The Role and Importance of Clinical Trial Registries & Results Databases

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http://ClinicalTrials.gov

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Outline

- Background
- Current Policies
- About ClinicalTrials.gov
- Registering Clinical Trials at ClinicalTrials.gov
  - Points to Consider
- Reporting Results to ClinicalTrials.gov
  - Points to Consider
- Individual Participant-Level Data (IPD)
- Final Thoughts

Background

Why is disclosure important?

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Evidence Based Medicine (EBM)

- Clinical and policy decisions should be informed by evidence regarding the benefits, risks and other burdens associated with all possible alternatives.
- Clinical trials are a key component of the body of scientific evidence that must be used to make decisions.
- Most decision makers depend on summary data from journal articles

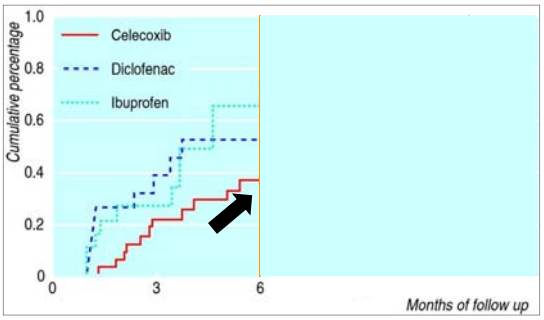
What's All The Fuss About?

- Suppression of research results impedes scientific process
- Suppression of clinical trial data is particularly problematic:
  - Trials depend on human volunteers
  - Trial results inform our medical decisions

Three Key Problems

- Not all trials are published
- Publications do not always include all prespecified outcome measures
- Unacknowledged changes are made to the trial protocol that would affect the interpretation of the findings
  - e.g., changes to prespecified outcome measures

Kaplan-Meier estimates for ulcer complications according to traditional definition. Results are truncated after 12 months, no ulcer complications occurred after this period. Adapted from Lu 2001.



Source: Jüni P, Rutjes AW, Dieppe PA. *BMJ*. 2002 Jun 1;324(7349):1287-8.

Internal Corporate Email

"They swallowed our story, hook, line and sinker…"

ClinicalTrials.gov and Levels of "Transparency"

Source: Zarin DA, Tse T. *Science*. 2008.

Trial Reporting System (TRS)

1. **Prospective Registration**
   - Documents existence and enables tracking of trials
     - Assists potential participants in finding trials
     - Provides a "denominator" to assess research enterprise
   - Date stamped protocol details
     - Supports assessing fidelity of reporting to pre-specified research plan
2. **Summary Results Reporting**
   - Provides a minimum set of results data for each trial
   - Structured data enables accurate search and retrieval
     - Contribute to evidence-based medicine
3. **Individual Participant Data (IPD) Sharing**
   - Audit trail for summary results reporting
   - Enables re-analysis of trial data
   - Enables combining of trial data with other data

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Zarin DA, Tse T. PLoS Med 2016;13(1):e1001946.

Definitions

- **Registration**: "the process for making key summary information about interventional studies using human volunteers accessible to the public via a web-based system, from study initiation to completion"
- **Results Reporting**: "making summary information about study results available in a structured, publicly accessible web-based results database"

Registration

- 208,114 registered studies (trials & observational)
  - About 500 new studies registered each week
  - Study locations in all 50 states and > 190 countries
  - 1/3 of trials are registered "late" (> 3 mo. after start)
- 300,000+ studies accessible in World Health Organization (WHO) Search Portal
  - Includes ClinicalTrials.gov and 15 other registries
- Total number of trials in U.S. and worldwide not known
  - Registries likely to be most comprehensive for trials that are subject to legal reporting requirements

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ClinicalTrials.gov and WHO data as of 2/8/2016

Summary Results Reporting

- 20,000 registered studies with results
  - About 100 studies with results submitted each week
- FDAAA 801 requires "applicable clinical trials" of approved or cleared drugs and devices to have results submitted within 1 year of primary completion date
  - About 42% of results posted on ClinicalTrials.gov are not subject to FDAAA 801
- Public interest in overall rates of results reporting

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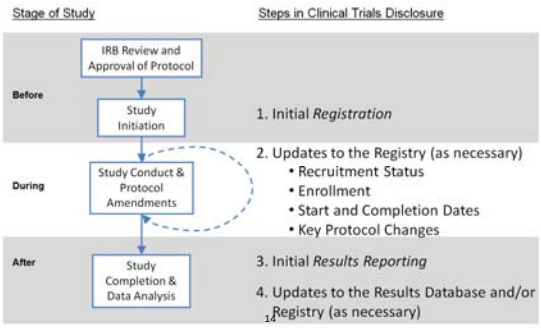
ClinicalTrials.gov data as of 2/8/2016

Stages in Disclosure Parallel the Research Life Cycle



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Category	Reasons
Human subject protections	• Allow potential participants to find studies • Assist ethical review boards and others to determine appropriateness of studies being reviewed (e.g., harms, benefits, redundancy) • Promote 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)

Current Policies

US and International

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Selected Int'l Policies & Laws

- **ICMJE** requires registration of all clinical trials
- **European Union** requires registration and results reporting of certain drug and biologic clinical trials
- **Declaration of Helsinki** states that all research studies involving human subjects must be registered & researchers have a responsibility to make research results publicly available
- **WHO** considers registration a "scientific, ethical and moral responsibility" & ethical imperative to report results
- **And many others …**

https://clinicaltrials.gov/ct2/manage-recs/background#WhyRegister

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Key Disclosure Policies for US investigators

- ICMJE – Journal Editors Policy (2004)
  - Prospective registration of all clinical trials as a precondition for publication of the study results
  - Effective Date: September 13, 2005
- FDA Amendments Act, Section 801 (2007)
  - Enacted on September 27, 2007
  - Expanded Trial Registration Requirements (FDAMA)
  - Added New Results Reporting Requirement
  - Added Enforcement Provisions: e.g.,
    - Civil monetary penalties (up to $10,000/day)
    - Withholding of NIH grant funds
  - Current Status: Proposed Rule issued for public comment (Deadline: March 23, 2015)

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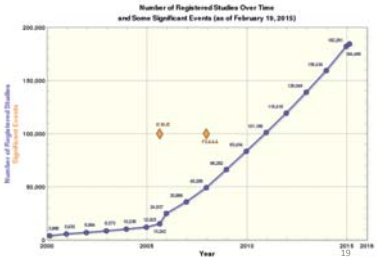
Rate of New Registrations

- After FDAMA (2000):
  25 – 30 registrations per week
- After ICMJE (2005):
  200 – 250 per week
- After FDAAA (2007):
  300 – 350 per week
- After NPRM (2014):
  ~500 per week



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ClinicalTrials.gov Reporting Policies

Reporting Requirement	FDAAA NAPRM	Draft NIH Policy	ICMJE Policy
Scope	Registration & Results Reporting	Registration & Results Reporting	Registration
Phase	Not Phase 1	All	All
Intervention Type	Drugs, Biologics, & Devices regulated by the FDA	All	All
Funding	Any	NIH	Any
Enforcement	Up to $10,000/day; Loss of US Federal funding	Loss of NIH funding	Refusal to publish

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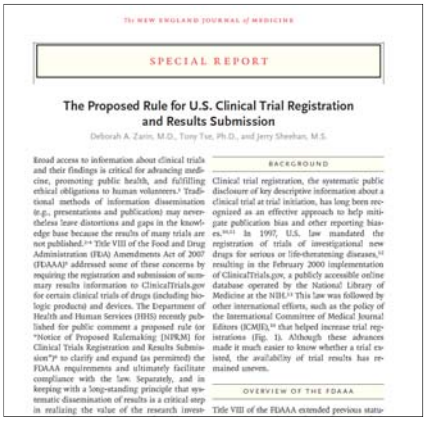

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

The Proposed Rule for U.S. Clinical Trial Registration and Results Submission

Deborah A. Zarin, M.D., Tony Tse, Ph.D., and Jerry Sheehan, M.S.

Broad access to information about clinical trials and their findings is critical for advancing medicine, promoting public health, and fulfilling ethical obligations to human volunteers.[1] Traditional methods of information dissemination (e.g., presentations and publication) may nevertheless leave distortions and gaps in the knowledge base because the results of many trials are not published.[2-4] Title VIII of the Food and Drug Administration (FDA) Amendments Act of 2007 (FDAAA)[5] addressed some of these concerns by requiring the registration and submission of summary results information to ClinicalTrials.gov for certain clinical trials of drugs (including biologic products) and devices. The Department of Health and Human Services (HHS) recently published for public comment a proposed rule (or "Notice of Proposed Rulemaking" [NPRM] for Clinical Trials Registration and Results Submission")[6] to clarify and expand (as permitted) the FDAAA requirements and ultimately facilitate compliance with the law. Separately, and in keeping with a long-standing principle that systematic dissemination of results is a critical step in realizing the value of the research investi-

BACKGROUND

Clinical trial registration, the systematic public disclosure of key descriptive information about a clinical trial at trial initiation, has long been recognized as an effective approach to help mitigate publication bias and other reporting biases.[7-11] In 1997, U.S. law mandated the registration of trials of investigational new drugs for serious or life-threatening diseases,[12] resulting in the February 2000 implementation of ClinicalTrials.gov, a publicly accessible online database operated by the National Library of Medicine at the NIH.[13] This law was followed by other international efforts, such as the policy of the International Committee of Medical Journal Editors (ICMJE),[14] that helped increase trial registrations (Fig. 1). Although these advances made it much easier to know whether a trial existed, the availability of trial results has remained uneven.

OVERVIEW OF THE FDAAA

Title VIII of the FDAAA extended previous statu-

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N Engl J Med. 2014 Dec 24. Published online

Status of Regulations and Policies

- Public comment period ended March 23, 2015
- HHS is currently reviewing and addressing submitted comments
- Publish Final Rule for FDAAA
- NIH will also publish final policy for trial reporting

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Studies Estimating Rates of FDAAA Results Reporting

	Prayle et al. (2012)	Anderson et al. (2015)	Anderson et al. (2015) – subsample
Sample	Trials likely to be subject to FDAAA* completed 1/1/2009 – 12/31/2009 (analyzed Jan 2011)	Trials likely to be subject to FDAAA* completed 1/1/2008 – 8/31/2012 (analyzed Sep 2013)	Main sample + assessment of approval status of product in trial
Trials in Sample	**738**	**13,327**	**205**
Study Follow-up after PCD	Up to 2 years	Up to 5 years	Up to 5 years
Overall Rate of Results Reporting			
All Trials	**22%**	**38%**	**--**
Industry	**40%**	**42%**	**79 – 80%**
NIH	**8%**	**39%**	**49 – 50%**
Other	**7%**	**28%**	**42 - 45%**

* Methods for determining "subject to FDAAA" were different in each analysis and both had limitations

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Prayle AP et al. *BMJ*. 2012: Anderson M et al. *N Engl J Med*. 2015.

STAT News – December 13, 2015

- Assessed whether institutions reported results and whether they were reported "on time"
  - Analysis included trials of unapproved drugs or devices (if a certification was not on file)
- "The worst offenders included four of the top 10 recipients of federal medical research funding from the National Institutes of Health: Stanford, the University of Pennsylvania, the University of Pittsburgh, and the University of California, San Diego."

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http://www.statnews.com/2015/12/13/clinical-trials-investigation/

RESEARCH

OPEN ACCESS

Publication and reporting of clinical trial results: cross sectional analysis across academic medical centers

Ruijun Chen,[1] Nihar R Desai,[2,3] Joseph S Ross,[3,4,5,6] Weiwei Zhang,[7] Katherine H Chau,[1] Brian Wayda,[7] Karthik Murugiah,[8] Daniel Y Lu,[9] Amit Mittal,[8] Harlan M Krumholz[2,3,5,6]

ABSTRACT

OBJECTIVE
To determine rates of publication and reporting of results within two years for all completed clinical trials registered in ClinicalTrials.gov across leading academic medical centers in the United States.

DESIGN
Cross sectional analysis.

SETTING
Academic medical centers in the United States.

PARTICIPANTS
Academic medical centers with 40 or more completed interventional trials registered on ClinicalTrials.gov.

METHODS
Using the Aggregate Analysis of ClinicalTrials.gov database and manual review, we identified all interventional clinical trials registered on ClinicalTrials.gov with a primary completion date between October 2007 and September 2010 and with a lead investigator affiliated with an academic medical center.

MAIN OUTCOME MEASURES
The proportion of trials that disseminated results, defined as publication or reporting of results on ClinicalTrials.gov, overall and within 24 months of study completion.

RESULTS
We identified 4,347 interventional clinical trials across 51 academic medical centers. Among the trials, 1005 (23%) enrolled more than 100 patients, 1216 (28%) were double blind, and 2769 (50%) were phase II through IV. Overall, academic medical centers disseminated results for 2892 (66%) trials, with 1560 (35.9%) achieving this within 24 months of study completion. The proportion of clinical trials with results disseminated within 24 months of study completion ranged from 16.2% (6/37) to 55.3% (57/103) across academic medical centers. The proportion of clinical trials published within 24 months of study completion ranged from 10.8% (4/37) to 40.3% (31/77) across academic medical centers, whereas results reporting on ClinicalTrials.gov ranged from 1.6% (2/123) to 40.2% (72/177).

CONCLUSIONS
Despite the ethical mandate and expressed values and mission of academic institutions, there is poor performance and noticeable variation in the dissemination of clinical trial results across leading academic medical centers.

Introduction
Randomized clinical trials are the ideal means for evaluating the efficacy and safety of medical drugs and devices. Timely dissemination of the findings from clinical trials is a prerequisite for ensuring that clinical decisions made by patients and physicians reflect the best scientific evidence, and that future scientific investigation benefits from previous inquiry. Dissemination is principally achieved through publication in peer reviewed biomedical journals as well as through public reporting of results on clinical trial registries.[1-6] However, a large body of research found that between 29% and 50% of clinical trials remain unpublished, sometimes years after study completion.[3-5] Similarly, studies have shown that the results of many clinical trials are

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Need for Org. Infrastructure to Support Results Reporting

ClinicalTrials.gov Reporting: Strategies for Success at an Academic Health Center

Erin K. O'Reilly, Ph.D., R.A.C.[1], Nancy J. Hassell, C.C.R.P.[1], Denise C. Snyder, M.S., R.D.[1], Susan Natoli, M.S.W., C.C.R.P.[1], Irwin Liu, Ph.D.[1,2], Jackie Rimmler, M.S.[1,3], Valerie Arnspacher, B.S.[1,2], Bruce K. Burnett, Ph.D., R.A.C.[1,2], Amanda B. Parish, Ph.D. R.A.C.[1], Jelena P. Berglund, Ph.D., R.A.C.[1], and Mark Stacy, M.D.[1,2]

Abstract
The Food and Drug Administration Amendments Act of 2007 (FDAAA 2007, US Public Law 110-985) mandated registration and reporting of results for applicable clinical trials. Meeting these registration and results reporting requirements has proven to be a challenge for the academic research community. Duke Medicine has made compliance with registration and results reporting a high priority. In order to create uniformity across a large institution, a written policy was created describing requirements for clinical trials disclosure. Furthermore, a centralized resource group was formed with three full time staff members. The group not only ensures compliance with FDAAA 2007, it also acts as a resource for study teams providing hands-on support, reporting, training, and ongoing education. Intensive resourcing for results reporting has been crucial for success. Due to implementation of the institutional policy and creation of centralized resources, compliance with FDAAA 2007 has increased dramatically at Duke Medicine for both registration and results reporting. A consistent centralized approach has enabled success in the face of changing agency rules and new legislation. Clin Trans Sci 2015; Volume 8: 48–51.

Keywords: trials registration, trials reporting, FDAAA 2007, ClinicalTrials.gov, applicable clinical trial

Introduction
Examples of selective publication bias historically made the case for clinical trials registries,[1] and led to the posting of the Clinical Trials Data Bank (http://clinicaltrials.gov) in February 2000 in response to the Food and Drug Administration Modernization Act of 1997 (FDAMA). Section 113 of FDAMA required the establishment of a registry for clinical trials of experimental treatments (drug and biological) for patients with serious or life-threatening diseases or conditions. Since then, the registry has been widely expanded to accommodate the requirements of FDAAA 2007. Specifically, section 801 of the Food and Drug Administration Amendments (ICMJE) incorporated the requirement for registration of clinical trials in a public trials registry at or before the time of first patient enrollment as a condition of consideration for publication.[4] While only 14 journals are official members of the ICMJE, over 1,600 other medical journals have purportedly committed to follow ICMJE recommendations.[5]

Finally, in addition to legal, funding, and publication considerations, mandatory inclusion of the NCT number on Medicare claims for routine costs of qualifying clinical trials became effective as of January 2014. Thus, studies that would not require

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O'Reilly EK, et al. Clin Transl Sci. 2015 8(1):48-51.

Examples of Other Relevant Policies

- Veterans Affairs funded clinical trials
- PCORI funded studies
- Trials conducted under the CMS "coverage with evidence development"

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Impact of Reporting Policies on US AMCs

- Most AMCs have over 50% of their trials under a reporting policy (median: 58.6%)
- AMCs need to modify their incentive structure, and need to provide support for their investigators
- Policies hold the AMC accountable, not just the investigator

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About ClinicalTrials.gov

http://ClinicalTrials.gov/

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Registration at ClinicalTrials.gov

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Scope of Registry

ClinicalTrials.gov permits the registration of any biomedical or health-related research studies in humans that meet the following two requirements:

1. Conformance with any applicable human subject protections or ethics review regulations (or equivalent) (e.g., institutional review board (IRB) approval) AND
2. Conformance with any applicable regulations of the national (or regional) health authority (or equivalent)

ClinicalTrials.gov Statistics

(as of 2/25/2016)

207 million pages views *monthly*
65,000 unique visitors *daily*

	Registration	Results
Total	209,390	20,300
Type of Trial		
Observational	39,740 (19%)	1,313 (6%)
Interventional*	168,702 (81%)	18,987 (94%)
- Drug & Biologic	105,525	15,454
- Behavioral, Other	47,402	2,995
- Surgical Procedure	18,254	979
- Device**	18,461	2,077

* Intervention types not additive; study record may include more than one type of intervention
**610 applicable device clinical trials submitted, but qualify for "delayed posting" under FDAAA

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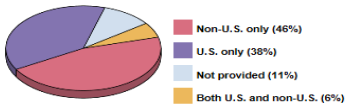
ClinicalTrials.gov Statistics

Percentage of Registered Studies by Location (as of February 25, 2016)
Total N = 209,390 studies



Location	Number of Registered Studies and Percentage of Total (as of February 25, 2016)
Non-U.S. only	96,225 (46%)
U.S. only	78,924 (38%)
Not provided	22,071 (11%)
Both U.S. and non-U.S.	12,170 (6%)
Total	209,390

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Content of ClinicalTrials.gov Records

- One record per trial
- Registration record
  - Submitted at trial initiation
  - Summarizes information from trial protocol
    - Condition
    - Interventions
    - Design, etc
  - Includes recruitment information (e.g., eligibility, locations)
- Results record
  - Submitted after trial completion
  - Summarizes trial results
    - Participant flow
    - Baseline characteristics
    - Outcome measures (including statistical analyses)
    - Adverse events

Public Archive for Records

- Changes can and should be made to records
  - Estimated dates become “actual” dates
  - Estimated enrollment becomes “actual”
  - Other protocol changes
  - Overall recruitment status changes
  - Results may be added or changed
- All changes are publicly “tracked”

Registry: Minimal Dataset
(Needed to Describe a Study)

- Descriptive information
  - e.g., phase, study design, outcomes
- Recruitment information
  - e.g., eligibility criteria, recruitment status
- Location and contact information
  - e.g., sponsor name, facility, and contact
- Administrative data
  - e.g., organization's protocol ID, secondary IDs

Registration: Points to Consider

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"Interventional" vs. "Observational"

- Interventional Study ("Clinical Trial)
  - Participants assigned to receive one or more or no interventions based on a protocol
- Observational Study
  - Participants identified as belonging to study groups, not assigned by researcher
- Note: Many Diagnostic studies are interventional

What is a Single Clinical Trial?

- Single core protocol, regardless of the number of sites
- Collected data are intended to be combined and analyzed in aggregate
- Systems to prevent "duplicate registration"
- Follow-on studies?
  - Considered a single trial if defined in one protocol and includes same participants
  - May be a separate trial if re-consent required and/or involves participants not in the "initial" study

Importance of the Protocol

- Research plan that includes
  - Prespecified hypotheses
  - Prespecified methods, including explicitly defined variables of interest
- The validity of any statistical analyses or conclusions is based on adherence to those prespecified methods.
- Registration provides a summary of the protocol
- Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT, 2013)

Keeping Information Up to Date

- All data must be current
- Some data elements expected to change
  - e.g., recruitment status, anticipated start and completion dates
- Others only change if the protocol has been amended
  - e.g., modification of a primary outcome measure
- All changes tracked in the Archive

Results Reporting to ClinicalTrials.gov

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The Results Database

- FDAAA enacted in September 2007
- Results Database launched in Sept 2008
- Design based on statutory language and informed by CONSORT and other relevant standards
- Requires reporting of “minimum data set” that was specified in the trial protocol
- Tabular format for data with minimal narrative
- EMA has developed a database based on our model

4 Scientific Modules

- Participant Flow
- Baseline Characteristics
- Outcome Measures
- Adverse Events

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Key Concepts

- The Basic Results Database requires the reporting of what was done; it does not require a change in study design or study procedures;
- The intended audience is "readers of the medical literature." It is not intended to inform the lay public. However, the tables need to be informative with minimal narrative text.

Results Review Focus

- Concept: Tables should convey the design, conduct and analysis of the data
- Logical table structure
- Measure Title/Description and Units of Measure consistent
- Complete scale information
  - Construct and domain
  - Best/worst values
  - "Units on a scale" if no other units

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Review Criteria Overview

- Complete and meaningful entries
  - ["Zarin scale" without further detail; "IOP" without explanation]
- Logic and internal consistency
  - [number of participants must be consistent across modules; time to event must be measured in a unit of time]
- Apparent validity
  - [624 years cannot be the mean age]

Examples of Incoherent Entries

- 823.32 mean hours sleep/day
- "time to survival"
- 36 eyeballs in study of 14 people
- "mean time to seizure" = 18 people
- "first occurrence of all cause mortality (adjudicated)"

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Results Reporting: Points to Consider

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Data Preparation

- Summarizing results is similar in complexity to preparation of results for journal publication
- Must understand the study design and analytic plan
- Must have basic understanding of principles of clinical trial conduct and analysis
- Must have access to necessary data:
  - Participant flow; Baseline characteristics
  - Outcome measures; Adverse events

Relation to Publication

- Both seek to report accurate and informative data
- ClinicalTrials.gov Results Reporting
  - Does not reject submissions
  - Permits disclosure of all outcome measures
  - Tabular data only
- Peer-reviewed Journal Publication
  - Selects quality research of interest to readers
  - Editors may limit the focus of the report
  - Narrative for providing context and conclusions

Reporting Specific Outcome Measures

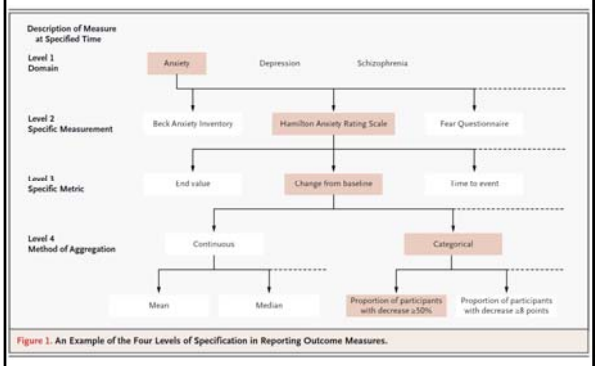


Figure 1. An Example of the Four Levels of Specification in Reporting Outcome Measures.

N *Engl J Med* 2011;364:852-60 (Figure 1)

BMJ

BMJ 2011;344:d7292 doi: 10.1136/bmj.d7292 (Published 3 January 2012) Page 1 of 10

RESEARCH

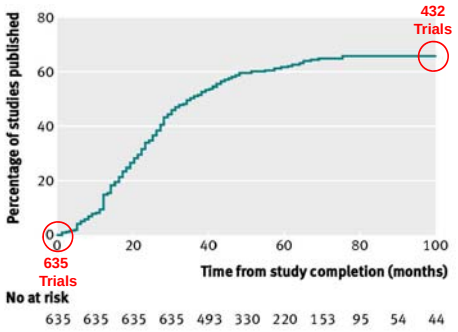
Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis

OPEN ACCESS

Joseph S Ross *assistant professor of medicine*[1 2], Tony Tse *program analyst at ClinicalTrials.gov*[3], Deborah A Zarin *director of ClinicalTrials.gov*[3], Hui Xu *postgraduate house staff trainee*[4], Lei Zhou *postgraduate house staff trainee*[4], Harlan M Krumholz *Harold H Hines Jr professor of medicine and professor of investigative medicine and of public health*[2 5 6]

[1]Section of General Internal Medicine, Department of Medicine, Yale University School of Medicine, New Haven, CT, USA; [2]Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, New Haven, CT; [3]Lister Hill National Center for Biomedical Communications, National Library of Medicine, National Institutes of Health, Bethesda, MD, USA; [4]Fuwai Hospital and Cardiovascular Institute, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [5]Robert Wood Johnson Clinical Scholars Program and Section of Cardiovascular Medicine, Department of Medicine, Yale University School of Medicine, New Haven, CT; [6]Section of Health Policy and Administration, Yale University School of Epidemiology and Public Health, New Haven, CT

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



Ross et al. *BMJ* 2012;344:d7292.

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On the Horizon:
Individual Participant-Level Data (IPD)

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The NEW ENGLAND JOURNAL of MEDICINE

Participant-Level Data and the New Frontier in Trial Transparency

Deborah A. Zarin, M.D.

Medical progress is possible only because altruistic volunteers put themselves at risk in clinical trials. The results of those trials are then used to inform medical decisions. The traditional system of relying on investigators, sponsors, and journal editors to decide whether, when, and how to report trial results was based on trust. There was no way to know what trials had been conducted, argue that the availability of such data will allow interested parties to use participant-level data for additional analyses as a preliminary test of a new idea or to combine data from multiple studies to seek previously unidentified associations.

Two articles in this issue of the *Journal* reflect this new frontier.[3,4] GlaxoSmithKline (GSK) offers detailed information about its policy of pro-

"The traditional system of relying on investigators, sponsors, and journal editors to decide whether, when, and how to report trial results was based on trust."

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Zarin DA. *N Engl J Med*. 2013 Aug 1;369(5):468-9.

Discrepant Reporting of Results

	Hartung et al. (2014)	Becker et al. (2014)
Sample	Phase 3 & 4 trials with results on Clinicaltrials.gov & journal publication	Trials with results on ClinicalTrials.gov & high-impact journal publication
Key Discrepancies		
POM Descriptions	15%	15%
POM Values	20%	16%
SAEs	35% (Frequent underreporting or omissions in publication)	39% (Frequent underreporting or omissions in publication)
Other AEs	37% (Among ≥1 AE reported on ClinicalTrials.gov)	48% (Among all trials)

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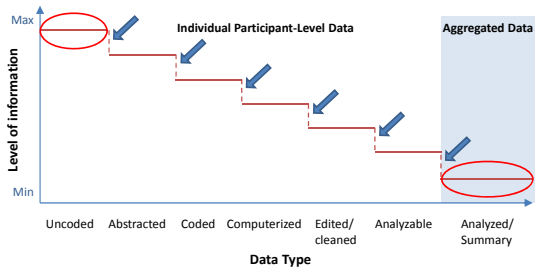
Becker & Ross. Unpublished manuscript; Hartung et al. *Ann Intern Med*. 2014:477-83; Becker et al. *JAMA*. 2014: 1063-5.

Figure. Information loss as clinical trials data progress from raw uncoded data to summary data



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Recent Developments in IPD

- **Institute of Medicine (IOM)**. Sharing clinical trial data: Maximizing benefits, minimizing risk. Washington, DC: National Academies Pr; 2015.
- Sharing Clinical Trial Data: A Proposal From the **International Committee of Medical Journal Editors (ICMJE)**. *Ann Intern Med.* 2016.
  - At time of registration, specify plan for data sharing
  - Share IPD supporting publication within 6 months
  - Effective 1 year from date policy finalized (only for clinical trials beginning to enroll participants)

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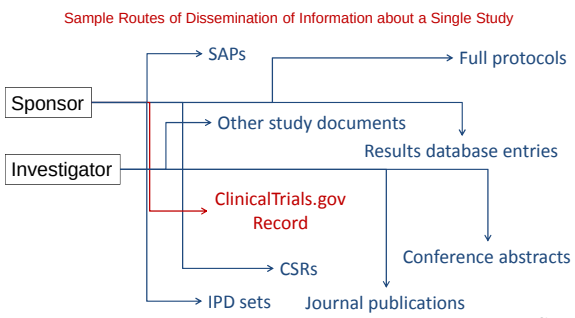
Current: "Informational Chaos"

Diffuse, hard-to-access information about a single study



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Potential Role for ClinicalTrials.gov

- Provide framework and access to key trial information
  - Registration
  - Results
  - Links
  - Documents
- Provide context for available information
  - List of all trials for given topic
  - Documentation of what information is available for each trial
  - Help to avoid "disclosure biases" of all sorts

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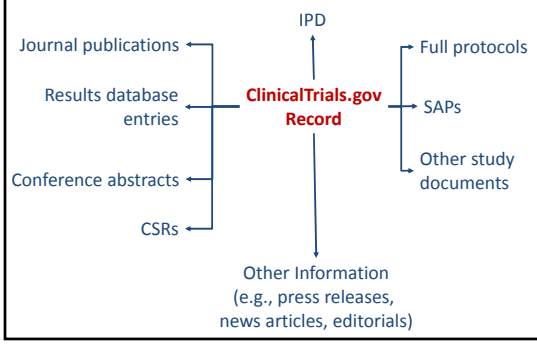
ClinicalTrials.gov: Informational Scaffold



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New IPD Data Elements in ClinicalTrials.gov (Dec. 2015)

- **At Time of Registration**
  - Plan to Share Data?: Whether there is a plan to make individual participant data (IPD) available.
  - Description: Brief description of what will be shared, when, and how data may be obtained (if known).
- **After Study Completion**
  - Available Study Data/Documents: Study data sets and documents that are being shared.
    - Type: Select from pick-list (data set, protocol, etc.)
    - URL: Web address of repository for accessing data
    - Identifier: Unique identifier assigned by repository
    - Comments: Additional information about accessing data

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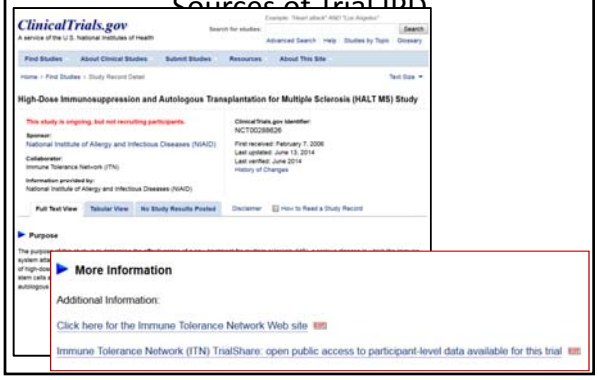
Linking ClinicalTrials.gov Records and Sources of Trial IPD



Linking Sources of Trial IPD to ClinicalTrials.gov Records

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Zarin DA, Tse T. PLoS Med 2016.

- Identifies types of IPD
- Describes IPD in context of TRS
- Illustrates, using a case study, the role of each component of the TRS

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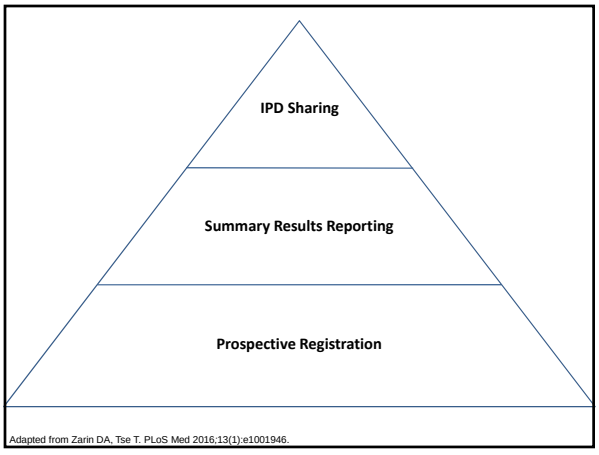

Adapted from Zarin DA, Tse T. PLoS Med 2016;13(1):e1001946.

Final Thoughts

- ClinicalTrials.gov reflects the "CRE"
- Its utility as a scientific tool depends on its accuracy and completeness.
- Your diligence in submitting accurate and timely reports will reflect on you and the "CRE"

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Select Publications

Available at: http://www.clinicaltrials.gov/ct2/resources/pubs

Hartung DM, Zarin DA, Guise JM, et al. Reporting discrepancies between the ClinicalTrials.gov results database and peer-reviewed publications. *Ann Intern Med*. 2014 Apr 1;160(7):477-83.

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.

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

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.

Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC. The ClinicalTrials.gov results database – update and key issues. *N Engl J Med* 2011;852-860.

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Additional Information

General ClinicalTrials.gov information:
http://clinicaltrials.gov/ct2/about-site/

FDAAA related information:
http://clinicaltrials.gov/ct2/manage-recs/fdaaa

Office of Extramural Research (OER)
http://grants.nih.gov/Clinicaltrials_fdaaa/

Questions?
register@clinicaltrials.gov

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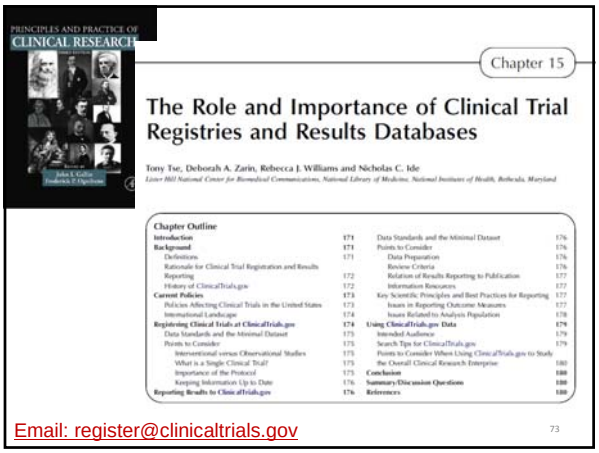
PRINCIPLES AND PRACTICE OF
CLINICAL RESEARCH
Chapter 15
The Role and Importance of Clinical Trial Registries and Results Databases
Tony Tse, Deborah A. Zarin, Rebecca J. Williams and Nicholas C. Ide
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