ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Overview of FDAAA and Other Trial Registration Policies

Results Database Train-the-Trainer Workshop
September 2015

http://ClinicalTrials.gov

Why Register and Report Results?

- **Required by most medical journals** (ICMJE*)
  - Registration for all clinical trials (all interventions)
    - http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html
- **It is Federal law!** (FDAAA 801**)
  - Registration & results submission for "applicable clinical trials"
    - http://www.clinicaltrials.gov/ct2/manage-recs/fdaaa
- **Encouraged for all NIH-supported trials**
  - Registration & results submission, even if not subject to FDAAA 801
    - http://grants.nih.gov/ClinicalTrials_fdaaa/
  - New NIH Policy Proposal to make this *required*

* International Committee of Medical Journal Editors
** Section 801 of the Food and Drug Administration Amendments Act of 2007

2

Other reasons …

- **Center for Medicare and Medicaid Services (CMS)** requires NCT Number for coverage of routine costs of qualifying clinical trials
- **U.S. Department of Veterans Affairs (VA)** requires registration and results reporting of VA-funded clinical trials
- **U.S. National Cancer Institute (NCI)** requires results reporting in a peer-reviewed scientific journal or ClinicalTrials.gov

https://clinicaltrials.gov/ct2/manage-recs/background#WhyRegister

3

And more reasons…

- **European Union** requires registration and results reporting of certain drug and biologic clinical trials
- **Declaration of Helsinki** states that all research studies involving human subjects must be registered & researchers have a responsibility to make research results publicly available
- **World Health Organization (WHO)** considers registration a “scientific, ethical and moral responsibility” and states that there is an ethical imperative to report results
- **And others!!**

https://clinicaltrials.gov/ct2/manage-recs/background#WhyRegister

4

Public Benefits of Access to Summary Clinical Trial Data

- Meet ethical obligation to human subjects (i.e., that results will be used to help others/inform science)
- Inform future research and research funding decisions
- Mitigate information bias (e.g., non publication)
- Assess research integrity (e.g., adherence to protocol)
- Prevent duplication of trials of unsafe or ineffective interventions
- Provide data to support evidence-based medicine
- Enhance patient access to enrollment in clinical trials

All contribute to increased public trust in clinical research.

5

ICMJE
International Committee of Medical Journal Editors

- 2004 Editorial (and updates)*
  - Effective Sept 2005
- Prospective registration is required to be eligible for publication
- Which trials?
  - Interventional studies
    - All phases
    - All intervention types
- When to register?
  - Prior to enrollment of first participant
- What to register?
  - WHO† data items
- Where to register?
  - ClinicalTrials.gov or WHO Primary registry

* http://www.icmje.org
† http://www.who.int/ictrp/network/trds/en/index.html

6

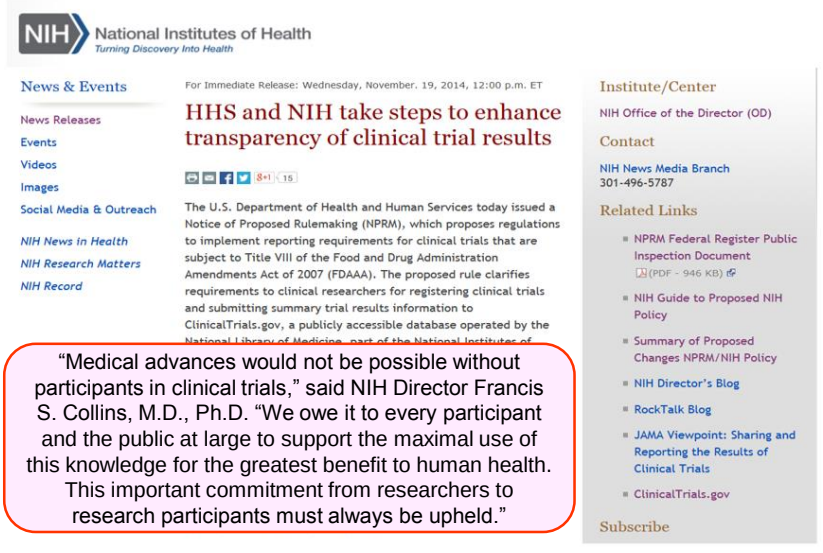
ICMJE Definition of Clinical Trial*

- "Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes"
  - Health-related interventions include drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes
  - Health outcomes include any biomedical or health-related measures in participants, including pharmacokinetic measures and adverse events

7

* http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/

NIH News Release


NIH National Institutes of Health
Turning Discovery Into Health

News & Events

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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

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

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"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."

8

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

NIH Policy Proposal
Guide Notice: NOT-OD-15-019

- NIH-funded awardees & investigators conducting clinical trials, funded in whole or in part by NIH
- NIH-funded clinical trials must be registered and have summary results, including adverse event information, submitted to ClinicalTrials.gov
  - NIH revised definition of clinical trial (Oct 2014)
    - Includes Phase 1, all intervention types (broader than "ACT")
  - Same type of registration and results data and in the same timeframes as the trials subject to FDAAA
- Comment period closed March 2015

NIH Policy Proposal: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-019.html
Revised NIH Definition of "Clinical Trial": http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html

9

NCI Clinical Trial Access Policy
Guide Notice: NOT-CA-15-011

- Released: January 28, 2015
  - http://grants.nih.gov/grants/guide/notice-files/NOT-CA-15-011.html
- Final Trial Results are expected to be reported in a publicly accessible manner (peer-reviewed scientific journal or ClinicalTrials.gov) within twelve (12) months of the Trial's Primary Completion Date regardless of whether the clinical trial was completed as planned or terminated earlier
- Will be incorporated as a Term and Condition of the award

10

NCI = U.S. National Institutes of Health, National Cancer Institute

What does FDAAA 801 require?

The responsible party for an applicable clinical trial (ACT) subject to FDAAA must :

1. Register the ACT in ClinicalTrials.gov no later than 21 days after enrollment of the first participant;

2. Update the ACT in ClinicalTrials.gov at least once every 12 months (Recruitment Status and Primary Completion Date within 30 days)

3. Submit summary results (including adverse event information) for certain trials not later than 1 year after the trial's Primary Completion Date.

- Delays allowed in some circumstances

11

What is an ACT?

- **"Applicable Clinical Trials"* (ACTs) subject to FDAAA are:**
  - Interventional studies of drugs, biologics, & devices
  - Not phase 1 (drugs/biologics), not small feasibility (devices)
  - US FDA jurisdiction (e.g., IND/IDE or US site)
  - ACTs initiated after 9/27/07 or if initiated on or before 9/27/07, "ongoing" as of 12/26/07

12

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

Other Considerations

- Is it an interventional study?
  - Are the interventions being given as part of the research protocol?
  - Would the participants have received the interventions in the same manner and intensity, whether or not they were in the study?
- Does it include a device?
  - FDA regulatory definitions apply
  - Includes diagnostic devices (e.g., CT scan, x-ray)

13

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

NCI News Release

National Cancer Institute
U.S. National Institutes of Health | www.cancer.gov

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News

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Posted: 11/04/2010

Lung cancer trial results show mortality benefit with low-dose CT:

Twenty percent fewer lung cancer deaths seen among those who were screened with low-dose spiral CT than with chest X-ray

The National Cancer Institute (NCI) is today releasing initial results from a large-scale test of screening methods to reduce deaths from lung cancer by detecting cancers at relatively early stages.

The National Lung Screening Trial (NLST), a randomized national trial involving more than 53,000 current and former heavy smokers ages 55 to 74, compared the effects of two screening procedures for lung cancer -- low-dose helical computed tomography (CT) and standard chest X-ray -- on lung cancer mortality and found 20 percent fewer lung cancer deaths among trial participants screened with low-dose helical CT. The NLST was sponsored by NCI, a part of the National Institutes of Health, and conducted by the American College of Radiology Imaging Network (ACRIN) and the Lung Screening Study group. A paper describing the design and protocol of the NLST, "The National Lung Screening Trial: Overview and Study Design" by the NLST research team, was published yesterday by the journal Radiology and is openly available at http://radiology.rsna.org/cgi/content/abstract/radiol.10091808 [1].

14

Study Record in ClinicalTrials.gov

Full Text View | Tabular View | No Study Results Posted | Related Studies

National Lung Screening Trial (NLST)

This study is ongoing, but not recruiting participants.

First Received: October 3, 2002 Last Updated: June 15, 2010 History of Changes

Sponsor:	National Cancer Institute (NCI)
Collaborator:	American College of Radiology Imaging Network
Information provided by:	National Cancer Institute (NCI)
ClinicalTrials.gov Identifier:	NCT00047385

Purpose

RATIONALE: Screening tests may help doctors detect cancer cells early and plan more effective treatment for lung cancer. It is not yet known whether helical CT scan is more effective than chest x-ray in reducing death from lung cancer.

PURPOSE: Randomized clinical trial to compare the effectiveness of helical CT scan with that of chest x-ray in screening individuals who are at high risk for developing lung cancer.

(Device) (Device)

Condition	Intervention
Lung Cancer	Procedure: bronchoscopic and lung imaging studies Procedure: comparison of screening methods

Study Type: Interventional
Study Design: Allocation: Randomized
Control: Active Control
Primary Purpose: Screening

Official Title: National Lung Screening Trial

15

Study Record in ClinicalTrials.gov (cont.)

National Lung Screening Trial (NLST) Screening

This study has been completed.

Sponsor:
National Cancer Institute (NCI)

Collaborator:
American College of Radiology Imaging Network

Information provided by (Responsible Party):
National Cancer Institute (NCI)

ClinicalTrials.gov Identifier:
NCT00047385

First received: October 3, 2002
Last updated: October 16, 2012
Last verified: October 2012
History of Changes

Full Text View | Tabular View | Study Results | Disclaimer | How to Read a Study Record

Purpose

RATIONALE: Effective screening tests should help doctors detect lung cancer early and plan curative treatment. It is not yet known whether low-dose helical computed tomography (LDCT) screening is more effective than chest radiography (CXR) screening in reducing death from lung cancer.

PURPOSE: Randomized clinical trial to compare the effectiveness of LDCT scan with that of CXR in screening individuals who are at high risk for developing lung cancer.

Condition	Intervention	Phase
Lung Cancer	Device: low-dose helical computed tomography Device: chest radiography	Phase 3

Study Type: Interventional
Study Design: Allocation: Randomized
Intervention Model: Parallel Assignment
Masking: Open Label
Primary Purpose: Screening

Official Title: National Lung Screening Trial A Randomized Trial Comparing Low-dose Helical CT With Chest Xray for Lung Cancer

16

Who is the Responsible Party?

- **"Responsible Party"* is defined as:**
  - Sponsor [only one per trial]
    - IND/IDE holder; if none, then
    - Person or entity who "initiated" the trial
      - Funding recipient if grant or sponsored research agreement
      - Funder if procurement funding agreement (contract)
  - Sponsor may designate the Principal Investigator (PI) as Responsible Party [only one per trial]
    - If PI meets certain requirements (e.g., has access to and control over data, right to publish)

17

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

FDAAA Results Requirements

- **Which trials must have results submitted?**
  - "Applicable clinical trials" of **FDA-approved or cleared** drugs, biologics or devices
    - Interventional studies of drugs, biologics, or devices
    - Not phase 1 (drug/biologic) or not small feasibility (device)
    - US FDA jurisdiction (e.g., IND/IDE or US site)
  - Initiated after 9/27/07 or if initiated on or before 9/27/07, "ongoing" as of 12/26/07

18

http://www.clinicaltrials.gov/ct2/manage-recs/fdaaa

FDAAA Results Requirements (cont.)

- **When must summary results be submitted?**
  - Within 12 months of (primary) completion date
    - "The date that the final subject was examined or received an intervention for the purposes of final collection of data for the **primary outcome**, whether the clinical trial concluded according to the prespecified protocol or was terminated."
  - OR within 30 days of product approval or clearance
  - Delays possible
    - Seeking approval of a new use
    - Extensions for "good cause"

http://www.clinicaltrials.gov/ct2/manage-recs/fdaaa

19

Delayed Results Submission

- **Certification**
  - "Certify Initial Approval" – the trial reached its (Primary) Completion Date before the drug, biologic, or device is initially approved, licensed, or cleared by FDA for any use
  - "Certify New Use" - the manufacturer of a drug, biologic or device is the sponsor of the trial and has filed or will file within a year, an application seeking FDA approval, licensure, or clearance of the new use studied in the trial

http://www.clinicaltrials.gov/ct2/manage-recs/fdaaa

20

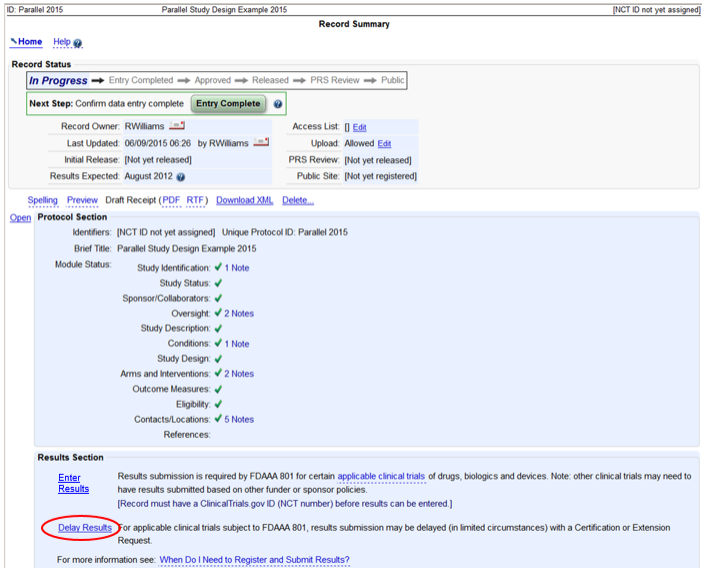
Delayed Results Submission (cont.)

- **Request for extension** of the deadline for "good cause"
  - Request must include sufficient information to evaluate reason for extension request
  - Pending publication is not considered "good cause"

http://www.clinicaltrials.gov/ct2/manage-recs/fdaaa

21

Delayed Results Submission (cont.)



22

Delayed Results Deadlines

- Certify Initial Approval
  - Not later than 30 days after the drug or device is initially approved, licensed or cleared ("approved") by the FDA
- Certify New Use
  - The earlier of the date that is 30 days after:
    - New use of the drug or device is approved by FDA
    - FDA issues a letter for the new use of the drug or device, such as a complete response letter
    - Application or premarket notification for the new use is withdrawn without resubmission for 210 days
  - Or two years after the date certification submitted, if none of the events above has occurred
- Extension Request - NIH-approved date

23

Registration, Results Submission, and Publication

- International Committee of Medical Journal Editors (ICMJE) requires registration of all clinical trials as a condition of publication
  - Must register prior to enrollment of first participant
- Deadlines for submitting results to ClinicalTrials.gov are independent of publication status
- Submitting results to ClinicalTrials.gov will not interfere with publication*
  - But, failing to register the trial will!

* Laine C, Horton R, DeAngelis C, et al. *Ann Intern Med.* 2007; http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/

24

Results and non-ACTs

- Non-ACTs registered in ClinicalTrials.gov are *not* required to submit results to ClinicalTrials.gov
  - Phase 1 trials
  - Observational studies
    - Exception: Pediatric postmarket surveillance of devices
- NOTE: Other policies may apply

25

FDAAA – Other Considerations

- NIH Grantee Requirements
  - Certification of compliance is required for competing (new and renewal) applications and non-competing continuation progress reports
    - See: http://grants.nih.gov/clinicaltrials_fdaaa/
    - See: http://grants.nih.gov/grants/rppr/index.htm
- FDA Requirements
  - Certification of Compliance to FDA – Form 3674
    - Form 3674 must accompany human drug, biological, and device product submissions
      - **FDA Form**: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048364.pdf
      - **Guidance (2009)**: http://www.fda.gov/RegulatoryInformation/Guidances/ucm125335.htm

26

http://www.clinicaltrials.gov/ct2/manage-recs/fdaaa

FDAAA – Other Considerations

- FDA Requirements (cont.)
  - Informed Consent (21 CFR § 50.25(c))
    - A statement must be included in informed consent documents of applicable clinical trials initiated on or after March 7, 2012 regarding availability of information at ClinicalTrials.gov
      - **21 CFR 50.25(c)**: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.25
      - **FDA Guidance (2012)**: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM291085.pdf
  - FDA Compliance Program 7348.810: Sponsors, Contract Research Organizations, and Monitors
    - Instructs FDA staff to identify SOPs and determine if studies were registered on ClinicalTrials.gov appropriately
      - **Manual:** http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133777.htm

27

http://www.clinicaltrials.gov/ct2/manage-recs/fdaaa

FDAAA Enforcement Provisions

- Notices of noncompliance
- Civil monetary penalties (up to $10,000/day)
- Withholding of NIH grant funds

28

Studies Evaluating Rates of Reporting

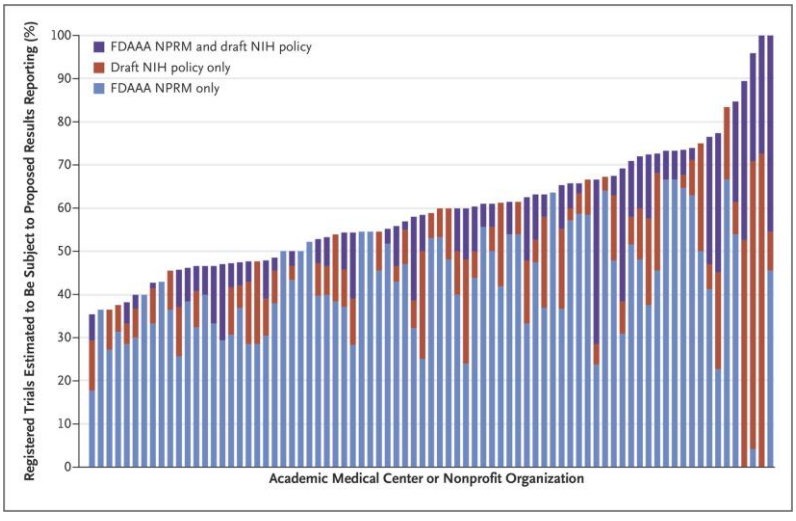
	Prayle et al. (2012)	Anderson et al. (2015)		
Sample	Trials likely to be subject to FDAAA* completed 1/1/2009 – 12/31/2009 (analyzed Jan 2011)	Main sample: Trials likely to be subject to FDAAA* completed 1/1/2008 – 8/31/2012 (analyzed Sep 2013)		Subsample: Main sample + assessment of approval status of product in trial
Trials in Sample	738	13,327		205
Study Follow-up after PCD	Up to 2 years	By 12 months	Up to 5 years	Up to 5 years
Overall Rate of Results Reporting				
All Trials	22%	13.4%	38.3%	--
Industry	40%	17.0%	41.5%	~ 79 – 80%
NIH	8%	8.1%	38.9%	~ 49 – 50%
Other	7%	5.7%	27.7%	~ 42 - 45%

* Methods for determining "subject to FDAAA" were different in each analysis and both had limitations

29

Prayle AP et al. *BMJ*. 2012; Anderson M et al. *N Engl J Med*. 2015.

Trials by 80 Sponsors Estimated to Be Subject to Proposed Results Reporting



Zarin DA et al. N Engl J Med 2015. DOI: 10.1056/NEJMc1505965 The NEW ENGLAND JOURNAL of MEDICINE

30

NIH Grants

- **Are the costs (including staff time) of registration and results reporting (including summary adverse event information) in ClinicalTrials.gov allowable charges on an NIH grant?**
  - Given the nature of this requirement and that the project staff will generally be in the best position to submit and maintain these data, the costs of FDAAA compliance will be generally be allowable as direct charges to NIH supported grants. While it is expected that these costs will be covered by the funds provided with the grant, administrative supplements could also be considered.

31

NIH Office of Extramural Research (OER) Resources

"What NIH Grantees Need to Know about FDAAA"
http://grants.nih.gov/ClinicalTrials_fdaaa/

- Step-by-step guidance
- Flowcharts for ascertaining ACTs and RP
- "At-a-glance" requirements
- FAQs for NIH Grantees

32

Web Site Resource
FDAAA 801 Requirements

33

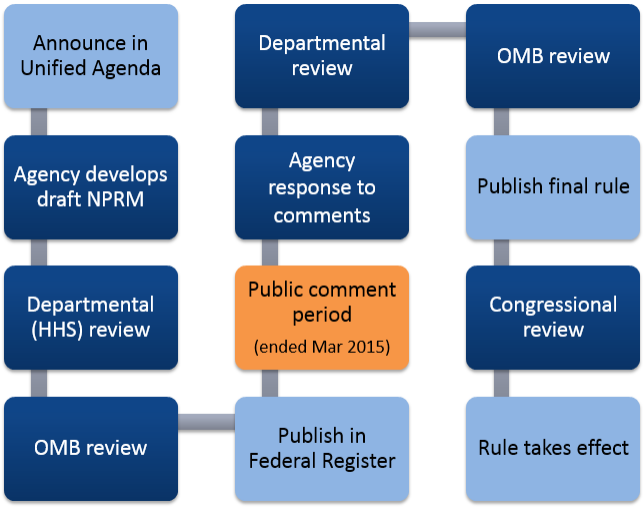
FDAAA - Next Steps

- Notice of Proposed Rulemaking (NPRM) issued for public comment in November 2014
- Comment period closed March 2015
  - Over 900 comments received
- Final Rule: Spring 2015 Unified Agenda estimated publication in Federal Register in February 2016

34

Federal Rulemaking Process

Consistent with the Administrative Procedures Act [5 U.S.C. 533]



35

Determining if a Trial is an ACT

Use registration data elements to determine if study meets definition of ACT

	Devices	Drugs (and Biologics)
Study Type	• Interventional	• Interventional
Study Phase	• Other than Feasibility	• Other than Phase 1
Controlled	•Number of Arms ≥ 2 OR •Single Arm Controlled = Yes	• Number of Arms ≥ 2 OR • Single Arm Controlled = Yes
Intervention Type	• Not Combination product	
Studies FDA-Regulated Device? / Drug?	• Yes	• Yes
FDA Jurisdiction	• Facility Location in U.S. OR • Product Manufactured in U.S. OR • FDA IDE Number	•Facility Location in U.S. OR •Product Manufactured in U.S. OR •FDA IND Number
	-OR-	
Pediatric Postmarket Surveillance of a Device?	• Yes	

36

NPRM: Section IV.B.2 and 4; IDE = Investigational Device Exemption; IND = Investigational New Drug application

Results Submission
Additional Issues Addressed in NPRM

Topic	
EXTEND RESULTS SUBMISSION DEADLINE? Extend the deadline for submitting results from 12 to 18 mos.	**NO**. Little support from industry or patient groups
NARRATIVE SUMMARIES? Include technical and lay summaries if Secretary determines can be included without being misleading or promotional.	**DEFERS DECISION**. Invites additional public comment
PROTOCOLS? Require submission of the full protocol *or* such information as may be necessary to help to evaluate the results of the trial.	**DEFERS DECISION**. Invites additional public comment.
RESULTS FOR UNAPPROVED PRODUCTS? Require results for trials of drugs and devices that have not been approved by FDA? If so, deadline for submitting those results.	**YES**. Due within 12 months of completion date. May delay for up to 2 years w/ certification.

37

NPRM: Section III.C.5 to 8.

NPRM: Unapproved Products and Results

- Requires results submission for ACTs of products not approved, cleared, or licensed for any use
- Deadline: within 1 year of completion date
  - Certifications to delay deadline up to 2 years:
    - Drug, biologic, or device is not yet approved by FDA for any use *and* sponsor or manufacturer intends to continue product development and is seeking or may seek approval, licensure or clearance
    - Manufacturer is sponsor and will seek approval of new use within 1 year of certification
  - Extensions for "good cause" also available

38

NPRM: Sections IV.C.2 and 3

Select Publications

Available at: http://www.clinicaltrials.gov/ct2/resources/pubs

Zarin DA, Tse T, Ross JS. Trial-results reporting and academic medical centers. *N Engl J Med*. 2015 May 20.

Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC. The ClinicalTrials.gov results database – update and key issues. *N Engl J Med* 2011;852-860.

Tse T, Williams RJ, Zarin DA. Reporting basic results in ClinicalTrials.gov. *Chest* 2009;136:295-303.

39

Additional Resources

Questions?
register@clinicaltrials.gov

ClinicalTrials.gov information (Submit Studies page):
http://clinicaltrials.gov/ct2/manage-recs

Office of Extramural Research (OER)
http://grants.nih.gov/Clinicaltrials_fdaaa/

Food and Drug Administration (FDA)
http://www.fda.gov/scienceresearch/specialtopics/runningclinicaltrials/fdasroleclinicaltrials.govinformation/default.htm

40

Questions?

41