ClinicalTrials.gov

How Does it Affect Me?
What Do I Need to Know?
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
• Help Resources (institutional & national)
What is ClinicalTrials.gov?

Why should I be concerned?
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
Policies and Users

CMS

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 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
  o 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, 2014 - mandatory reporting of the NCT# on claims for items and services provided in “qualified clinical trials” for Medicare coverage.

**BUT**.... If don’t have ability to comply currently, may use the generic # 99999999 until January 1, 2015. After that, you need the NCT#!

See
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=BAABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABABAB
• 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

Source: http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/
ICMJE - Registration

• When to register:
  o Prior to enrollment of 1st 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 Results & AE Reporting

FDAAA and FDAMA Registration

ICMJE Registration

Increasing Recruitment

CMS 2014

NIH encouragement 2012
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
Assuming FDAAA applies...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
Assuming FDAAA applies... Who is the RP? (Let’s practice)

1. Department funded/ PI initiated research: PI
2. NIH funded research/“Your U” is the grantee institution: “Your U” – BUT, may designate to appropriate PI; ask about institutional policy
3. Pharmaceutical company funded research/ multi-center study including site at “Your U”: Pharma
4. Device company funded research/ “Your U” PI is the IDE holder: PI as IDE holder
5. Cooperative Group study: Stay tuned; This is still unclear. The law and database don’t have all possible scenarios spelled out.
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? 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 #1

– Yes, the study should be registered for FDAAA and ICMJE because it is an applicable clinical trial and also meets ICMJE standards. (It is an applicable clinical trial because it is a clinical investigation, a controlled study, using an FDA-regulated drug, and has one or more sites in the US.)

– The Responsible Party is either the Pharmaceutical company, if they began it, or the overall PI who controls the protocol etc. – unless the study is funded by the government, in which case it’s the grantee institution until delegated
Study #2

Effects of Chronic Sleep Restriction in Young and Older People

• Study Design: Open label, 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 #2

– Here there is no need to register or report results for FDAAA as it is not an applicable clinical trial because it involves only process of care, not testing an FDA regulated or approved product. However, ICMJE standards do apply, as there is assignment into groups regarding process of care and a health outcome. So registration is recommended to protect publication options.

– No results are required for ICMJE.

– Responsible Party? Who controls the data? Can we tell here? Some follow up questions are required.
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 #3

– As a prospective observational study, there is no obligation to register here. This description doesn’t show any signs of a drug, device, or even controlled process of care being evaluated. However, since ICMJE says, “when in doubt, register,” some RPs might want to register before enrolling participants, just to be certain that publication options wouldn’t be curtailed subsequently.

– The Responsible Party may be the pharmaceutical company or may be the academic organization/data coordinating center; it will depend on the contract.
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

Register? For FDAAA? For ICMJE?
Results?
Responsible Party?
Study #4

– Is this an applicable device trial? Let’s see:

– This is a device trial, but it doesn’t compare an intervention with a device against a control.

– Is it other than a small clinical trial to determine the feasibility of a device? No, it IS a small feasibility study.

– Therefore it’s exempt from the requirement to register according to FDAAA, and therefore will not require results reporting.

– This does not fall under FDAAA but does fall under ICMJE. Intervention prospectively assigned to study the cause & effect relationship between a medical intervention & a health outcome. Comparison groups not needed for ICMJE to apply!

– The IDE holder would be the responsible party.

– Results do not need to be entered for ICMJE purposes.
Study #5

Dental graduate student is the investigator for a medical device study.

• Study Design: Randomized
• Intervention: Treatment with 1 of 3 different FDA approved medical devices
• Primary Outcome: Which device increases fluoride in saliva the most?

Register? For FDAAA? For ICMJE?
Results?
Responsible Party?
Who will follow up when she graduates?
Study #5

This is an applicable device trial because it is:

– A prospective clinical study of health outcomes
– It compares an intervention with a device against a control in human subjects
– The studied device is subject to section 510k, 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act (FDC Act)
– It is other than a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes.

Therefore, register and report results because it’s required under FDAAA. Register prior to the first subject enrollment to meet ICMJE requirements.

RP may depend on if student is conducting the trial, or has access and control of the data. Once the student graduates, RP depends on who has access and control of the data. (Note: many institutions would not allow a student to be a responsible party; a staff member mentoring the student would be the RP.) Follow up is critical; someone at the institution has to accept responsibility to be the RP and enter the results.
Study #6 – 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

Register? For FDAAA? For ICMJE? Results? Responsible Party?
Study #6 – Last one

– This is a retrospective observational study. There is no requirement to register the study from FDAAA or ICMJE because this is an observational study.

– However the PI may want to register to be sure there are no future problems in acceptance for publishing, and some PIs like to share their work; however, no results reporting is needed.
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:

Find your local contact via the Harvard Catalyst Regulatory Atlas:
http://connects.catalyst.harvard.edu/regulatoryatlas/?mode=c&id=50
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

CMS

• Mandatory Reporting of NCT# Requirement

• Qualifying Trial information:
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