ClinicalTrials.gov

How Does it Affect Me?
What Do I Need to Know?

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Be aware that...

- Any PowerPoint presentation can only be an introduction to a topic.
- This subject is complex – this will point you to many other resources – and our office is happy to assist you further.
- PowerPoint bullets are neither the law nor the regulations that apply.
Learning Objectives

• Explain what ClinicalTrials.gov is and what it can do

• Explain why you should register your study
  o FDAAA
  o CMS
  o ICMJE
  o Voluntary (Recruitment etc.)

• Identify who is responsible for registration

• Provide practice examples

• Explain how registration works at YOUR INSTITUTION

• Help Resources (institutional & national)
What is ClinicalTrials.gov?

Why should I be concerned?
http://www.ClinicalTrials.gov

ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. Learn more about clinical studies and about this site, including relevant history, policies, and laws.

ClinicalTrials.gov currently lists 170,410 studies with locations in all 50 states and in 187 countries.

Search for Studies
Example: "Heart attack" AND "Los Angeles"

Search Help
- How to search
- How to find results of studies
- How to read a study record

Locations of Recruiting Studies
- Non-U.S. Only (51%)
- U.S. Only (43%)
- Both U.S. & Non-U.S. (6%)

Total N = 33,192 studies
Data as of July 07, 2014

For Patients & Families
- How to find studies
- See studies by topic
- Learn about clinical studies
- Learn more...

For Researchers
- How to submit studies
- Download content for analysis
- About the results database
- Learn more...

For Study Record Managers
- Why register?
- How to register study records
- FDAAA 801 Requirements
- Learn more...

Learn More
- ClinicalTrials.gov Online Training
- Glossary of common site terms

For the Press
Using our RSS Feeds
Help for Registering Studies on ClinicalTrials.gov

• “Submit Studies”
  http://clinicaltrials.gov/ct2/manage-recs

• “For Researchers”
  http://clinicaltrials.gov/ct2/help/for-researcher

• “For Study Record Managers”
  http://clinicaltrials.gov/ct2/help/for-manager
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
Rationale

• Increase research transparency

• Help people find trials

To learn more, visit: http://clinicaltrials.gov/ct2/manage-recs/background
Evolution of Clinical Trial Disclosure Requirements

1997: FDAMA establishes ClinicalTrials.gov

2000: ClinicalTrials.gov launched

2005: ICMJE requires registration of trials (including at ClinicalTrials.gov)

2007: FDAAA expands ClinicalTrials.gov to require registration of more studies and results and adds penalties for noncompliance

2008: ClinicalTrials.gov adds basic results modules, including adverse events

2014: MS billing rule implemented requiring NCT # (Full obligatory compliance required as of 1/1/2015)

2014: Notice of Proposed Rulemaking (NRPM) for FDAAA 801 and NIH Draft Reporting Policy for NIH-Funded Trials made available for public comment

Adapted from http://clinicaltrials.gov/ct2/about-site/history
Clinical Trials Final Regulation Expected in February

- NIH said in a June 10 *Federal Register* notice it is seeking Office of Management and Budget (OMB) approval to continue a "data collection project," namely the requirements related to registration of trials and related information at clinicaltrials.gov. However, this does not mean NIH has abandoned its plans for a final rule that would expand the requirements to more trials and additional information about them (*RRC 2/15, p. 6*). NIH clarified that while the "extension request does not include any changes to the information submission requirements for ClinicalTrials.gov that were proposed in the Notice of Proposed Rulemaking on Clinical Trial Registration and Results Submission that was issued on November 21, 2014 and for which the public comment period closed on March 23, 2015," the agency "is continuing to review submitted public comments as it prepares the final rule. The NIH will make any corresponding changes to the ClinicalTrials.gov information collection via separate procedure." Comments on the information collection will be accepted for 60 days from the date of the *Federal Register* publication. According to the most recent OMB list of regulations in development, the final clinicaltrials.gov rule is expected to be published in February 2016.

- **Link to Federal Register notice:** [https://federalregister.gov/a/2015-14169](https://federalregister.gov/a/2015-14169)
Policies and Users

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](http://clinicaltrials.gov/ct2/manage-recs/fdaaa)
It’s the law (a final detail)

Some Phase I trials, though they are not Applicable Clinical Trials under FDAAA, are required to register under FDAMA – the earlier law -- which is still in effect.

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:
FDAAA - Registration

Required for “Applicable Clinical Trials”:

• Interventional studies (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 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)

http://clinicaltrials.gov/ct2/manage-recs/fdaaa
FDAAA – Results Submission

Required for:

- Applicable Clinical Trials
- In which the study product is approved *(for any use)* by FDA

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

http://clinicaltrials.gov/ct2/manage-recs/fdaaa
#2 Centers for Medicare & Medicaid Services (CMS) Billing Rule

- Effective January 1, 2015 - mandatory reporting of the NCT# on claims for items and services provided in “qualified clinical trials” for Medicare coverage.

CMS: 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 slide represents a 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=BAABAAAAAA
#3 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-following-the-icmje-recommendations/](http://www.icmje.org/journals-following-the-icmje-recommendations/)
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

ICMJE - Registration

• When to register:
  o **Prior to enrollment of 1\textsuperscript{st} subject**

• ICMJE doesn’t require results submission, but does encourage it

• ICMJE will not consider results data posted in the tabular format required by ClinicalTrials.gov to be prior publication

The Trial is NIH funded

Source: http://grants.nih.gov/ClinicalTrials_fdaaa/index.htm
Reasons to Register in Clinicaltrials.gov

FDAAA and FDAMA Registration

ICMJE Registration

CMS 2014

FDAAA Results & AE Reporting

NIH encouragement 2012

Increasing Recruitment
Who is responsible for registering?
Who is responsible for registering the trial?

**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

**ICMJE and CMS:**

Anyone can register, but for ICMJE the author is responsible for ensuring complete registration
FDAAA: Designation of Responsible Party

RP can be designated by the Sponsor to a PI who

- 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 “Your U” funded by NHLBI
  - “Your U” is the Sponsor (grant funding recipient)
  - “Your U” can be the RP or designate the PI as the RP
    - Note: even if not designated as RP, the PI can still enter data into ClinicalTrials.gov
Who is the RP? (Let’s practice)

1. Department funded/ PI initiated research
2. NIH funded research/ “Your U” is the grantee institution
3. Pharmaceutical company funded research/ multi-center study including site at “Your U”
4. Device company funded research/ “Your U” 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**
- Billing will be affected: delayed or denied

**ICMJE**
- Cannot publish in journals following ICMJE policy, and other select journals
What are my responsibilities for the following studies? Hmm...
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](http://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. For more information or questions, contact the “YOUR U” IRB office or office of regulatory affairs.
“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!
Coming Soon ... Perhaps

Notice of Public Rulemaking (NPRM) for FDAAA 801 – issued November 2014

Notable changes from current requirements and practice:

- A streamlined approach for determining which trials are subject to the proposed regulations and who is responsible for submitting required information.
- Expansion of the set of trials subject to summary results reporting to include trials of unapproved products.
- Additional data elements that must be provided.
- Clarified procedures for delaying results submission.
- More rapid updating of several data elements.
- Procedures for timely corrections to any errors discovered by the responsible party or by the Agency as it processes submissions prior to posting.

Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information – issued November 2014

- “… all NIH-funded awardees and investigators conducting clinical trials, funded in whole or in part by NIH, who have committed to NIH that they will comply with NIH policies, are expected to ensure that their NIH-funded clinical trials are registered and summary results, including adverse event information, are submitted to ClinicalTrials.gov in accord with the timelines that will be set forth at ClinicalTrials.gov.”

What if I have more questions here or in general?
Local Contacts:

For Additional Information:

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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/

- Frequently Asked Questions for NIH Grantees
  http://grants.nih.gov/Clinicaltrials_fdaaa/faq.htm

- Instructions for Authors sections of ICMJE journals all have information regarding
  clinical trial registration
  http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-
  registration.html

CMS

- Mandatory Reporting of NCT# Requirement

- Qualifying Trial information:
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