www.ClinicalTrials.gov
What Trials Need to be Registered and Why

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Be aware that...
• Any PowerPoint presentation can only be an introduction to a topic.
• This subject is complex – DOCR is happy to assist you further.
• PowerPoint bullets are neither the law nor the regulations that apply.

Learning Objectives
• Describe ClinicalTrials.gov and recent updates
• Explain reasons to register your study
• Discuss the use of FDAAA required language in the Informed consent Document
• Work through practice examples
• Discuss registration and results reporting practice tips
• Identify Help Resources (institutional & national)
What is ClinicalTrials.gov?

Why should I be concerned?

http://www.ClinicalTrials.gov

ClinicalTrials.gov
A service of the U.S. National Institutes of Health
ClinicalTrials.gov can be searched in real time to find enrolling and completed studies including
• Conditions
• Interventions
• Outcome measures
• Sponsors/collaborators
• Locations
• Phases
• Dates (Start and Completion)
• Results
Original Rationales

• Increase research transparency and speed

• Help people find trials

To learn more, visit: http://clinicaltrials.gov/ct2/manage-recs/background

Cherry-picked Results

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.


ClinicalTrials.gov’s perspective: THIS IS THE LAW

Scientists (largely Pharma) changed endpoints in order to cherry-pick data, hiding unfavorable results;

ICMJE and Congress say: Nevermore!

With approved articles, the public interest in the results including adverse events is greater, so results will be required.
Evolution of Clinical Trial Disclosure Requirements

1997 FDAMA calls for public registry

1999 FDAMA requires ClinicalTrials.gov to include results

2000 ClinicalTrials.gov launched

2003 ICMJE requires registration of trials

2004 ClinicalTrials.gov results modules added

2005 FDAAA expands ClinicalTrials.gov to include results

2007 FDAAA requires ClinicalTrials.gov to include results

2008 ClinicalTrials.gov results modules added

2011 ICMJE requires affiliation of trials

2012 NIH requires individual data availability...

2014 Proposed Rulemaking goes to OIG

Adapted and expanded from: http://clinicaltrials.gov/ct2/about-site/history

Recent News

• NIH grant applications ask for NCT #s.
• NIH institutes transferred trials to PIs.
• FDA is checking when it investigates trials.
• CMS rule planned went live on January 1, “grace period” ends January 1, 2015
• Draft Regs went to OIG

Policies and Users

ClinicalTrials.gov

FDAAA

Sponsor Policy (e.g., NIH, VA)

ICMJE

Declaration of Helsinki

World Health Organization (WHO)

FDAMA 113

Recruitment (e.g., patients, physicians)

BPDA

Journal Editors

Researchers & Funders

Institutional Review Boards (IRBs)

Ottawa Statement

Health Policy-makers
Why should I register a trial in ClinicalTrials.gov?

# 1 It’s the law!

FDA Amendments Act of 2007 (FDAAA)
Most prospective clinical trials involving regulated drugs, biological products, and devices must be registered on ClinicalTrials.gov. (The law also requires reporting of results and adverse events for a subset of these studies.)

To learn more about FDAAA 801 Requirements, visit:
http://clinicaltrials.gov/ct2/manage-recs/fdaaa

It’s really two laws

An earlier law, FDAMA, already required certain IND trials, if testing efficacy, to register.

These involve primarily experimental treatments for serious or life-threatening diseases whether using an IND, Group C Cancer drug, or other FDA regulated product.

Thus, many studies for cancer and other serious and life-threatening diseases must register regardless of Phase.

For more information:
**Applicable Clinical Trials**

- A composite term for two separate tests:
  - Applicable Drug
  - Applicable Device
  - Clinical Trial
  - Clinical Trial

**FDAAA - Registration**

Required for “Applicable Clinical Trials”:
- Interventions studies (drugs, biologics, devices)
- Phase 2 – 4 (not phase 1 drug; not small scale feasibility OF device)
- US FDA jurisdiction (e.g., IND/IDE or US site)
- Studies initiated after September 27, 2007, or initiated on or before that date and were still ongoing as of December 26, 2007

When:
- Within 21 days of enrollment of 1st subject
- Update at least every 12 months (30 days for Recruitment Status and Primary Completion Date)


**FDAAA – Results Submission**

Required for:
- Applicable Clinical Trials
- In which the study product is approved by FDA (for any population, any use)

When:
- Within 12 months of Primary Completion Date (final data collection for primary endpoint)
- If product not approved by Primary Completion Date but is approved later, then results due 30 days after approval
- Delays are possible, primarily for manufacturer or under limited special circumstances
  - Pending publication is NOT considered a good cause for delay

#2 You Want to Publish!

International Committee of Medical Journal Editors (ICMJE)
- Requires registration in a publicly available, searchable system.
- Scope is broader than FDAAA (i.e., all clinical trials).
- Includes 1000+ journals that have adopted the ICMJE policy, such as BMJ, JAMA, and NEJM.

Source: http://www.icmje.org/journals.html

ICMJE – Registration: Which studies?

Required for Prospective studies that:
- Assign subjects to an intervention or concurrent comparison or control groups
- Study the cause/effect relationship between medical intervention and a health outcome.

ICMJE scope is much broader than the scope of FDAAA:
- Interventions include procedures, behavioral treatments, dietary interventions
- Health outcomes include any biomedical or health-related measure obtained in participants, including pharmacokinetic measures and adverse events

Source: http://www.icmje.org/about-icmje/faq/clinical-trials-registration/

ICMJE - Registration

- When to register:
  - Prior to enrollment of 1st subject
- ICMJE doesn’t require results submission
- ICMJE will not consider results data posted in the tabular format required by ClinicalTrials.gov to be prior publication

Source: http://www.icmje.org/about-icmje/faq/clinical-trials-registration/
#3: The Trial is NIH funded

![Image of NIH Funded Studies](image-url)

#4: CMS jumps on board

January 1, 2014:

- Voluntary rule becomes mandatory, but one year grace period is allowed

- Any items or services billed to Medicare for clinical trials that are qualified for coverage need ClinicalTrials.gov registration number (NCT #)

Source: MLN Matters Number SE1344

Reasons to Register in Clinicaltrials.gov

- FDAAA Results & AE Reporting (2007)
- FDAAA and FDAMA Registration (2007)
- ICMJE Registration (2005 soft; 2011 firm)
- NIH encouragement 2012
- CMS 2014
- Looking for Participants (2000)
Who is responsible for registering the trial?

**ICMJE:**
Anyone can register, but the author is responsible for ensuring complete registration

**FDAAA:**
The **Responsible Party** (RP) defined as...
- The Sponsor (or Sponsor-Investigator):
  - IND/IDE holder
  - If no IND/IDE, the industry, academic institution or other organization that initiated the study

Who is the RP? (Let’s practice)

1. Department funded/ PI initiated research
2. NIH funded research/ Duke is grantee institution
3. Pharmaceutical company funded research/ multi-center study including site at Duke
4. Device company funded research/ Duke PI is the IDE holder
5. Cooperative Group study
What happens if I don’t register?

Consequences of Noncompliance

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

CMS
- Cannot bill CMS for procedures or devices

ICMJE
- Cannot publish in journals following ICMJE policy, and other select journals

What are my responsibilities for the following studies? Hmmm…
Study #1
Effectiveness of Bupropion for Treating Nicotine Dependence in Young People

- Study Design: Multi-center, Randomized, Efficacy Study
- Interventions: Bupropion, Placebo
- Primary Outcome: Smoking behavior over 6 months

Register? For FDAAA? For ICMJE? Results? Responsible Party?

Study #2
Effects of Chronic Sleep Restriction in Young and Older People

- Study Design: Crossover Assignment
- Interventions: Chronic sleep restriction
- Primary Outcome: Changes in sleep and waking EEG measures, frequent measures of performance, attention, alertness
- Other fact: Two universities collaborating, Dr. A @ AU and Dr. B at BU; Dr. B designed study, but A will enroll more

Register? For FDAAA? For ICMJE? Results? Responsible Party?

Study #3
Assess the impact on Quality of Life (QoL) of long term caregivers of patients with multiple sclerosis.

- Centers/sample size: Multi-site, 450 subjects
- Intervention/method: Caregivers take QoL survey monthly for 2 years
- Other fact: Funded by Pharmaceutical Co.

Register? For FDAAA? For ICMJE? Results? Responsible Party?
Study #4
Implantable device designed to relieve the symptoms of heart failure through counter-pulsation technology.
• Study Design: Open Label
• Intervention: Implantable device (IDE obtained)
• Primary outcome: to test the feasibility of the device
• 8 people enrolled, 6 month study

Study #5 – Last one
Hip Fracture Study
• Method: Compile data from electronic medical record (EMR) over a two year period for 1700 subjects
• Data elements: smoking status, use of alcohol, bone marrow density, weight, and height
• Primary Outcome: Determine the validity of a new hip fracture risk assessment method compared to FRAX, World Health Organization’s fracture risk tool

What is the FDAAA requirement for informed consent language?
Informed Consent Language

• FDA Mandated Changes in Consent Form Language
  The FDA has added a new element of consent that is required for "applicable clinical trials." All applicable clinical trials are required to include this new element of consent by March 7, 2012.

• By federal regulation, the required language must be incorporated verbatim and cannot be altered in any way. "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."

“As required by law”

• Note: you should only include that section if the trial is an "applicable clinical trial" required by law to post in ClinicalTrials.gov.

• If not, do not use this language.

Guidance for Sponsors, Investigators, and Institutional Review Boards
Questions and Answers on Informed Consent Elements,
21 CFR § 50.25(c)
(Small Entity Compliance Guide) Feb. 2012
Nonbinding on government!

Reasons to Register & Use Informed Consent Language

FDAAA Results & AE Reporting
FDAAA and FDAMA Registration
ICMJE Registration
Looking for Participants
Challenge: #1

Does Academic leadership recognize the work involved?
We estimate that each results record will submitted once and updated twice. We have increased our estimate of the average response time to 25 hours from the 10 hour estimate included in the previous OMB clearance request. We estimate that updates take 8 hours...

Federal Register / Vol. 77, No. 27 / Thursday, February 9, 2012

PRACTICE TIP:
- Make sure you discuss registration with your PI –
- Help him/her realize this is insurance for an article, and if it needs results, it IS an article (just in different format!)

Challenges #2 & 3

- Trials with unusual features, like adaptive trial design, are even harder to enter than Pharma “cookie cutter” trials.
- Minimal free text; all charts
- NOTHING in Clinicaltrials.gov EVER goes away!

Biggest Mistake in Registrations

- Do not use AIMS as Outcome Measures.
- Outcome Measures need to be specific, measurable, and really part of the clinical trial, not part of research project broadly painted
- Otherwise they’ll have to be amended or deleted – looks bad – an ounce of prevention!
Challenges # 4 & #5

• Researchers’ fear of others “scooping” their trials
• One Year Time clock to posting primary endpoint results

PRACTICE TIP: Update every 6 months, at Scheduled Continuing Review and at “1/2 years”

Best Time Saving Tip

• Look at Adverse Event Reporting Modules to get a feel for how AE information will go in.
• Arrange to have your data collection prepared for these modules if you have an ACT with an already approved drug or device

Challenge # 6

• Results take time like publication
• Results go public like publication
• Results advance science like publication
• But... RESULTS, not having Peer review don’t get tenure credit like publication
Looming Issues

- FDAAA expansion, clarification, or elaboration
  - Proposed Rulemaking was set for September 2010 now say December 2014
  - Stay tuned... When Proposed Rulemaking comes out possible additions include:
    - Statute specifies results may be required of all ACTs
    - Statute allows expansion to 18 month time frame for results reporting
- Enforcement

What if I have more questions?

Getting Started:
http://clinicaltrials.gov/

See Submit Studies
Submit Studies Helps

• Frequently Asked Questions
  Review frequently asked questions for sponsors or investigators regarding PRS and entering study data.
• Support Materials
  Find data element definitions and resources related to registration and results submission, as well as links to relevant laws and policies. Includes links to resources on external sites such as the Food and Drug Administration and International Committee of Medical Journal Editors.
• Training Materials
  View National Library of Medicine presentations and workshop materials for researchers and study record managers on submitting data to ClinicalTrials.gov and related laws and policies.

Can a study record be deleted off of ClinicalTrials.gov?

• Only if the study record has never been published on ClinicalTrials.gov
• Otherwise, No.
• ClinicalTrials.gov serves as a long-term public registry. Once a study record is published, it remains in the system even after a trial has closed.
• If you find a duplicate, contact ClinicalTrials.gov at register@clinicaltrials.gov.

Checking your Problem Records

PRS System identifies current ‘Problem Records’
• Records that have not been marked as completed
• Active studies that have not been updated in the past 6 months
• Records missing one or more data elements required by FDAAA, such as: Responsible Party, Study Start Date, Primary Completion Date and Primary Outcome Measure
• Records that appear to be overdue for registration of results per FDAAA
Additional Resources

- General ClinicalTrials.gov information: http://clinicaltrials.gov/ct2/about-site
- FDAAA related information: http://clinicaltrials.gov/ct2/manage-recs/fdaaa
- For specific questions or comments: register@clinicaltrials.gov
- Office of Extramural Research (OER): http://grants.nih.gov/ClinicalTrials_fdaaa/
- Instructions for Authors sections of ICMJE journals all have information regarding clinical trial registration
- Duke Office of Clinical Research (DOCR.Help@duke.edu) http://docr.som.duke.edu/study-support/clinicaltrialsgov

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