit the data, (2) the complexity of study designs, and (3) a diffusion of responsibility for ensuring complete and accurate data.

7. **FDA Risk Communication Advisory Committee (RCAC) Meeting. Silver Spring, MD November 2009.**

Dr. Zarin briefed the RCAC on key issues in reporting trial information at ClinicalTrials.gov under FDAAA 801, including the requirement to submit adverse events information with summary results starting in September 2009.

3. Selected Collaborations

- Yale University School of Medicine Center for Outcomes Research and Evaluation (CORE): Harlan M. Krumholz, MD, and Joseph S. Ross, MD
    - Yale University Open Data Access (YODA) Project (http://medicine.yale.edu/core/projects/yodap/index.aspx): Dr. Zarin serves on the YODA Steering Committee.
    - Ross JS, Mocanu M, Lampropulos JF, Tse T, Krumholz HM. Time to publication among completed clinical trials. *JAMA Intern Med*. 2013;():1-3. doi:10.1001/jamainternmed.2013.136.[60]
    - Ross JS, Tse T, Zarin DA, Xu H, Zhou L, Krumholz HM. Publication of NIH funded trials registered in ClinicalTrials.gov: cross-sectional analysis. *BMJ*. 2012;344:d7292.[64]

- Evidence-based Practice Center (EPC) at Tufts Medical Center, Tufts University (current affiliation: Brown University): Joseph Lau, MD
    - The Comprehensive Clinical Trial Database (CCT DB) project: ongoing
    - The Systematic Review Data Repository (SRDR) project (Supported by AHRQ)
    - Earley A, Lau J, Uhlig K. Haphazard reporting of deaths in clinical trials: a review of cases of ClinicalTrials.gov records and matched publications-a cross-sectional study. *BMJ Open*. 2013 Jan 18;3(1). pii: e001963.[51] (Supported by NLM under a professional services contract)

- Clinical Trials Transformation Initiative (CTTI), Duke University: Robert M. Califf, MD
    - Development of the CTTI database for the Aggregate Analysis of ClinicalTrials.gov (AACT) (https://www.ctti-clinicaltrials.org/project-topics/clinical-trials.gov/aact-database)
    - Califf RM, Zarin DA, Kramer JM, Sherman RE, Aberle LH, Tasneem A. Characteristics of clinical trials registered in ClinicalTrials.gov, 2007-2010. *JAMA*. 2012;307(17):1838-47.[62]
    - Tasneem A, Aberle L, Ananth H, Chakraborty S, Chiswell K, McCourt BJ, Pietrobon R. The database for aggregate analysis of ClinicalTrials.gov (AACT) and subsequent regrouping by clinical specialty. *PLoS One*. 2012;7(3):e33677.[73]

- Office for Human Research Protections (OHRP), U.S. Department of Health and Human Services (DHHS): Jerry A. Menikoff, MD, JD
    - Zarin DA, Tse T, Menikoff J. Scope of scientific and ethical review of clinical trials in the United States. *In progress*.

- Oregon Evidence-Based Practice Center (EPC), Oregon Health Sciences University (OHSU): Mark Helfand, MD, MS, MPH
    - Hartung D, Zarin DA, Guise J-M, McDonagh M, Paynter R, Helfand M. Reporting discrepancies between the ClinicalTrials.gov results database and peer-reviewed publications. *Submitted*. (Supported by NLM under a professional services contract)

    - Carson S, Cohen A, Hersh W, Brown N, Helfand M. Systematic evaluation of web-based, publicly accessible clinical trials results databases. Presentation at the *14th Cochrane Colloquium*, Dublin, 23-26 October 2006. Abstract available at http://www.imbi.uni-freiburg.de/OJS/cca/index.php?journal=cca&page=article&op=view&path[]=5338. (Supported by NLM under a professional services contract)
    - Systematic Evaluation of Four Publicly-Accessible Clinical Trial Registries and Results Databases. Internal Report. 2005. (Supported by NLM under a professional services contract)

- Harvard Medical School: Jerry Avorn, MD
    - Evaluating the Design and Public Display of a Clinical Trial Results Database (Supported by NLM under a professional services contract)

- University of Ottawa: David Moher, PhD
    - Developing Frequently Asked Questions on Adverse Events for posting on ClinicalTrials.gov (Supported by NLM under a professional services contract)

Appendix B: List of Figures and Tables