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
October 2012

http://ClinicalTrials.gov

ClinicalTrials.gov – Milestones

- 1997 - Food and Drug Administration Modernization Act (FDAMA)
- 2000 - ClinicalTrials.gov launched
- 2005 - International Committee of Medical Journal Editors (ICMJE) policy
- 2007 - FDAAA (Title VIII of Public Law 110-85)
  - Expanded clinical trial registration requirement and imposed new results submission requirements
  - Added enforcement provisions including up to $10,000/day in civil monetary penalties and withholding remaining or future grant funds

2

FDAAA = Food and Drug Administration Amendments Act of 2007

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
† World Health Organization

3

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

* http://www.icmje.org/faq_clinical.html

4

What does FDAAA 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

5

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

6

* 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)

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

7

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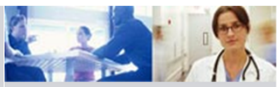


Posted: 11/04/2010

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].

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

Determining Potential ACTs

Table 1. Sample Checklist for Identifying Potential Applicable Clinical Trials Subject to *FDAAA*

A study may be subject to the requirements of FDAAA*, if YES is answered to all 5 questions:	YES	NO
1. Was the study either a. initiated after 27 September 2007? b. initiated on or before 27 September 2007, and ongoing as of 26 December 2007?		
2. Is the study "interventional" (i.e., participants are assigned to interventions by protocol)?		
3. Does the study evaluate a "drug," "biological product" or "medical device" (whether or not approved for marketing in the United States)?		
4. Is the study **other than** either a a. "Phase 1" drug or biological product trial (e.g., it is a Phase 2 study)? b. "small feasibility" device trial (e.g., it is a pivotal study)?		
5. Does the study have at least one site located in the United States **or** is the study conducted under an IND or IDE?		

* For a complete definition and description of "applicable clinical trial", please see http://prsinfo.clinicaltrials.gov/fdaaa.html.(1,2)

10

Wong E, Williams R. *RAPS Regulatory Focus*. May 2012.

A Rheumatoid Arthritis Study in Patients on a Background Treatment of Methotrexate (FLEX M)

This study is currently recruiting participants.

NCT01198002

Condition	Intervention	Phase
Rheumatoid Arthritis	Drug: LY2127399 Drug: Placebo every 2 weeks Drug: Placebo every 4 weeks	Phase 3

Study Type: Interventional
Study Design: Allocation: Randomized
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Investigator)
Primary Purpose: Treatment

Estimated Enrollment: 990
Study Start Date: December 2010
Estimated Study Completion Date: December 2015
Estimated Primary Completion Date: December 2013

Locations: United States, Australia, Brazil, Bulgaria, Colombia, Croatia…
Health Authority: United States: Food and Drug Administration

11

Study in Children to Evaluate the Immunogenicity and Safety of 4 Formulations of GSK Bio MenACWY-TT Conjugate Vaccine

This study has been completed.

NCT00126984

Condition	Intervention	Phase
Meningitis, Meningococcal	Biological: Conjugated meningococcal ACWY-TT (vaccine) Biological: DTPa/Hib containing vaccine Biological: Meningitec Biological: Mencevax ACWY	Phase 2

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

Estimated Enrollment: 508
Study Start Date: July 2005
Estimated Study Completion Date: February 2008
Estimated Primary Completion Date: February 2008

Locations: Austria, Germany
Health Authority: Austria: Human Research Ethics Committee

12

Efficacy and Safety Study of Genetically Targeted Enzyme Replacement Therapy for Advanced Heart Failure (CUPID)

This study is ongoing, but not recruiting participants.

NCT00454818

Condition	Intervention	Phase
Heart Failure, Congestive Dilated Cardiomyopathy	Genetic: MYDICAR® Procedure: Placebo Infusion	Phase 1/ Phase 2

Study Type: Interventional
Study Design: Allocation: Randomized
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Caregiver, Investigator, Assessor)
Primary Purpose: Treatment

Estimated Enrollment: 46
Study Start Date: March 2007
Estimated Study Completion Date: August 2012
Primary Completion Date: August 2012

Locations: United States
Health Authority: United States: Food and Drug Administration

13

Endoscopic Suturing System for Tissue Apposition

This study has been completed

NCT00495222

Condition	Intervention
Obesity	Procedure: Tissue plication Device: Endoscopic Suturing System Device: Tissue Plication

Study Type: Interventional
Study Design: Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Estimated Enrollment: 9
Study Start Date: February 2007
Study Completion Date: June 2008
Primary Completion Date: April 2008

Locations: United States
Health Authority: United States: Institutional Review Board

14

Go Fish: Omega-3 Fatty Acid Supplementation in Diabetes-Related Kidney Disease

This study has been completed.

NCT01092390

Condition	Intervention	Phase
Diabetes	Dietary Supplement: Lovaza (fish oil)	Phase 3

Study Type:	Interventional
Study Design:	Allocation: Randomized Intervention Model: Crossover Assignment Masking: Double Blind (Subject, Outcomes Assessor) Primary Purpose: Treatment
Estimated Enrollment:	31
Study Start Date:	March 2010
Study Completion Date:	May 2011
Primary Completion Date:	May 2011
Locations:	Baltimore, Maryland
Health Authority:	United States: Institutional Review Board

15

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)

16

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

NIH's role

- **Can the NIH IC that funded an ACT register or report results on behalf of the responsible party?**
  - No; the NIH cannot register or report results for applicable clinical trials when the NIH is not the responsible party for the trial. Responsible parties are solely responsible for the content, quality and timeliness of registration and results reporting in accord with FDAAA. For further information, please see NOT-OD-09-147 "Clarification of NOT-OD-08-014 Regarding Obtaining Assistance from NIH for Registration and Reporting of Results in ClinicalTrials.gov".

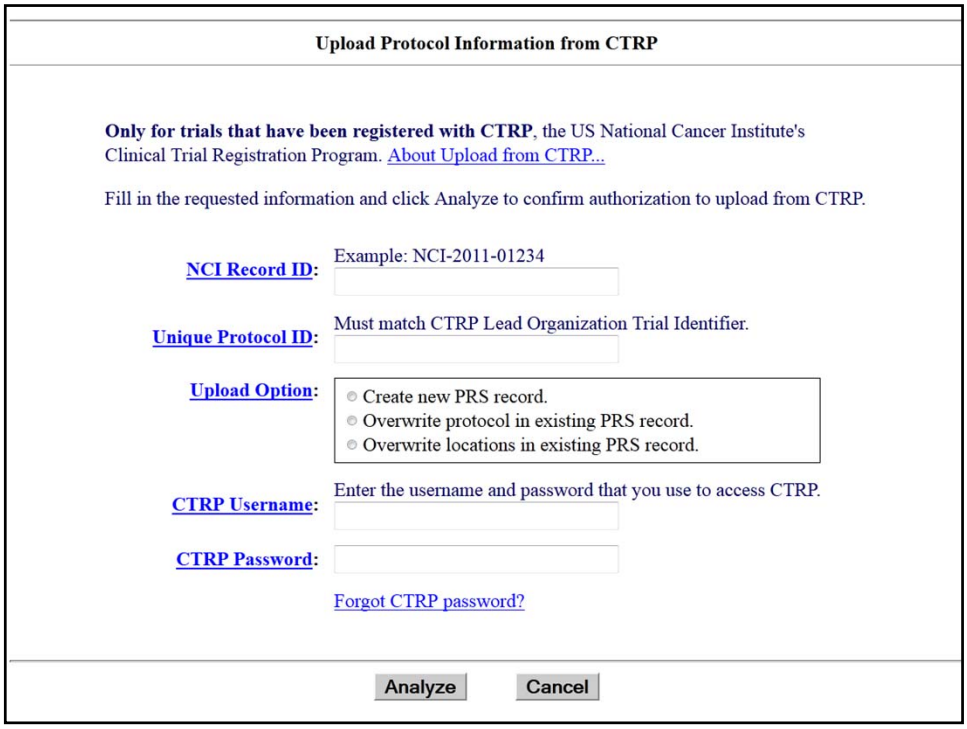
http://grants.nih.gov/clinicaltrials_fdaaa/faq.htm#834

17

Trials Registered with NCI's CTRP

- Upload Protocol Information from CTRP to PRS (access from PRS Main Menu > XML Upload)
- Information needed:
  - NCI Record ID
  - Unique Protocol ID
  - CTRP Username and Password
- Recommended Uses:
  - Create a new PRS record
  - Update locations in an existing PRS record

18



Upload Protocol Information from CTRP

Only for trials that have been registered with CTRP, the US National Cancer Institute's Clinical Trial Registration Program. About Upload from CTRP...

Fill in the requested information and click Analyze to confirm authorization to upload from CTRP.

NCI Record ID: Example: NCI-2011-01234

Unique Protocol ID: Must match CTRP Lead Organization Trial Identifier.

Upload Option:
- Create new PRS record.
- Overwrite protocol in existing PRS record.
- Overwrite locations in existing PRS record.

CTRP Username: Enter the username and password that you use to access CTRP.

CTRP Password:

Forgot CTRP password?

Analyze Cancel

Case 1: Responsible Party

- NIH Grantee: Brigham and Women's Hospital

20

Case 2: Responsible Party

- More than one NIH grantee:
  - University of Wisconsin – Madison
  - Brigham and Women's Hospital

21

Case 3: Responsible Party

- Investigator-initiated trial
- Pharmaceutical company provides drug

22

FDAAA Registration Requirements

- **When must trials be registered?**
  - Register at trial initiation, but not later than 21 days after enrollment of the first participant
- **What information?**
  - ClinicalTrials.gov and FDAAA-required data elements*
    - Responsible Party
    - NIH Grant Number as a Secondary ID (if applicable)
- **Where?**
  - ClinicalTrials.gov Protocol Registration System (PRS)
- **How?**
  - Online data entry or XML file upload

23

*Protocol Data Element Definitions: http://prsinfo.clinicaltrials.gov/definitions.html

FDAAA Results Requirements

- **Which trials must submit results?**
  - "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

24

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

25

FDAAA Definition: "Completion Date"

- Potential Issues
  - More than one primary outcome
  - Terminated studies

26

A Rheumatoid Arthritis Study in Patients on a Background Treatment of Methotrexate (FLEX M)

This study is currently recruiting participants.

NCT01198002

Condition	Intervention	Phase
Rheumatoid Arthritis	Drug: LY2127399 Drug: Placebo every 2 weeks Drug: Placebo every 4 weeks	Phase 3

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Estimated Primary Completion Date: December 2013

Locations: United States, Australia, Brazil, Bulgaria, Colombia, Croatia…
Health Authority: United States: Food and Drug Administration

27

Study in Children to Evaluate the Immunogenicity and Safety of 4 Formulations of GSK Bio MenACWY-TT Conjugate Vaccine

This study has been completed.

NCT00126984

Condition	Intervention	Phase
Meningitis, Meningococcal	Biological: Conjugated meningococcal ACWY-TT (vaccine) Biological: DTPa/Hib containing vaccine Biological: Meningitec Biological: Mencevax ACWY	Phase 2

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

Estimated Enrollment: 508
Study Start Date: July 2005
Estimated Study Completion Date: February 2008
Estimated Primary Completion Date: February 2008

Locations: Austria, Germany
Health Authority: Austria: Human Research Ethics Committee

28

Delayed Results Submission

- **Certification**
  - "Certify Initial Approval" – an applicable clinical trial (ACT) that is completed before a drug, biologic, or device studied in the trial is initially approved, licensed, or cleared by the 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

29

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

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"

30

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

Delayed Results Submission (cont.)

- Edit Protocol Record screen in PRS

Edit	**Unique Protocol ID:**	Test 1
	ClinicalTrials.gov ID:	
	Brief Title:	Test 1 - Efficacy and Safety Study of DX-88 to Treat Acute Attacks of Hereditary Angioedema (HAE)
	Official Title:	A Double-blind, Placebo-controlled Study (72 Patients, Randomized 1:1) Followed by a Repeat-dosing Phase to Assess the Efficacy and Safety of DX-88 (Ecallantide; Recombinant Plasma Kallikrein Inhibitor) for the Treatment of Acute Attacks of Hereditary Angioedema
		NOTE: Official Title should have no more than 240 characters.
	Study Type:	Interventional
	FDA Regulated Intervention?	Yes
	IND/IDE Protocol?	Yes
Edit	**Secondary IDs:**	

For completed studies: [Record must have a ClinicalTrials.gov ID (NCT number) before results can be entered.]
About Results Data Entry | Delayed Results Posting...

31

Delayed Results Submission (cont.)

Delay Results Type:*	-- Please Select -- (-- Please Select -- / Certify Initial Approval / Certify New Use / Extension)
Intervention Name(s):	
FDA Application Number(s):	Not Applicable
Requested Submission Date:	Not Applicable
Explanation:	Not Applicable

OK Cancel Delete

32

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

33

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!

34

* Laine C, Horton R, DeAngelis C, et al. *Ann Intern Med.* 2007; http://www.icmje.org/faq_clinical.html

ICMJE v. FDAAA (key points)

	ICMJE	FDAAA
Which Trials?	Interventional studies - All Phases - All Intervention Types	Interventional Studies - Not Phase 1/feasibility - Drugs, Biologics, Devices
When to Register?	Prior to enrollment of first participant	Within 21 days of enrollment of first participant
What to Register?	WHO Data Items	ClinicalTrials.gov and FDAAA Data Items
Where to Register?	ClinicalTrials.gov or WHO Primary Registry	ClinicalTrials.gov
When to Report Results?	Not Applicable	Within 12 months of final data collection for the primary outcome

35

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

36

FDAAA – Other Considerations

- NIH Grantee Requirements
  - Certification of compliance is required for competing (new and renewal) applications and non-competing continuation progress reports
    - http://grants.nih.gov/ClinicalTrials_fdaaa/index.htm#howdoapplicants
- FDA Requirements
  - Certification of Compliance to FDA – Form 3674
    - Form 3674 must accompany human drug, biological, and device product applications/submissions (December 2007)
    - Guidance document available (January 2009)
      - http://www.fda.gov/RegulatoryInformation/Guidances/ucm125335.htm

37

FDAAA – Other Considerations

- FDA Requirements (cont.)
  - Informed Consent (21 CFR § 50.25(c))
    - Must include a specific statement for ACTs that clinical trial information will be available on http://www.ClinicalTrials.gov (effective March 2012)
    - Guidance document available (February 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
    - http://www.fda.gov/ICECI/ComplianceManuals/ComplianceProgramManual/default.htm

38

FDAAA Enforcement Provisions

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

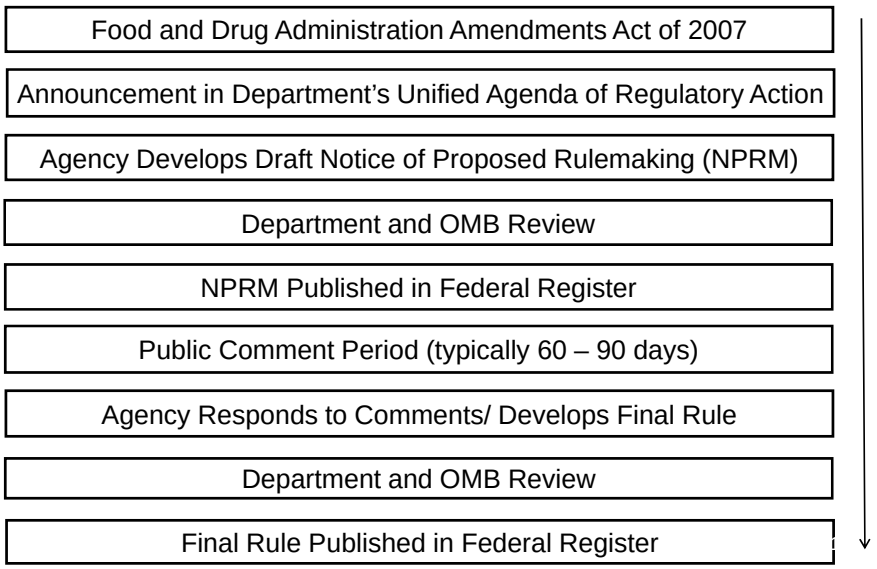
39

FDAAA - Next Steps

- HHS plans to issue regulations that will prescribe procedures for registering and submitting results of clinical trials to ClinicalTrials.gov in accordance with FDAAA
- Notice of Proposed Rulemaking (NPRM)
  - Fall 2011 HHS Unified Agenda estimated publication in the Federal Register in April 2012

40

Overview of Rulemaking Process



Additional Issues in Rulemaking

- Expand results reporting to trials of unapproved products?
- Include narrative summaries? Can it be done without being promotional and misleading?
  - Technical; Lay language
- Data quality verification
  - Process
  - External sources
- Full protocol versus extract "necessary to help evaluate the results"

42

Thank you!

Questions?

43