Clinical Trials Registration Requirements: What You Should Know

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Outline

• Regulatory context
• Current Requirements
• ClinicalTrials.gov database: Bird’s Eye View
• Heads up: Possible Expansion of Requirements
• Considerations for Implementation at Academic Centers
• Resources
Evolution of Clinical Trial Disclosure Requirements

1997: FDAMA calls for public registry

2000: ClinicalTrials.gov launched

2007: FDAAA expands ClinicalTrials.gov to include results

2008: ClinicalTrials.gov results modules added

2005: ICMJE requires registration of trials

2007: ClinicalTrials.gov expanded

2008: ClinicalTrials.gov results modules added

2010: Proposed Rulemaking due...

2009: ClinicalTrials.gov adds Adverse Event Module

2011: EMA rule

2008: ClinicalTrials.gov results modules added

2013: BMJ requires anonymized patient level data availability

2014: CMS requires qualified trials to list NCT #s by 1/1/15 for Medicare claims

CURRENT: In public comment period for HHS/NIH Proposals to enhance transparency

Adapted and expanded from: http://clinicaltrials.gov/ct2/about-site/history
Regulatory Context – Why?

• What’s the problem?
  – Not all trials are published
  – Publications do not always include all pre-specified outcome measures or reflect the study design
  – Unacknowledged changes are made to protocols that might affect the interpretation of the findings

• People are unable to find relevant research protocols
Lilly Sold Drug for Dementia Knowing It Didn’t Help, Files Show

By Margaret Cronin Fisk, Elizabeth Lopatto and Jef Feeley - June 12, 2009 00:01 EDT

June 12 (Bloomberg) -- Eli Lilly & Co. urged doctors to prescribe Zyprexa for elderly patients with dementia, an unapproved use for the antipsychotic, even though the drugmaker had evidence the medicine didn’t work for such patients, according to unsealed internal company documents.

In 1999, four years after Lilly sent study results to the U.S. Food and Drug Administration showing Zyprexa didn’t alleviate dementia symptoms in older patients, it began marketing the drug to those very people, according to documents unsealed in insurer suits against the company for overpayment.

Regulators required Lilly and other antipsychotic drug-makers in April 2005 to warn that the products posed an increased risk to elderly patients with dementia. The documents show the health dangers in marketing a drug for an unapproved use, called off-label promotion, said Sidney Wolfe, head of the health research group at Public Citizen in Washington.

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.

Rationale

• Transparency
• Identify clinical trials for participants
Policies and Users

Current Requirements for Clinical Trials Registration
Should this study be registered?

- Effectiveness of Bupropion for treating Nicotine Dependence in Young People
  - Multi-center, Randomized, Efficacy Study
  - Interventions: Bupropion, Placebo
  - Primary Outcome: Smoking behavior over 6 months
FDAAA – High Level Summary of Registration Requirements

• Enacted December 26, 2007
• Required for “Applicable Clinical Trials”:  
  – Interventional trials (drugs, biologics, devices)  
  – Phase 2 – 4 (not phase 1 drug; not small feasibility device)  
  – US FDA jurisdiction (e.g. IND/IDE or US site)  
  – Studies initiated on or after September 27, 2007 or ongoing as of December 26, 2007

• When:  
  – Within 21 days of enrollment of 1st subject  
  – Update at least every 12 months

http://prsinfo.clinicaltrials.gov/fdaaa.html
FDAAA: A Closer look at Registration Requirements

DRAFT March 9, 2009

ELABORATION OF DEFINITIONS OF RESPONSIBLE PARTY AND APPLICABLE CLINICAL TRIAL

The elaboration of definitions of “Responsible Party” and “Applicable Clinical Trial” represent the National Institutes of Health’s (NIH’s) current thinking on this topic. They do not create or confer any rights for or on any person and do not operate to bind NIH, the Department of Health and Human Services or the public. NIH will interpret these terms in regulations or guidance to be issued at a later date. Prior to the issuance of draft regulations or guidance for comment, comments on these draft definitions are welcome and should be addressed to register@clinicaltrials.gov. Please include “Comment on Elaborated Definitions” in the subject line.

NIH’s Elaboration Document:
FDAAA: A *Closer look at* Registration Requirements - Drugs/Biologics

- Is it a *Clinical Investigation*?
  - Defined as “any experiment in which a drug is administered or dispensed to one or more human subjects
- Is the clinical investigation *controlled*?
  - Is it designed to permit a comparison of a test intervention with a control to provide a quantitative assessment of the drug effect? Concurrent & Non-concurrent controls
- Is the clinical investigation *other than a phase 1* clinical trial?
  - Per FDAAA, Phase 1 includes initial introduction of an investigational drug into humans, metabolism, and pharmacologic actions of a drug, mechanism of action, and early evidence of effectiveness

NIH’s Elaboration Document:
FDAAA: A Closer look at Registration Requirements - Devices

• Is it a prospective study of health outcomes?
  – FDAAA defines ‘health outcome’ where primary purpose is to evaluate a defined clinical outcome directly related to human health

• Does the study ‘compare an intervention with a device against a control in human subjects’?
  – ‘Intervention defined broadly to include various techniques using the device such as (among other things): device regimens and procedures, use of prophylactic, diagnostic, or therapeutic agents’

• Is the clinical study other than:
  – a small clinical trial to determine the feasibility of a device
  – a clinical trial to test prototype devices (primary outcome measure related to feasibility, not to health outcomes)

NIH’s Elaboration Document:
FDAAA – Results Reporting

• Required for:
  – “Applicable Clinical Trial” AND
    • Interventional trials (drugs, biologics, devices)
    • Phase 2 – 4 (not phase 1 drug; not small feasibility device)
    • US FDA jurisdiction (e.g. IND/IDE or US site)
    • Studies initiated on or after September 2007 or ongoing as of December 26, 2007
  – Study product approved or cleared (for any use) by FDA

• When:
  – Within 12 months of primary endpoint completion date
  – Delays are possible
    • If you are the manufacturer seeking initial approval or approval for a new use
    • You request an extensions for “good cause”. *Pending publication is not considered good cause*

http://prsinfo.clinicaltrials.gov/fdaaa.html
Of Note:
FDAAA Informed Consent

• FDA requires that Applicable Clinical Trials include the following informed consent language:

“A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.”

• Subjects who were consented before March 7, 2012 will NOT have to be re-consented or otherwise sign addendum consent with this language.
International Committee of Medical Journal Editors (ICMJE)

- New England Journal of Medicine
- Journal of the American Medical Association
- Annals of Internal Medicine
- The Lancet
- The Medical Journal of Australia
- The New Zealand Medical Journal
- Norwegian Medical Journal
- Canadian Medical Association Journal
- Croatian Medical Journal
- Dutch Journal of Medicine
- Journal of the Danish Medical Association

...Plus many more
ICMJE

Which studies are required to register?

• Any human research project that prospectively assigns human subjects to *intervention* or comparison groups to study the cause-and-effect relationship between a medical intervention and a *health outcome*.

  – *Intervention*: Any intervention used to modify a biomedical or health-related outcome
    • Examples: drugs, surgical procedures, devices, behavioral treatments, dietary interventions

  – *Health outcome*: Include any biomedical or health-related measure obtained in participants, including pharmacokinetic measures and adverse events
ICMJE

• Registration only – NO result reporting required

• Must register before 1\textsuperscript{st} subject is enrolled

• ICMJE does NOT consider results data posted on ClinicalTrials.gov as prior publication

See ICMJE, \url{http://www.icmje.org/about-icmje/faqsclinical-trials-registration/}
Centers for Medicare & Medicaid Services (CMS)

- Mandatory reporting of the NCT# on claims for items and services provided in “qualified clinical trials” for Medicare coverage.
- Became effective on January 1, 2014. Grace period until January 1, 2015 allowing generic #99999999 to be used if NCT# not yet obtained.
- **Now – you need the actual NCT#!**

What is a “qualifying trial”? *

- Purpose of trial must be the evaluation of an item/service that falls within Medicare benefit category (e.g. physicians’ service, durable medical equipment, diagnostic test)
- Trial must have therapeutic intent
- Trial must enroll patients with diagnosed disease not only healthy volunteers

* This is summary definition. For a complete definition, see 100-03 Medicare NCD at http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=1&ncdver=2&bc=BAABAAAAAAA&
Current Requirements Recap

FDAAA Results & AE Reporting

FDAAA Registration

ICMJE Registration

?? CMS ??
Who is responsible for registering the trial?

ICMJE:
• Anyone can register, but generally the PI

CMS
• No language addressing this. Likely the person that initiated the study.

FDAAA:
• The **Responsible Party** (RP) defined as...
  – IND / IDE holder
  – If no IND/IDE:
    • The industry, cooperative group, consortium or other external sponsor that initiated the study
    • If initiated by a Principal Investigator
      – The grantee institution (e.g. BWH, MGH)
      – If no external funding, the PI
FDAAA: Designation of Responsible Party

- RP can be designated to another party that:
  - Is responsible for conducting the study
  - Has access to and control over the data
  - Has the right to publish the trial results, AND
  - Has the ability to meet the requirements

- Example of RP designation
  - PI initiated study at BU funded by NHLBI
    - BU is the RP
    - BU can designate the PI as the RP
Case Studies

• Does this study need to be registered?
• Does this study need results posted?
• Who is the Responsible Party?
Study #1

• Effectiveness of Bupropion for Treating Nicotine Dependence in Young People
  – Multicenter, Randomized, Efficacy Study
  – Interventions: Bupropion, Placebo
  – Primary Outcome: Smoking behavior over 6 months
  – NIH funded research/BU is the grantee institution
Study #2

• Effects of Chronic Sleep Restriction in Young and Older People
  – Interventions: Chronic sleep restriction
  – Primary Outcome: Changes in sleep and waking EEG measures, frequent measures of performance, attention, alertness
  – Department funded/ PI initiated research
Study #3

- Implantable device designed to relieve the symptoms of heart failure through counter-pulsation technology.
  - Intervention – IDE
  - Purpose: to test the feasibility of the device
  - 8 people enrolled, 6 month study
  - Device company funded research/ BU PI is the IDE holder
What if you don’t register?

- **FDAAA**
  - Public notices of noncompliance
  - Withholding of NIH funds
  - FDA sanctions
  - Civil monetary penalties (up to $10,000/day)

- **ICMJE**
  - Cannot publish in ICMJE and other select journals

- **CMS**
  - Will reject billing claim
Enforcement to Date

- ICMJE is rejecting journal articles - both for no registration as well as late registration.
- FDAAA enforcement has not yet occurred, but is simmering!
- CMS – will reject billing claim
ClinicalTrials.gov Database:  
A Bird’s Eye View
ClinicalTrials.gov

- Database operated by the National Library of Medicine (NLM)
- Every organization (e.g. BU) has an institutional account
  - Individual investigators/employees are given user profiles on that account
- One record per trial
- Many records/trials under a user profile
- Type of information in ClinicalTrials.gov
  - Registration
  - Results
  - Adverse Events

**ClinicalTrials.gov database can be used to satisfy FDAAA, ICMJE & CMS**
Public view of study registration

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Search for studies: [Search]
Advanced Search | Help | Studies by Topic | Glossary

Find Studies > Search Results > Study Record Detail

Trial record 2 of 8826 for: Completed | Studies With Results | Interventional Studies

Effects of Exenatide and Insulin Glargine in Subjects With Type 2 Diabetes

This study has been completed.

Sponsor: Bristol-Myers Squibb
Collaborator: Eli Lilly and Company

Information provided by (Responsible Party): Bristol-Myers Squibb

ClinicalTrials.gov Identifier:
NCT00097500

First received: November 24, 2004
Last updated: September 16, 2013
Last verified: September 2013

History of Changes

Public website: https://clinicaltrials.gov/
Protocol Registration System (PRS)

System Login

ClinicalTrials.gov PRS
Protocol Registration and Results System

Welcome to the ClinicalTrials.gov Protocol Registration and Results System (PRS).

Organization: [Input field]
One-word organization name assigned by PRS (sent via email when account was created)

Username: [Input field]
Password: [Input field]  Forgot password

Login

The PRS System is where you create & edit the record for your study

PRS System: https://register.clinicaltrials.gov/
PRS Home page: New Record & Help
How is information provided to CT.gov?

• Tables are constructed by data providers
  – “Stand alone” tables - must be meaningful to people who are not already familiar with the study.
  – No Narratives
  – Columns are study arms
  – Rows are measures
  – Type of measure determines specific design of cells
Registration Content

• Description of study
  – Study Type, Phase, Design, Outcome measures

• Recruitment information
  – Eligibility criteria, locations, recruitment status

• Administrative and other information
  – Key dates and contact information

• NLM inserts helpful links
  – Medline publications, Consumer health information, FDA information
Results Reporting content

- 4 Modules
  - Participant Flow
  - Baseline Characteristics
  - Outcome Measures (and Statistical Analysis)
  - Adverse Events

- Results and Adverse events are:
  - Entered once
  - Aggregate
  - Information you should already be collecting...in a different format
**PRS System Snapshot: Participant Flow**

<table>
<thead>
<tr>
<th>Arm/Group Title and Description</th>
<th>Add Arm/Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic syndrome Salsalate first, then Placebo</td>
<td>Remove Arm/Group</td>
</tr>
<tr>
<td>Healthy Salsalate first, then placebo</td>
<td>Remove Arm/Group</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Crossover design: Metabolic...</th>
<th>Edit Arm/Group Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls receiving Sal...</td>
<td>Edit Arm/Group Description</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Period Title*</th>
<th>Add Arm/Group</th>
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</thead>
<tbody>
<tr>
<td>First Intervention (28 days)</td>
<td>Remove Period</td>
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</table>

<table>
<thead>
<tr>
<th>Enrollment: 110 (Actual)</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>STARTED*</th>
<th>Add Comment</th>
<th>Add Milestone</th>
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<tbody>
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<td>55</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>COMPLETED*</th>
<th>Add Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Not Completed Period (Calculated = Started - Completed)</th>
<th>Add Reason Not Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>37 (Calculated)</td>
<td></td>
</tr>
<tr>
<td>38 (Calculated)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total (calculated = sun across row)</th>
<th>Add Arm/Group</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Typically, Study Enrollment equals the Total Number of Participants who start the first Period.
ClinicalTrials.gov Review Process

Data Provider Inputs Registration or Results Data. RP “approves” & “releases” data to CT.gov.

CT.gov conducts QA review of data (Registration (5-7 days) & Results (30 days).

**APPROVES:** CT.gov posts data on public website.

**RESETS** to “in-progress”: CT.gov provides QA comments to Data Provider.
Highlights of Proposed Expansion of Clinical Trial Registration Requirements

(Public Comment period ends 3/23/15)
“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.”
Highlights: Proposed NPRM (FDAAA)

- Additional registration data elements
- If drug in ACT study is available under expanded access, must submit separate expanded access protocol
- Results reporting for ALL ACTs (currently only those with approved/cleared products are required to post results)
- Corrections required to record within 15 days of receipt of CT.gov QA Comments
Highlights: Proposed NIH Policy

• All NIH funded “clinical trials”. must register and post results. Revised NIH “clinical trial” definition:

"A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes."

NIH Notice of Revised Definition of Clinical Trial
Considerations for Implementation at an Academic Institution
Issues to Consider

• Policy considerations:
  – Obtaining institutional support
  – Determining appropriate scope for the institution
  – Determination of responsible party
  – Identifying who will be the CT.gov expert in-house

• Process considerations:
  – Identifying studies that need registration
  – Providing education to researchers
  – Identifying who will input the data
  – Designing internal compliance plan
Strategies for Registration

Full Service

Automated System

Incorporate into existing system

Self Service

Investigators are ‘on their own

Greatly based on available resources and size of institution
Partners Healthcare:

• Founded by Massachusetts General Hospital and Brigham & Women’s Hospital
• Network of 11 hospitals in Massachusetts
• *Partners Human Research Affairs* overseas IRB and other systems that support regulatory oversight at MGH & BWH & McLean
• Over 7000 ongoing protocols at MGH, BWH & McLean
Centralized Process at Partners: MGH, BWH, McL, NWH, NSMC, SRH

• Utilizes IRB submission to identify relevant studies to register and report results per FDAAA
  – Initial & Continuing review eIRB submission

• IRB approval conditioned on receipt of NCT#  
  – Modifications/Deferral letters include language regarding trial registration

• Designation of Responsible Party to Investigator in all cases
  – Designates registration/reporting to the PI who best knows the study
  – PI is required to sign an appropriate *Clinical Trials Designation Letter*
  – Required prior to IRB approval

• PRS Administrators
  – Create profiles on Organizational accounts
  – Provide support regarding requirements and mechanics of database
  – Internal compliance activities to ensure FDAAA & ICMJE requirements are met
Resources
ClinicalTrials.gov

- Public website: https://clinicaltrials.gov/
- PRS system: https://register.clinicaltrials.gov/
- Registration resources: http://clinicaltrials.gov/ct2/manage-recs/how-register
- Results resources: http://clinicaltrials.gov/ct2/manage-recs/how-report
- More questions? Contact the ClinicalTrials.gov staff at register@clinicaltrials.gov.
Additional Resources

FDAAA


ICMJE

- ICMJE Clinical Trial Registration Requirements: [http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/](http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/)

CMS

Information re: Proposed Expansion of Requirements

NIH News & Events: *HHS and NIH take steps to enhance transparency of clinical trial results*

Questions?