The Role and Importance of Clinical Trial Registries & Results Databases

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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

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 the prespecified outcome measures
"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."

"instead of publishing the results, the company spent the next 11 years trying to cover them up"

"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."

"instead of publishing the results, the company spent the next 11 years trying to cover them up"
Internal Corporate Email

“They swallowed our story, hook, line and sinker…”

ENHANCE: Prespecified Endpoints


“…it appears that the study itself was not registered with ClinicalTrials.gov until October 31, 2007, a full 18 months after completion of the study. In addition, the endpoint indicated in the ClinicalTrials.gov website appears to differ from the endpoint described in the initial study design.”
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.”

“The primary outcome was changed in the case of 5 of 8 published trials for which statistically significant differences favoring gabapentin were reported.”
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.

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

<table>
<thead>
<tr>
<th>Stage of Study</th>
<th>Steps in Clinical Trials Disclosure</th>
</tr>
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<tbody>
<tr>
<td>Before</td>
<td>IRB Review and Approval of Protocol</td>
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<tr>
<td></td>
<td>Study Initiation</td>
</tr>
<tr>
<td>During</td>
<td>Study Conduct &amp; Protocol Amendments</td>
</tr>
<tr>
<td></td>
<td>1. Initial Registration</td>
</tr>
<tr>
<td></td>
<td>2. Updates to the Registry (as necessary)</td>
</tr>
<tr>
<td></td>
<td>• Recruitment Status</td>
</tr>
<tr>
<td></td>
<td>• Enrollment</td>
</tr>
<tr>
<td></td>
<td>• Start and Completion Dates</td>
</tr>
<tr>
<td></td>
<td>• Key Protocol Changes</td>
</tr>
<tr>
<td>After</td>
<td>Study Completion &amp; Data Analysis</td>
</tr>
<tr>
<td></td>
<td>3. Initial Results Reporting</td>
</tr>
<tr>
<td></td>
<td>4. Updates to the Results Database and/or Registry (as necessary)</td>
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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>
</thead>
</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

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
  - Current Status: Rulemaking
Rate of New Registrations

- After ICMJE (2005): 200 – 250 per week
- After FDAAA (2007): 300 – 350 per week

<table>
<thead>
<tr>
<th>ICMJE</th>
<th>FDAAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Why?</td>
<td>Required for journal publication</td>
</tr>
<tr>
<td>Which Trials?</td>
<td>Interventional Studies - All Phases</td>
</tr>
<tr>
<td></td>
<td>- All Intervention Types</td>
</tr>
<tr>
<td>Who?</td>
<td>Author</td>
</tr>
<tr>
<td>When to Register?</td>
<td>Prior to enrollment of first participant</td>
</tr>
<tr>
<td>What to Register?</td>
<td>WHO Data Items</td>
</tr>
<tr>
<td>Where to Register?</td>
<td>ClinicalTrials.gov or WHO Primary Registry</td>
</tr>
<tr>
<td>When to Submit Results?</td>
<td>Not Applicable</td>
</tr>
</tbody>
</table>

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)
Source: American Customer Satisfaction Index (ACSI) Online Consumer Survey, 4th Quarter 2012

ClinicalTrials.gov Statistics
(as of 3/4/2013)

<table>
<thead>
<tr>
<th></th>
<th>Registration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>141,470</td>
<td>8,285</td>
</tr>
<tr>
<td>Type of Trial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observational</td>
<td>26,148 (18%)</td>
<td>551 (6%)</td>
</tr>
<tr>
<td>Intervention*</td>
<td>111,253 (81%)</td>
<td>7,734 (93%)</td>
</tr>
<tr>
<td>- Drug &amp; Biologic</td>
<td>77,195</td>
<td>6,602</td>
</tr>
<tr>
<td>- Behavioral, Other</td>
<td>28,009</td>
<td>841</td>
</tr>
<tr>
<td>- Surgical Procedure</td>
<td>12,909</td>
<td>326</td>
</tr>
<tr>
<td>- Device**</td>
<td>9,894</td>
<td>712</td>
</tr>
</tbody>
</table>

*Intervention types not additive; study record may include more than one type of intervention
**Not applicable where clinical trial submitted, but qualify for “delayed posting” under FDAAA
ClinicalTrials.gov Statistics
(as of 3/4/2013)

Locations of Registered Studies

<table>
<thead>
<tr>
<th>Location</th>
<th>Number of Registered Studies and Percentage of Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-U.S. Only</td>
<td>60,928 (43%)</td>
</tr>
<tr>
<td>U.S. Only</td>
<td>58,347 (41%)</td>
</tr>
<tr>
<td>Not Specified*</td>
<td>10,173 (9%)</td>
</tr>
<tr>
<td>Both U.S. &amp; Non-U.S.</td>
<td>6,007 (4%)</td>
</tr>
<tr>
<td>Total</td>
<td>141,479</td>
</tr>
</tbody>
</table>

*Not Specified: The location of the study was not provided by the sponsor.

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 08
- 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 is developing a DB based on our model

4 Scientific Modules

- Participant Flow
- Baseline Characteristics
- Outcome Measures
- Adverse Events
Results DB: Minimal Dataset
(Needed to Describe Summary Results)

<table>
<thead>
<tr>
<th>Module (Tabular Format)</th>
<th>Brief Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant Flow</td>
<td>Progress of research participants through each stage of a trial, including the number of trial participants who dropped out (identical in purpose to a CONSORT flow diagram, but represented as tables)</td>
</tr>
<tr>
<td>Baseline Characteristics</td>
<td>Demographic and baseline data for the entire trial population and for each arm or comparison group</td>
</tr>
<tr>
<td>Adverse Events and Statistical Analyses</td>
<td>Data for each outcome measure by arm or comparison group. Accommodates categorical, continuous, and time-to-event data types and a variety of statistical analyses.</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>Listing of (1) all serious adverse events and (2) other adverse events (not including serious adverse events) exceeding a specified frequency threshold within an arm or group. Both tables include anticipated and unanticipated adverse events by arm and are grouped by organ system.</td>
</tr>
</tbody>
</table>

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)”

“This isn't right. This isn't even wrong.”

Wolfgang Pauli, on a paper submitted by a physicist colleague. Swiss (Austrian-born) physicist (1900 - 1958)
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
Specification in Reporting Outcome Measures

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]

Characteristics of Clinical Trials Registered in ClinicalTrials.gov, 2007-2010

"Conclusion: 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."
Table 2. Number of trials subject to mandatory reporting which had reported results, grouped by funder of study [as of 01/19/11]

<table>
<thead>
<tr>
<th>Funder</th>
<th>No with results</th>
<th>Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Industry</td>
<td>126</td>
<td>317</td>
<td>40</td>
</tr>
<tr>
<td>Mixed</td>
<td>25</td>
<td>265</td>
<td>6</td>
</tr>
<tr>
<td>NIH/government</td>
<td>4</td>
<td>48</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>108</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>163</td>
<td>738</td>
<td>22</td>
</tr>
</tbody>
</table>

NIH = National Institutes of Health.
Fisher’s exact test for effect of funder influencing proportion of trials with results: P = 2.2 × 10⁻¹⁰.
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”
Additional Background


Email: register@clinicaltrials.gov