Clinical Trials Registration Requirements: What You Should Know

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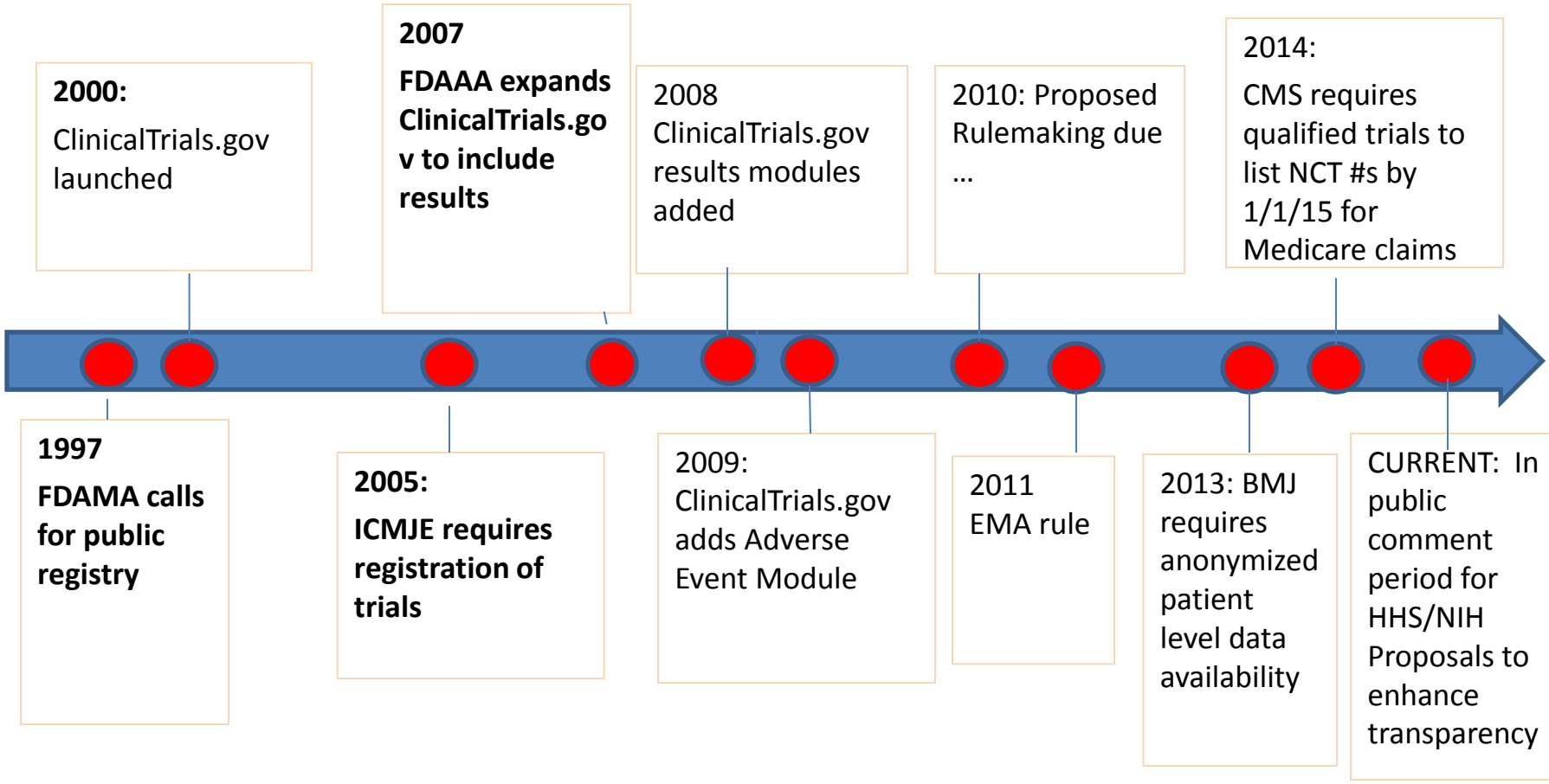
Outline

- 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



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

Eli Lilly & Co.'s Zyprexa schizophrenia medication

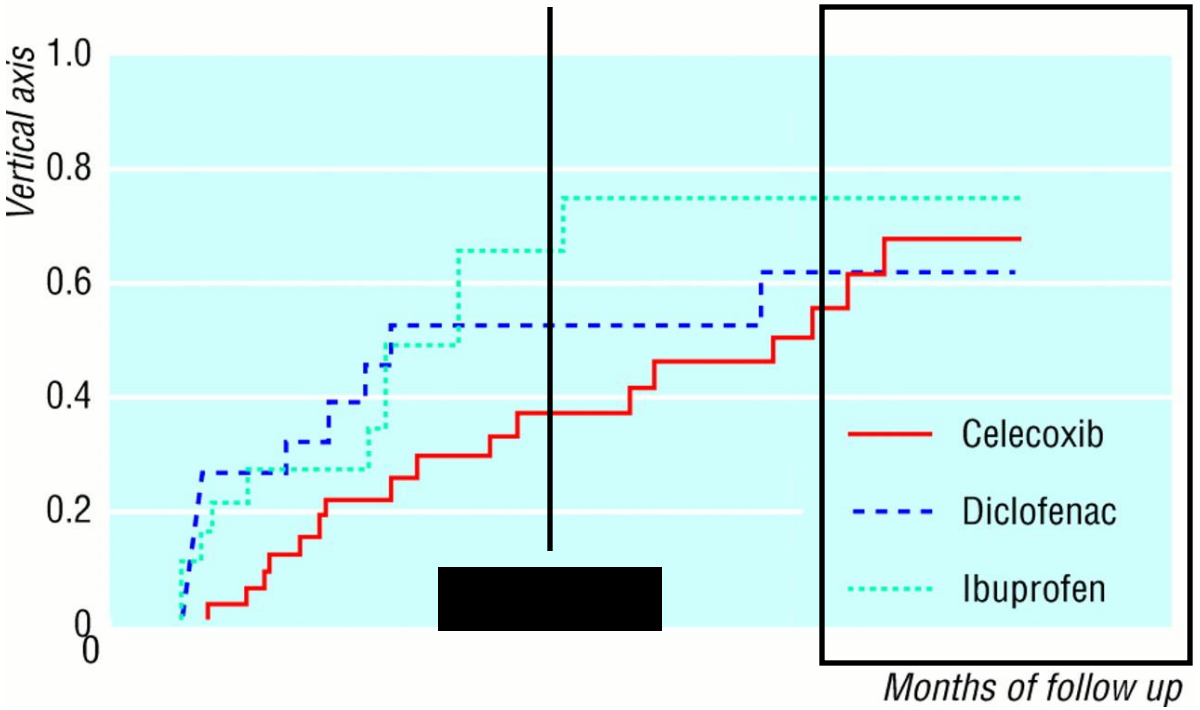
June 12 (Bloomberg) -- Eli Lilly & Co. urged doctors to prescribe Zyprexa for elderly patients with dementia, an unapproved use for the antipsychotic, even though the drugmaker had evidence the medicine didn't work for such patients, according to unsealed internal company documents.

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.

See Bloomberg, June 2009, at
http://www.bloomberg.com/apps/news?pid=newsarchive&sid=aTLcF3zT1Pdo

2000 – JAMA



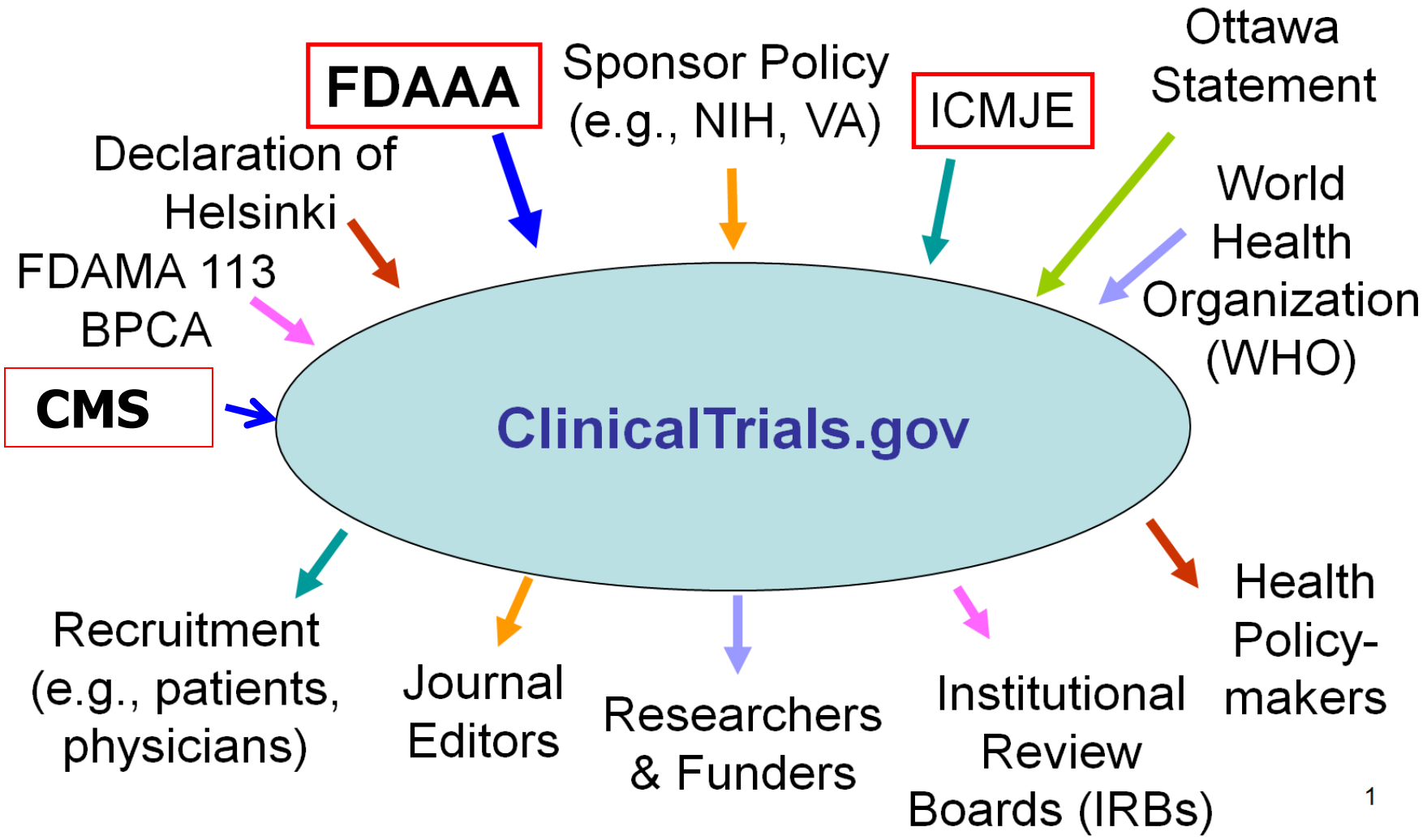
Kaplan-Meier estimates for ulcer complications according to traditional definition. Results are truncated after 12 months, no ulcer complications occurred after this period. Adapted from Lu 2001.

Juni, P. et al. BMJ 2002;324:1287-1288

Rationale

- Transparency
- Identify clinical trials for participants

Policies and Users



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Updated from D. Zarin, ClinicalTrials.gov, *Overview of ClinicalTrials.gov* presentation, December 2008, http://prsinfo.clinicaltrials.gov/webinars/module1/resources/Overview_Handouts.pdf.

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:
http://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf

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:
http://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf

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:
http://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf

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 1st subject is enrolled
- ICMJE does NOT consider results data posted on ClinicalTrials.gov as prior publication

See ICMJE, http://www.icmje.org/about-icmje/faqs/clinical-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#!**

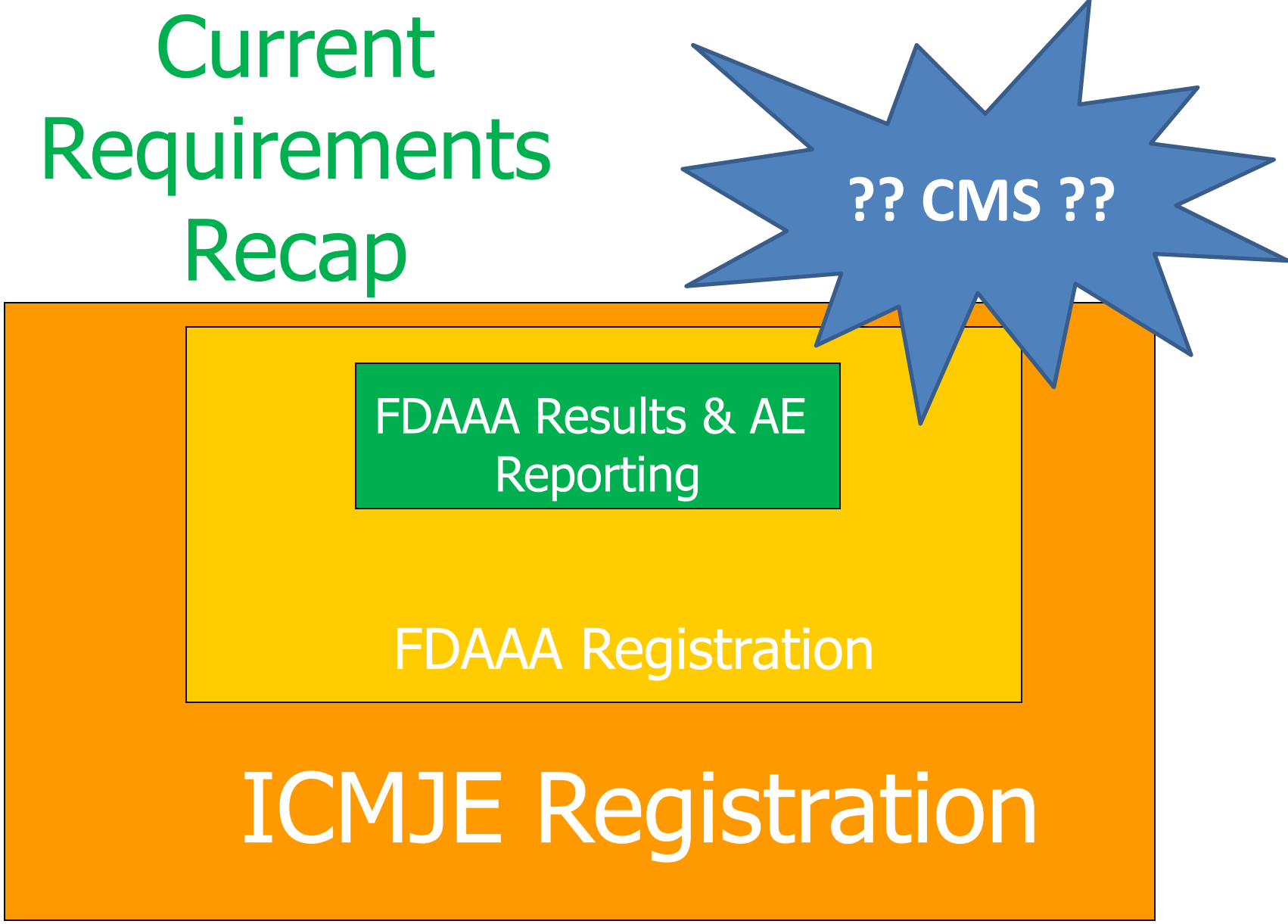
  See http://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/Downloads/SE1344.pdf

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 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=BAABAAAAAAAA&

Current Requirements Recap



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
  - Mulit-center, Randomized, Efficacy Study
  - Interventions: Bupropion, Placebo
  - Primary Outcome: Smoking behavior over 6 months
  - NIH funded research/BU is the grantee institution

Study #2

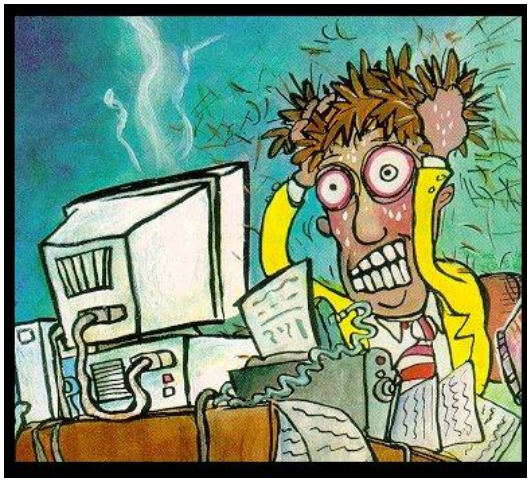
- Effects of Chronic Sleep Restriction in Young and Older People
  - Interventions: Chronic sleep restriction
  - Primary Outcome: Changes in sleep and waking EEG measures, frequent measures of performance, attention, alertness
  - Department funded/ PI initiated research

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

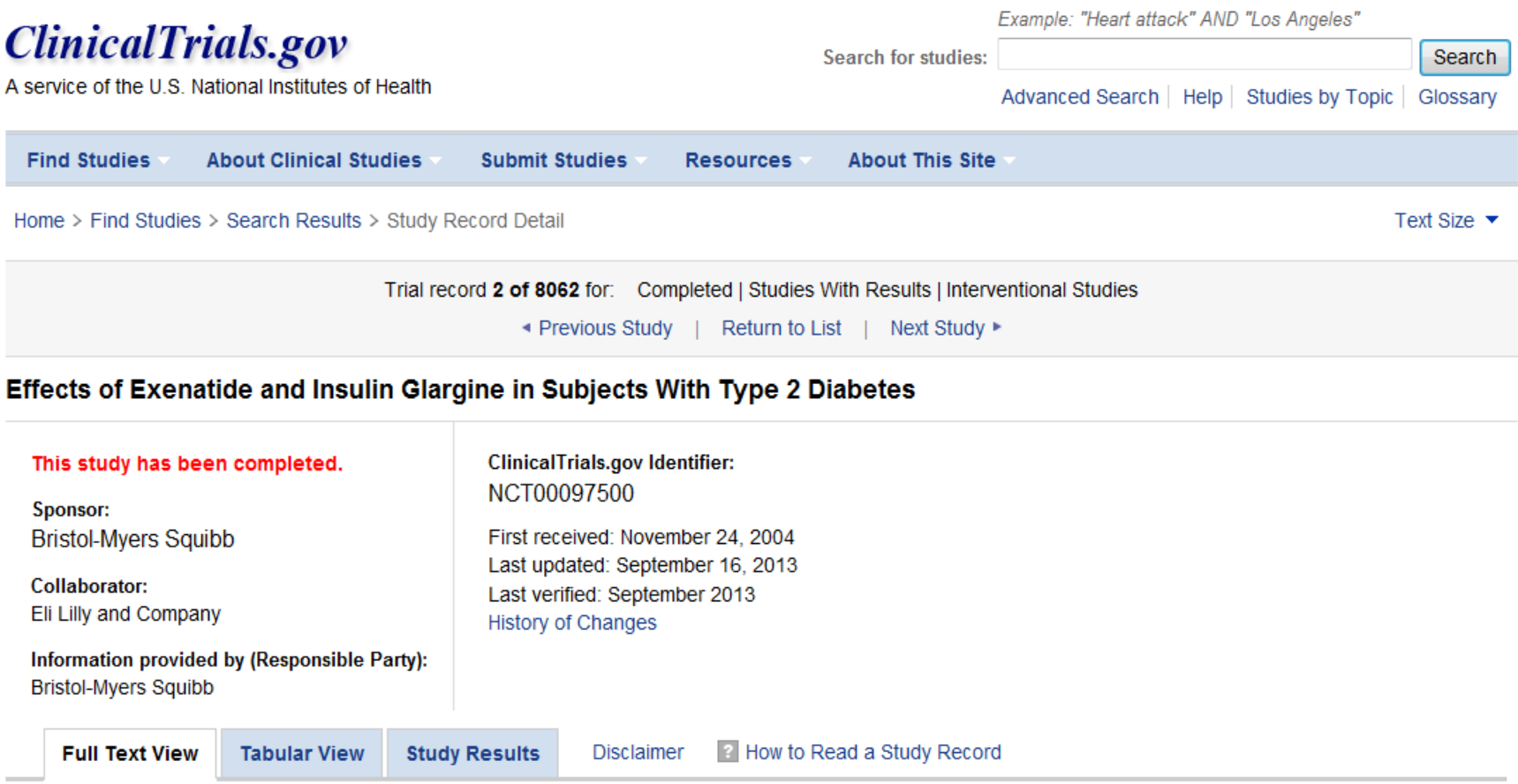
ClinicalTrials.gov Database: A Bird's Eye View

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



Public website: https://clinicaltrials.gov/

Protocol Registration System (PRS) System 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

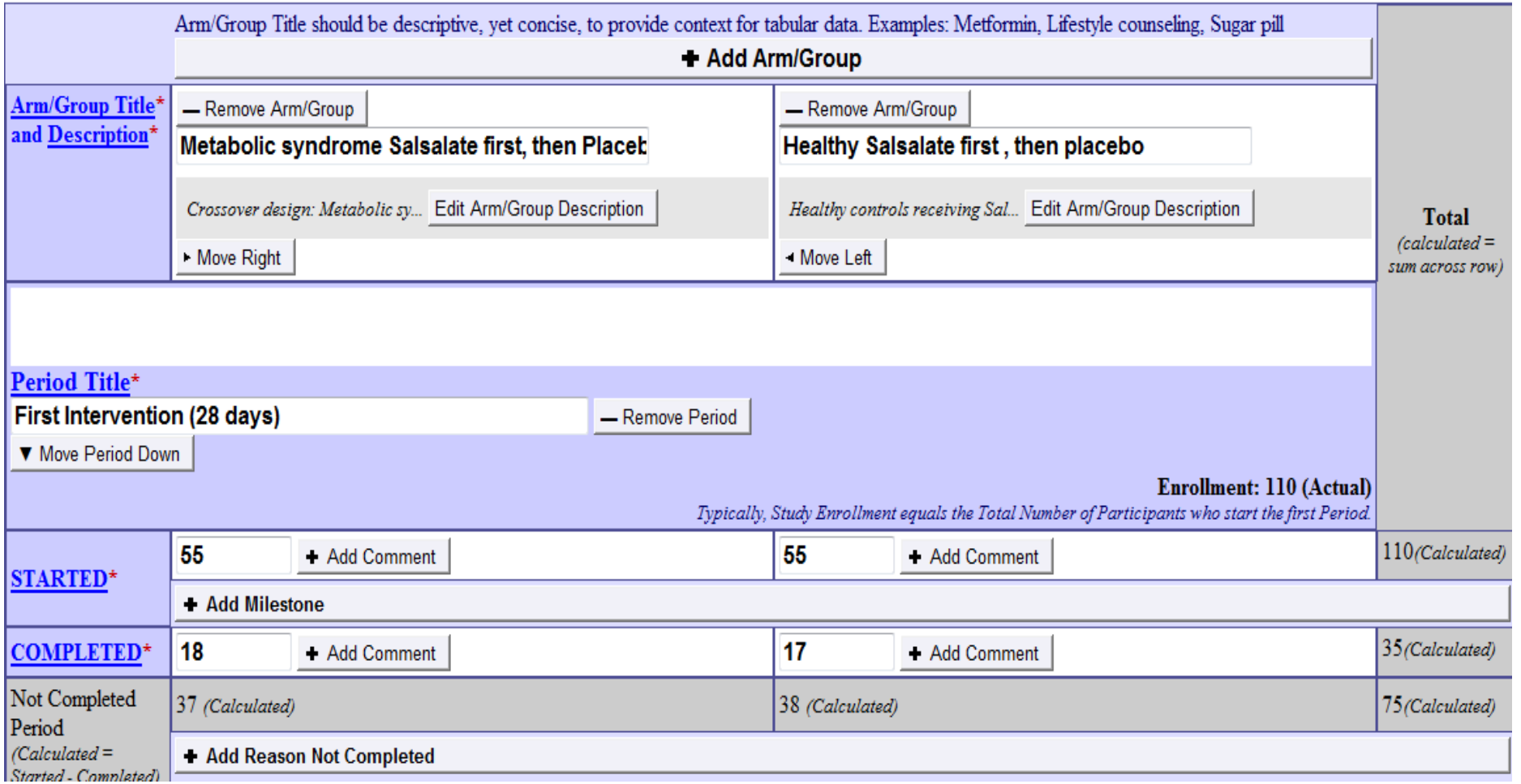
Registration Content

- 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

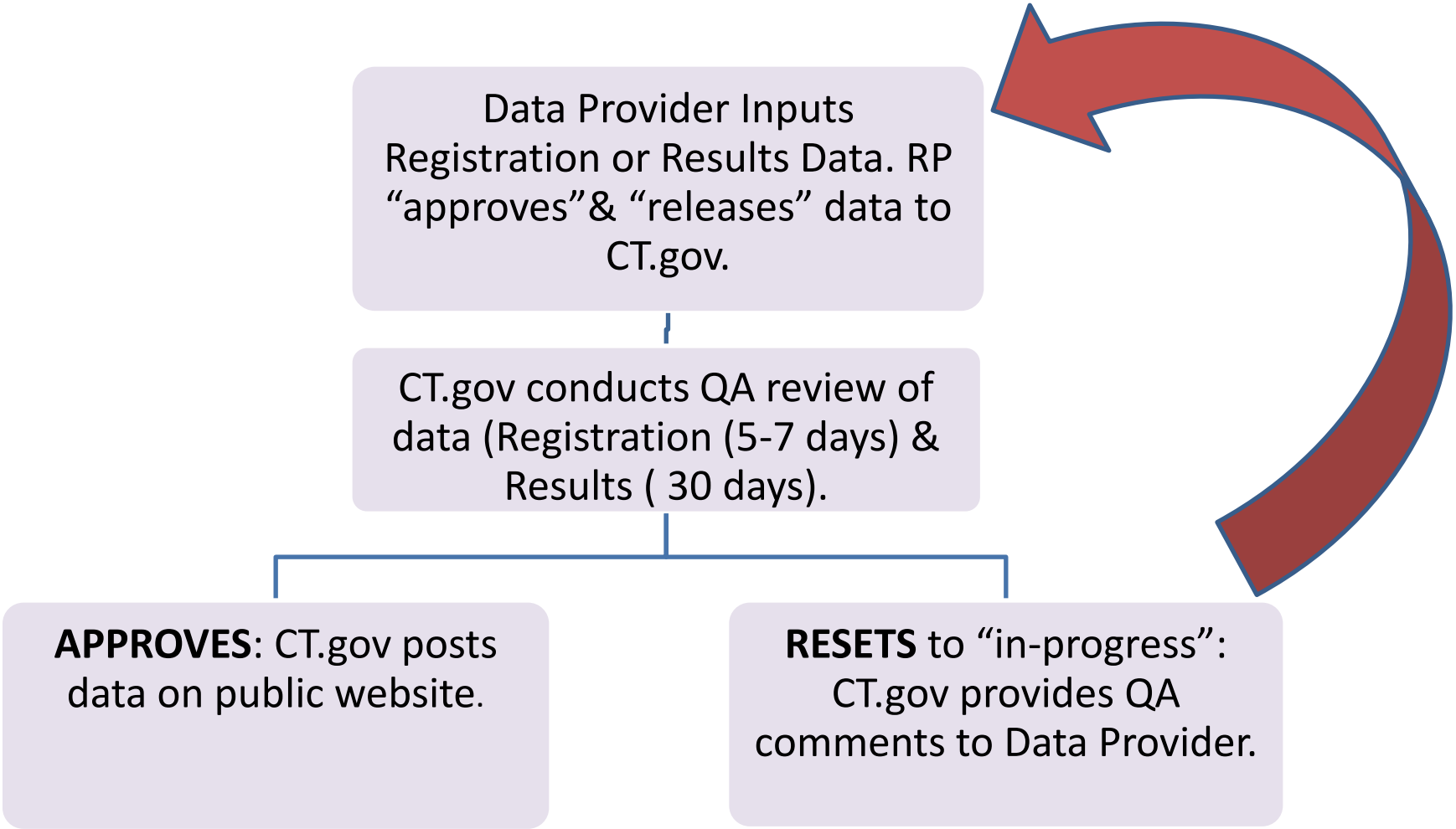
Results Reporting content

- 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



ClinicalTrials.gov Review Process



Highlights of Proposed Expansion of Clinical Trial Registration Requirements

(Public Comment period ends 3/23/15)

National Institutes of Health
Turning Discovery Into Health

News & Events

- News Releases
- Events
- Videos
- Images
- Social Media & Outreach

NIH News in Health
NIH Research Matters
NIH Record

For Immediate Release: Wednesday, November. 19, 2014, 12:00 p.m. ET

HHS and NIH take steps to enhance transparency of clinical trial results

The U.S. Department of Health and Human Services today issued a Notice of Proposed Rulemaking (NPRM), which proposes regulations to implement reporting requirements for clinical trials that are subject to Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA). The proposed rule clarifies requirements to clinical researchers for registering clinical trials and submitting summary trial results information to ClinicalTrials.gov, a publicly accessible database operated by the

"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."

Institute/Center

NIH Office of the Director (OD)

Contact

NIH News Media Branch
301-496-5787

Related Links

- NPRM Federal Register Public Inspection Document (PDF - 946 KB)
- NIH Guide to Proposed NIH Policy
- Summary of Proposed Changes NPRM/NIH Policy
- NIH Director's Blog
- RockTalk Blog
- JAMA Viewpoint: Sharing and Reporting the Results of Clinical Trials
- ClinicalTrials.gov

Subscribe

From Rebecca Williams, Asst. Director ClinicalTrials.gov, 12/18/2014 Presentation , ,http://www.nih.gov/news/health/nov2014/od-19.htm

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[3] 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

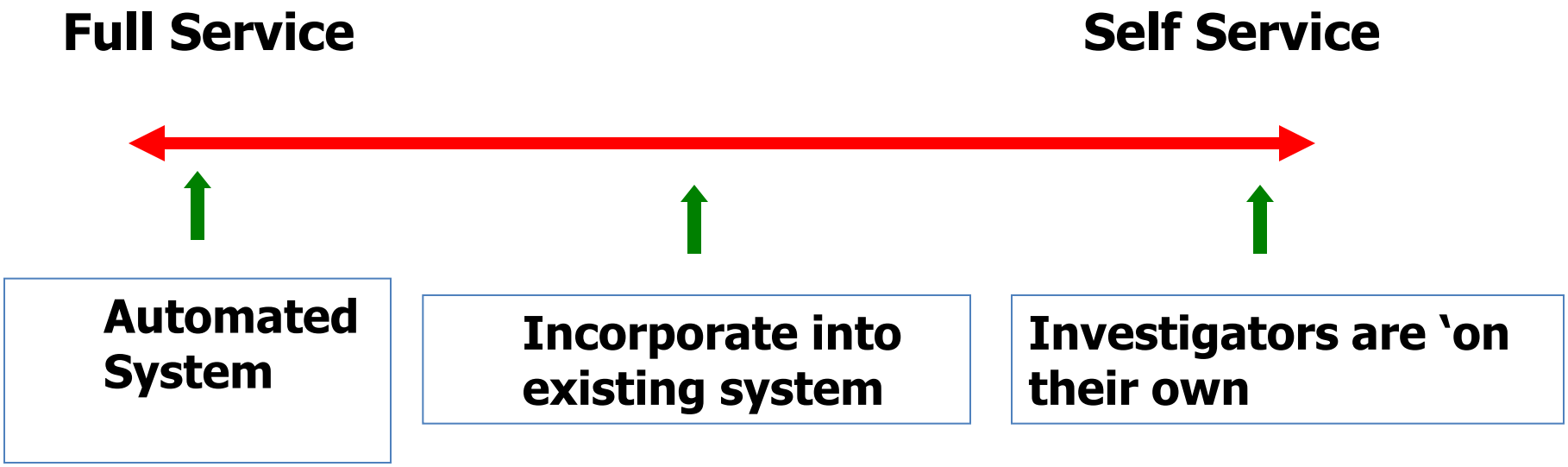
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html

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



Greatly based on available resources and size of institution

PARTNERS®
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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

- FDAAA related information: http://clinicaltrials.gov/ct2/manage-recs/fdaaa
- *Office of Extramural Research (OER):* http://grants.nih.gov/Clinicaltrials_fdaaa/

ICMJE

- ICMJE Clinical Trial Registration Requirements: http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/ l

CMS

- Mandatory Reporting of NCT# Requirement: http://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/Downloads/SE1344.pdf
- Qualifying Trial information: http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=1&ncdver=2&bc=BAABAAAAAAAA&

Information re: Proposed Expansion of Requirements

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

http://www.nih.gov/news/health/nov2014/od-19.htm

Questions?