The Role and Importance of Clinical Trial Registries & Results Databases

Deborah A. Zarin, M.D.
Director, ClinicalTrials.gov
February 2015
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?
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
Diabetes Drug Maker Hid Test Data, Files Indicate

By GARDINER HARRIS

In the fall of 1999, the drug giant SmithKline Beecham secretly began a study to find out if its diabetes medicine, Avandia, was safer for the heart than a competing pill, Actos, made by Takeda.

Avandia’s success was crucial to SmithKline, whose labs were otherwise all but barren of new products. But the study’s results, completed that same year, were disastrous. Not only was Avandia no better than Actos, but the study also provided clear signs that it was riskier to the heart.

But instead of publishing the results, the company spent the next 11 years trying to cover them up, according to documents recently obtained by The New York Times. The company did not post the results on its Web site or submit them to federal drug regulators, as is required in most cases by law.

“This was done for the U.S. business, was covered up, and never got to the light of day to anyone outside of GSK,” said the executive, who declined to be identified by name.

The heart risks from Avandia first became clear when SmithKline Beecham, which had known of the drug’s potential heart problems, was forced by a lawsuit to release an internal report in 2006. But the latest documents demonstrate that the drug was introduced in 1999, and so the company had months to seek the FDA’s approval and had ample time to craft a marketing plan for it.

But the latest documents demonstrate that instead of publishing the results, the company spent the next 11 years trying to cover them up.

Mary Anne Rhyne, a GlaxoSmithKline spokeswoman, said that the company had not provided the results of its study because they “did not contribute any significant new information.”
Glaxo Agrees to Pay $3 Billion in Fraud Settlement

By KATIE THOMAS and MICHAEL S. SCHMIDT
Published: July 2, 2012 | 264 Comments

In the largest settlement involving a pharmaceutical company, the British drugmaker GlaxoSmithKline agreed to plead guilty to criminal charges and pay $3 billion in fines for promoting its best-selling antidepressants for unapproved uses and failing to report safety data about a top diabetes drug, federal prosecutors announced Monday. The agreement also includes civil penalties for improper marketing of a half-dozen other drugs.

The fine against GlaxoSmithKline over Paxil, Wellbutrin, Avandia and the other drugs makes this year a record for money recovered by the federal government under its so-called whistle-blower law, according to a group that tracks such numbers.

In May, Abbott Laboratories settled for $1.6 billion over its marketing of the antiseizure drug Depakote. And an
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.

“They swallowed our story, hook, line and sinker...”
The new study, published in the *Spine Journal*, reveals that serious complications ... occurred in 10% to 50% of patients ... in 13 clinical trials funded by Medtronic and conducted by the surgeons between 2000 and 2010. Yet these complications weren't reported in the research papers the surgeons wrote on those trials, even though the papers were peer reviewed. Some of the complications are mentioned on the product's label.
ClinicalTrials.gov and Levels of “Transparency”

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”
Stages in Disclosure Parallel the Research Life Cycle

**Stage of Study**

**Before**

1. IRB Review and Approval of Protocol

2. Study Initiation

**During**

3. Study Conduct & Protocol Amendments

**After**

4. Study Completion & Data Analysis

**Steps in Clinical Trials Disclosure**

1. Initial *Registration*

2. Updates to the Registry (as necessary)
   - Recruitment Status
   - Enrollment
   - Start and Completion Dates
   - Key Protocol Changes

3. Initial *Results Reporting*

4. Updates to the Results Database and/or Registry (as necessary)
Rationale for Trial Disclosure

• Simes (1986) - Call for systematic registration to mitigate publication bias

• Declaration of Helsinki (2008)
  – Article 19: Registration of all clinical trials
  – Article 30: Disclosure of negative and inconclusive as well as positive results.

• World Health Organization: “The registration of all interventional studies is a scientific, ethical, and moral responsibility.”
<table>
<thead>
<tr>
<th>Category</th>
<th>Reasons</th>
</tr>
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</table>
| **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) |
History of ClinicalTrials.gov

- FDAMA* 113 (1997) mandates registry
  - Investigational New Drug application (IND) trials for serious and life-threatening diseases or conditions
- ClinicalTrials.gov launched in February 2000
- Calls for increased transparency of clinical trials
  - Maine State Law; State Attorneys General
- ClinicalTrials.gov accommodates other policies
- FDAAA† Section 801 (2007): Expands registry & adds results reporting requirements
  - Issued for public comment in November 2014
    - Notice of Proposed Rulemaking for Implementing FDAAA 801
    - Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information

* Food and Drug Administration Modernization Act of 1997
† Food and Drug Administration Amendments Act of 2007
Current Policies

US and International
Two Disclosure Policies

  – 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
Rate of New Registrations

- After ICMJE (2005): 200 – 250 per week
- After FDAAA (2007): 300 – 350 per week
- After NPRM (2014): ~500 per week
FDAAA Implementation

• Law in effect since September 2007
• Notice of Proposed Rulemaking (NPRM)
  – Describes the procedures for registering and submitting summary results of clinical trials to ClinicalTrials.gov
  – Clarifies definitions (e.g., “applicable clinical trial”; “voluntary submissions”)
  – Timelines for updates and corrections
  – Effective date and compliance date
HHS and NIH take steps to enhance transparency of clinical trial results

The U.S. Department of Health and Human Services today issued a Notice of Proposed Rulemaking (NPRM), which proposes regulations to implement reporting requirements for clinical trials that are subject to Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA). The proposed rule clarifies requirements to clinical researchers for registering clinical trials and submitting summary trial results information to ClinicalTrials.gov, a publicly accessible database operated by the National Library of Medicine, part of the National Institutes of Health. A major proposed change from current requirements is the expansion of the scope of clinical trials required to submit summary results to include trials of unapproved, unlicensed, and uncleared products.

“Medical advances would not be possible without participants in clinical trials,” said NIH Director Francis S. Collins, M.D., Ph.D. “We owe it to every participant and the public at large to support the maximal use of this knowledge for the greatest benefit to human health. This important commitment from researchers to research participants must always be upheld.”
ClinicalTrials.gov Reporting Policies

<table>
<thead>
<tr>
<th>Reporting Requirement</th>
<th>FDAAA NAPRM</th>
<th>Draft NIH Policy</th>
<th>ICMJE Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope</td>
<td>Registration &amp; Results Reporting</td>
<td>Registration &amp; Results Reporting</td>
<td>Registration</td>
</tr>
<tr>
<td>Phase</td>
<td>Not Phase 1</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>Intervention Type</td>
<td>Drugs, Biologics, &amp; Devices regulated by the FDA</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>Funding</td>
<td>Any</td>
<td>NIH</td>
<td>Any</td>
</tr>
<tr>
<td>Enforcement</td>
<td>Up to $10,000/day; Loss of US Federal funding</td>
<td>Loss of NIH funding</td>
<td>Refusal to publish</td>
</tr>
</tbody>
</table>
Rulemaking Process – Next Steps

• Public comment period **will be extended (March 23, 2015)**
  – Comments welcome on all aspects of proposed rule; NPRM contains explicit requests for comment on certain topics

• HHS will review and address all submitted comments

• Publish Final Rule
Clinical Trials Registration and Results Submission

A Proposed Rule by the Health and Human Services Department on 11/21/2014

This document has a comment period that ends in 83 days (02/19/2015)

ACTION
Notice Of Proposed Rulemaking.

SUMMARY
This Notice of Proposed Rulemaking proposes requirements for submitting registration and summary results information, including adverse event information, for specified clinical trials of drugs (including biological products) and devices and for pediatric postmarket surveillances of a device to ClinicalTrials.gov, the clinical trial registry and results data bank operated by the National Library of Medicine (NLM). This proposed rule provides for the expanded registry and results data bank specified in Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) to enhance patient enrollment, provide a mechanism to track subsequent progress of clinical trials, provide more complete results information, and enhance patient access to and understanding of the results of clinical trials. The proposed requirements would apply to the responsible party (meaning the sponsor or designated principal investigator) for certain clinical trials of

Dates:
Comments are due on or before February 19, 2015.

Comments Close:
02/19/2015
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 invest-

**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.\(^10\)–\(^11\) 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),\(^10\) 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-
Examples of Other Relevant Policies

• Veterans Affairs funded clinical trials
• PCORI funded studies
• Trials conducted under the CMS “coverage with evidence development”
About ClinicalTrials.gov

http://ClinicalTrials.gov/
Registration at ClinicalTrials.gov
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 2/19/2015)

112 million pages viewed *monthly*
57,000 unique visitors *daily*

<table>
<thead>
<tr>
<th>Type of Trial</th>
<th>Registration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>184,496</td>
<td>16,262</td>
</tr>
<tr>
<td>Type of Trial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observational</td>
<td>34,824 (18%)</td>
<td>1,018 (6%)</td>
</tr>
<tr>
<td>Interventional*</td>
<td>148,828 (80%)</td>
<td>15,244 (93%)</td>
</tr>
<tr>
<td>- Drug &amp; Biologic</td>
<td>95,466</td>
<td>12,558</td>
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<tr>
<td>- Behavioral, Other</td>
<td>39,932</td>
<td>2,233</td>
</tr>
<tr>
<td>- Surgical Procedure</td>
<td>16,204</td>
<td>779</td>
</tr>
<tr>
<td>- Device**</td>
<td>14,951</td>
<td>1,594</td>
</tr>
</tbody>
</table>

* Intervention types not additive; study record may include more than one type of intervention
** 557 applicable device clinical trials submitted, but qualify for “delayed posting” under FDAAA
ClinicalTrials.gov Statistics

Percentage of Registered Studies by Location (as of February 19, 2015)
Total N = 184,496 studies

- Non-U.S. Only (45%)
- U.S. Only (39%)
- Not Specified* (10%)
- Both U.S. and Non-U.S. (6%)

<table>
<thead>
<tr>
<th>Location</th>
<th>Number of Registered Studies and Percentage of Total (as of February 19, 2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-U.S. Only</td>
<td>83,866 (45%)</td>
</tr>
<tr>
<td>U.S. Only</td>
<td>72,066 (39%)</td>
</tr>
<tr>
<td>Not Specified*</td>
<td>17,535 (10%)</td>
</tr>
<tr>
<td>Both U.S. and Non-U.S.</td>
<td>11,029 (6%)</td>
</tr>
<tr>
<td>Total</td>
<td>184,496</td>
</tr>
</tbody>
</table>

* The location of the study was not provided.
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
“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
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

### Participant Flow

**Recruitment Details** — Key information relevant to the recruitment process for the overall study, such as dates of the recruitment.

**Pre-Assignment Details** — Significant events and approaches for the overall study following participant enrollment, but prior to assignment.

<table>
<thead>
<tr>
<th>Overall Study</th>
<th>Drug A</th>
<th>Drug B</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>STARTED</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>COMPLETED</td>
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<tr>
<td>Not Completed</td>
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<td></td>
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<tr>
<td>Lost to Follow-up</td>
<td></td>
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<tr>
<td>Adverse Event</td>
<td></td>
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</tbody>
</table>

### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Drug A</th>
<th>Drug B</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Participants</td>
<td></td>
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<td></td>
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<tr>
<td>Age</td>
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<tr>
<td>Gender</td>
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<tr>
<td>Male</td>
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</table>

### Outcome Measures

**Primary Outcome Measure**

- **Measure Name**
- **Measure Description**
- **Time Frame**

**Population Description** — Explanation of how the number of participants for analysis was determined.

**Measured Values**

<table>
<thead>
<tr>
<th>Measured Values</th>
<th>Drug A</th>
<th>Drug B</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Outcome Measure</td>
<td></td>
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</tbody>
</table>

**Statistical Analysis for Primary Outcome Measure**

- **Groups**
- **Method**
- **P-Value**
- **Mean Difference**
- **95% Confidence Interval**

**Additional Details About the Analysis** — e.g., null hypothesis, power calculation, and whether the p-value is adjusted for multiple comparisons.

### More Information

- **Certain Agreements** — Information about restrictions on the ability of the principal investigator to disseminate trial data after trial completion
- **Limitations and Caveats** — Limitations of the study, such as early termination leading to small numbers of subjects analyzed
- **Results Point of Contact** — Phone and/or email for additional information about the results

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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
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)”
Results Reporting: Points to Consider
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)
Importance of Precision

• Which of these three things just doesn’t belong?
  – Number of adjudicated [stroke or SE] events per 100 patient years
  – Percentage of [stroke or SE] events/100 patient years
  – [stroke or SE] Event rate [%/year]
Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis

Joseph S Ross assistant professor of medicine¹², Tony Tse program analyst at ClinicalTrials.gov³, Deborah A Zarin director of ClinicalTrials.gov³, Hui Xu postgraduate house staff trainee⁴, Lei Zhou postgraduate house staff trainee⁴, Harlan M Krumholz Harold H Hines Jr professor of medicine and professor of investigative medicine and of public health²⁵⁶

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

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

## Discrepant Reporting of Results

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

Figure. Information loss as clinical trials data progress from raw uncoded data to summary data.
Observations About Trial Reporting

• The “journey” from initially collected participant-level data to summary data is not completely objective
• Documented bias towards reporting greater benefits and fewer harms
• Greater transparency could help to inspire trust
• EMA: “the capacity for independent replication of clinical trial data is a legitimate societal objective…”
• Greater transparency could also help “the field” engage in internal quality improvement
IOM: Sharing Clinical Trial Data (2015)
## Basic IOM Recommendations

<table>
<thead>
<tr>
<th>When to Share</th>
<th>What to Share</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial Registration—Trial inception</td>
<td>Data Sharing Plan, <strong>Registration Data Elements</strong></td>
</tr>
<tr>
<td>12 Months after Study Completion</td>
<td><strong>Summary-level Results</strong>, Lay Summaries for participants</td>
</tr>
<tr>
<td>6 Months after Publication</td>
<td>Post-Publication Data Package*</td>
</tr>
<tr>
<td>18 Months after Study Completion</td>
<td>Full Data Package (i.e., full analyzable data set, full protocol (initial, final, all amendments), full SAP, analytic code)</td>
</tr>
<tr>
<td>18 Mos. after Product Abandonment OR 30 Days after Regulatory Approval</td>
<td>Post-Regulatory Data Package**</td>
</tr>
</tbody>
</table>

* subset of the Full Data Package supporting the published findings, tables, and figures

**Full Data Package + CSR (redacted for CCI or PII)
Current: “Informational Chaos”
Diffuse, hard-to-access information about a single study

Sample Routes of Dissemination of Information about a Single Study

- Sponsor
  - SAPs
  - Full protocols
  - Other study documents
  - Results database entries
- Investigator
  - ClinicalTrials.gov Record
  - CSRs
  - Conference abstracts
  - IPD sets
  - Journal publications
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
ClinicalTrials.gov: Informational Scaffold

- Journal publications
- Results database entries
- Conference abstracts
- CSR
- Full protocols
- SAPs
- Other study documents
- Other Information (e.g., press releases, news articles, editorials)
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”
Select Publications
Available at: http://www.clinicaltrials.gov/ct2/resources/pubs


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
Chapter 15

The Role and Importance of Clinical Trial Registries and Results Databases

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