ClinicalTrials.gov 101:
New Regulations and Tips for Success

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Today’s Session:

1. Registration Criteria
2. Registration Basics and Tips
3. New NIH Regulations
4. Record Updates and Results Basics and Tips
5. Resources at UW (and Future Sessions)
# Requirements for CT.gov in 2017

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Registration required

Registration encouraged

CT.gov Record Universe at UW-Madison
First Question: Who is responsible for registering the trial?

Study team/group *initiating* study is responsible for registering study

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

ICMJE:
Anyone can register, but for ICMJE the author is responsible for ensuring complete registration
If you’re unsure, check with other study players to make sure it gets registered
CMS Registration

Required for “qualifying trials”

- 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

When:

- Before study enrollment begins (as a part of SMPH sign-off)
  - Contact Nancy Lutz: nlutz@uwhealth.org, 262-7711
FDA 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)

When:

- Within 21 days of enrollment of 1st subject
Identifying an “Applicable Clinical Trial” under FDAAA

• This flowchart presents basic guidance on determining if a trial is considered an “applicable clinical trial” under FDAAA. It maps out the guidance provided in the “Elaboration of Definitions of Responsible Party and Applicable Clinical Trial” and is also available as an interactive flowchart at: https://grants.nih.gov/clinicaltrials_fdaaa/docs/Flow_chart-ACT_only.pdf

• This flowchart may not address every situation. The grantee’s sponsored research office, general counsel, or other similar official should be involved in determining whether or not the grant supports an applicable clinical trial that needs to be registered under FDAAA.

Does the trial include a drug, biologic or device?

Yes

Yes, a drug or biologic

Does the device trial meet all of the following 4 criteria?

1) It is a prospective clinical study of health outcomes;
2) It compares an intervention with a device against a control in human subjects;
3) The studied device is subject to section 510(k), 515, or 520(m) of the FDC Act; and
4) It is not an exempt small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary endpoint is not health outcomes but device performance.

Yes

The trial would generally be considered an applicable device clinical trial.

No

The trial would not be considered an applicable clinical trial.

Yes, a device

The trial would not be considered an applicable clinical trial.

No

The trial would generally be considered an applicable drug clinical trial.

Does the trial meet all of the following 4 criteria?

1) It is a clinical investigation;
2) It is a controlled clinical investigation;
3) It is other than a Phase 1 clinical investigation; and
4) It investigates a drug (including a biological product) subject to section 505 of the Federal Food, Drug, and Cosmetic Act (FDC Act) or section 351 of the Public Health Service Act.

Yes

The trial would generally be considered an applicable clinical trial.

No

The trial would not generally be considered an applicable clinical trial.

Review the following criteria to determine if the applicable clinical trial (ACT) needs to be registered under FDAAA:

If the trial was initiated after 9/27/2007 ...

If the trial was initiated on or before 9/27/2007 and ongoing as of 12/26/2007 and involves a serious or life threatening disease or condition ... Then the ACT must be registered not later than 21 days after the first patient is enrolled, or by 12/26/2007, whichever is later.

If the trial was initiated on or before 9/27/2007 and ongoing as of 12/26/2007 and does not involve a serious or life threatening disease or condition ...

Then the ACT must be registered by 12/26/2007.

If the trial was ongoing as of 9/27/2007, did involve a serious or life threatening disease or condition and was completed (meaning, not ongoing) by 12/26/2007 ...

Then the ACT must be registered by 12/26/2007.

If the trial was ongoing as of 9/27/2007, did not involve a serious or life threatening disease or condition and was completed (meaning, not ongoing) by 12/26/2007 ...

Then the ACT is not subject to FDAAA, although it is a drug clinical trial, it may be subject to pre-existing registration requirements under the Food and Drug Administration Modernization Act (FDAMA) of 1997.

If the trial was initiated on or before 9/27/2007 ...

If the trial was ongoing as of 9/27/2007 and involves a serious or life threatening disease or condition ...

Then the ACT must be registered by 9/27/2008.

If the trial was ongoing as of 9/27/2007, did not involve a serious or life threatening disease or condition and was completed (meaning, not ongoing) by 12/26/2007 ...

Then the ACT is not subject to FDAAA, and even if it is a drug clinical trial, it is also not subject to pre-existing registration requirements under FDAMA.

If the trial was initiated after 9/27/2007 ...

If the trial was initiated on or before 9/27/2007 and ongoing as of 12/26/2007 and does not involve a serious or life threatening disease or condition and was completed (meaning, not ongoing) by 12/26/2007 ...

Then the ACT is not subject to FDAAA, although it is a drug clinical trial, it may be subject to pre-existing registration requirements under the Food and Drug Administration Modernization Act (FDAMA) of 1997.
NIH Registration

Required for Clinical Trials
• 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.

When:
• Within 21 days of enrollment of 1st subject

Applies to all clinical trials funded by NIH and approved by the IRB on or after 1/18/2017
ICMJE Registration

Required for **clinical trials**
- Prospective assignment
- To an intervention
- To study cause and effect relationship between a health-related intervention used to modify a biomedical or health-related outcome

When:
- “...best practice dictates registration by the time of first patient consent.”
Should you Register this Study?

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?
Should you Register this Study?

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?
New NIH Policy on Dissemination of NIH–Funded Clinical Trial Information

• Applies to all clinical trials funded in whole or in part by NIH which begin on or after 1/18/2017

• Must follow FDAAA requirements
  • Must be registered on clinicaltrials.gov and report results
  • ClinicalTrials.gov must be referenced in informed consent document

• Summary Table of NIH policy: https://www.nih.gov/news-events/summary-table-hhs-nih-initiatives-enhance-availability-clinical-trial-information
Consent Form Language

• For FDA and NIH Studies:

“A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Website at any time.”
Results Reporting

• FDA regulated studies must report results (FDAAA 801)
• NIH funded studies must report results
• 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)

• Accurate Registration Entry is Essential for Results Reporting
  (Be sure your registration is as accurate and complete before entering results. Registration inaccuracies will be replicated in the results reporting module as some fields auto populate.)
Results Reporting

• The Four Results Modules
  1. Participant Flow
     – Provide information about the study design by documenting the “flow” of participants through different stages of the study.
     – The module should account for all enrolled participants, and make it clear which participants were analyzed.
     – Examples: Recruitment Details, Pre-assignment Details, Arm/Group, Milestones
  2. Baseline Characteristics
     – Demographic and clinical measures, such as baseline values of outcome measures or prior and concurrent treatment characteristics broken down by arm/group
     – Examples: Age, Gender
Results Reporting

• The Four Results Modules, continued

3. Outcome Measures
   – “...a table of values for each of the primary and secondary outcome measures for each arm of the clinical trial...including the results of scientifically appropriate tests of the statistical significance of such outcome measures.”
   – Example: Outcome Measure Description, Unit of Measure, Time Frame, Type (e.g., mean, median)

4. Adverse Events
   – Reported in accordance with the procedures for data collection as defined in the protocol
   – Reported as summary data at the end of the study (not real time)
   – Example: Total Number, Frequency, Number per Participant
Results Reporting Timeline

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
Partial Results/ Rolling Results

**Primary Completion Date:** Last data collection for primary outcome measure

**Study Completion Date:** Last data collection for primary, secondary and adverse events

- **Enrollment Begins**
- **Primary Completion Date**
- **Post Primary Outcome Results**
- **Last Secondary Completion Date**
- **Post Last Secondary Outcome Results**

12 months maximum

IRA Approval and Clinicaltrials.gov Registration

Record verification every 6 months
Preparing for Results Reporting

If you are new to Results Reporting, these general resources will help you prepare:

1. How to Submit Your Results homepage

2. Basic Results Data Elements Definitions
   http://prsinfo.clinicaltrials.gov/results_definitions.html

3. PRS User Guide
   Located on Main Menu in CT.gov database

4. 10 minute webinars for each results module
   http://clinicaltrials.gov/ct2/manage-recs/present

5. Helpful Hints (with common study designs examples)
   http://prsinfo.clinicaltrials.gov/ResultsExamples.pdf
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Clinicaltrials.gov Registration

Registration at Clinicaltrials.gov may be required for Federal Drug Administration (FDA) or International Committee of Medical Journal Editors (ICMJE) publication purposes as described below. Click on the help link above for additional information on these requirements.

20.1 Does this study need to be registered at Clinicaltrials.gov to meet the FDA’s registration requirements? Note: The FDA requires study registration along with results and adverse event reporting for:

- a) all phase II – IV interventional drug or biologic trials, and
- b) trials of devices that are either
  - i. controlled trials with healthy outcomes of devices subject to FDA regulation, other than small feasibility studies,
  - ii. pediatric postmarket surveillance required by FDA

* Yes ☐ No ☐ Clear

20.1.1 Does this study need to be registered at Clinicaltrials.gov to meet the ICMJE requirements? Note: The ICMJE requires the registration of all health-related interventional studies investigating relationships between the health-related intervention and any health outcomes (interventions include: drugs, surgical procedures, devices, behavioral treatments, educational programs, dietary interventions, and process-of-care changes).

* Yes ☐ No ☐ Clear

20.2 If yes to either question above, who has or will register the study prior to the enrollment of the first subject?

- UW-Madison principal investigator
- Industry sponsor of the study
- Cooperative group
- Other

Clear

20.2.1 If other, specify.


Consequences of Noncompliance

CMS
- Delayed initiation (institutional hold)
- Billing will be affected: delayed or denied.

FDAAA/NIH
- Public notices of noncompliance and violations
- Withholding of NIH funds
- FDA sanctions (483 letter)
- Civil monetary penalties (up to $10,000/day)

ICMJE
- Manuscripts can be refused
CT.gov Resources

• KnowledgeBase for ClinicalTrials.gov
  https://kb.wisc.edu/gsadminkb/page.php?id=34044

• General ClinicalTrials.gov information
  http://clinicaltrials.gov/ct2/about-site

• Reach out to CT.gov directly – they are fast, helpful!
  register@clinicaltrials.gov

• FDAAA related information
  http://clinicaltrials.gov/ct2/manage-recs/fdaaa

• ICMJE related information
Additional Resources

NIH
• Office of Extramural Research (OER)  
  http://grants.nih.gov/Clinicaltrials_fdaaa/
• Frequently Asked Questions for Grantees  
  http://grants.nih.gov/Clinicaltrials_fdaaa/faq.htm

CMS
• Mandatory Reporting of NCT# Requirement    
• Qualifying Trial information  

UW-Madison has a cross-campus ClinicalTrials.gov Committee that provides monitoring and end-user support for ClinicalTrials.gov.