ClinicalTrials.gov: Meeting Transparency and Reporting Requirements

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CDER | US FDA

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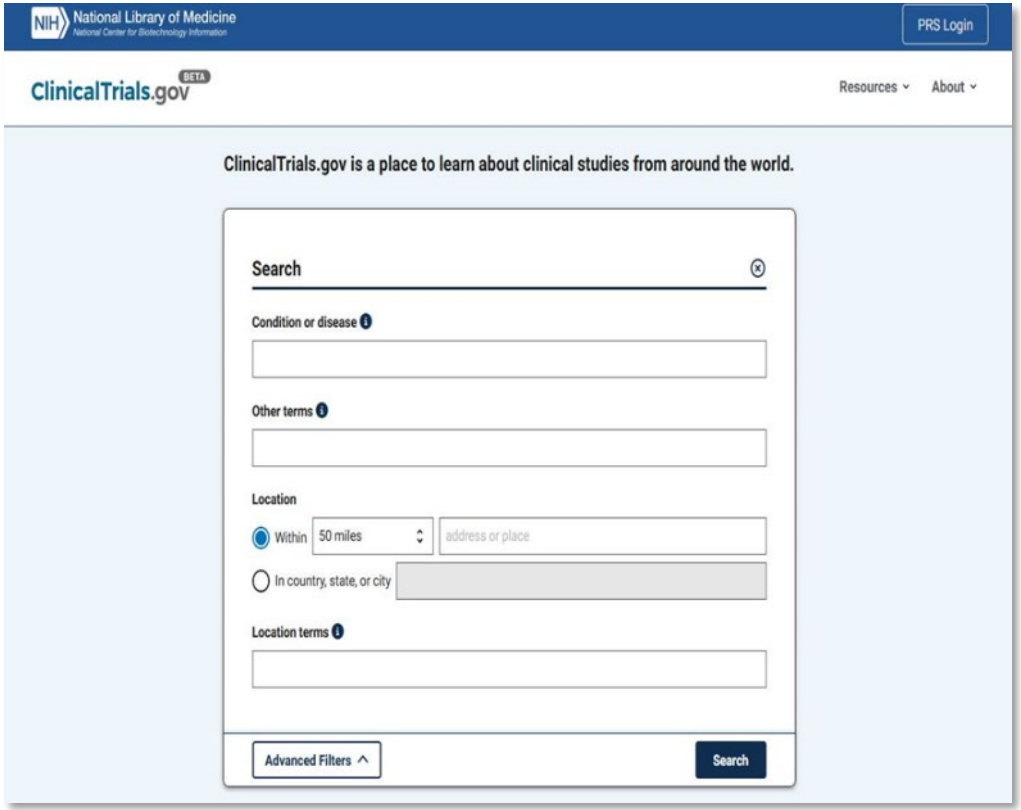
DISCLOSURES

I have no relevant financial relationship(s) in connection with this educational activity.

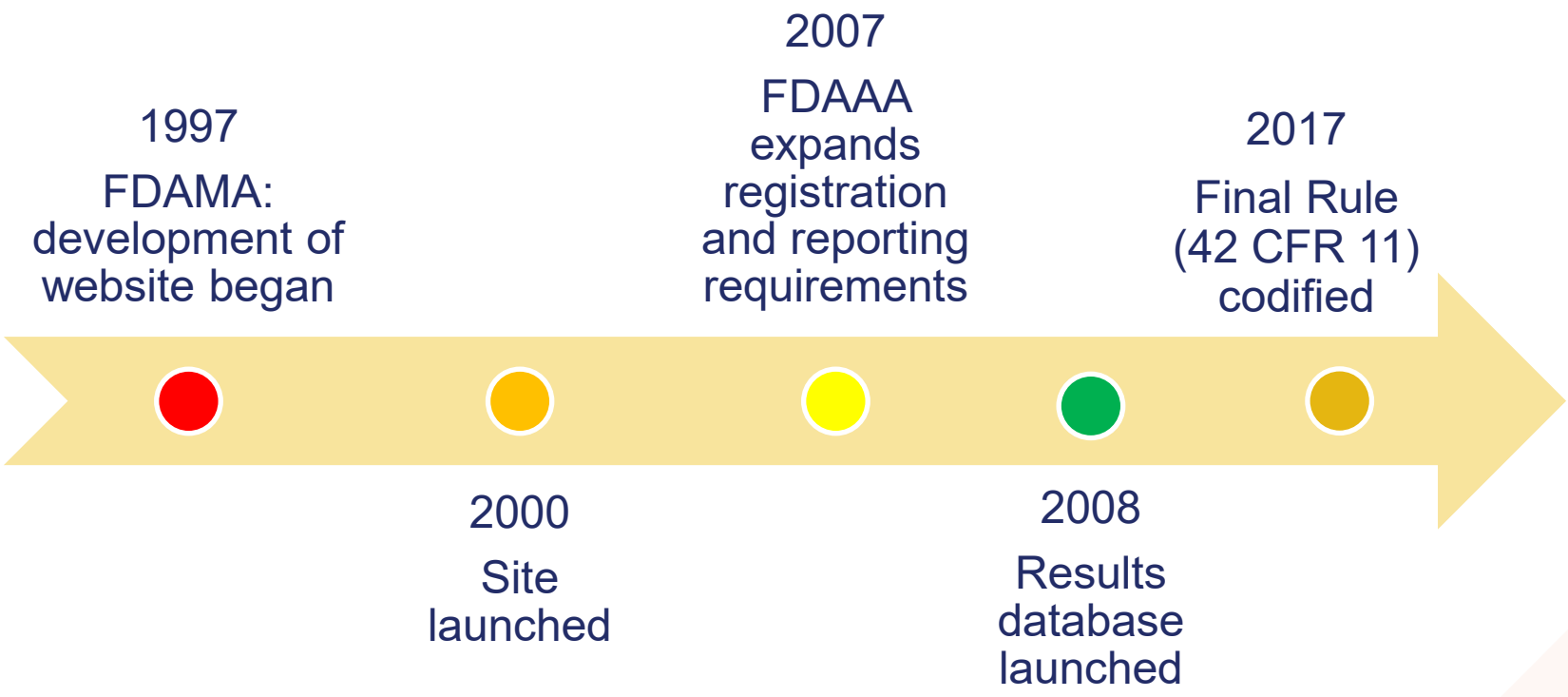
ClinicalTrials.gov Learning Objectives

- Recognize the roles of NLM, FDA, and study sponsors
- Understand the requirements for clinical trial registration and reporting
- Describe the potential consequences of noncompliance

What is ClinicalTrials.gov?



ClinicalTrials.gov Timeline



Applicable Clinical Trials (ACTs):

- Subset of clinical studies required by regulation to register and report clinical trial information
- Controlled* clinical investigation
- Not all trials are applicable clinical trials (e.g., Observational studies)

Responsibilities for ClinicalTrials.gov

- NIH/NLM: Implementation responsibilities
- Responsible Party: submit (and update) study registration and clinical trial information
- FDA: Compliance and enforcement activities for ACTs

Role of NLM

- Maintain and update the website
- Process and post registration and clinical trial information
- Review submitted study information (quality check)

ClinicalTrials.gov Registration and Reporting of Clinical Trial Information

Role of the Responsible Party

Who is the Responsible Party (RP)?

- The sponsor will be considered the RP unless and until a principal investigator has been designated
  - Responsible for registration and reporting of ACTs on ClinicalTrials.gov
  - Each ACT must have one *(and only one)* responsible party

So who is the sponsor???

See 42 CFR 11 Subpart A

Who is the Sponsor?

- ACT conducted under IND or IDE: the IND/IDE holder will be considered the sponsor
- ACT not conducted under an IND or IDE: the single person or entity who initiates the trial, by preparing and/or planning the trial, and who has authority and control over the trial, will be considered the sponsor.

See 42 CFR 11 Subpart A

Designating the RP

- Principal investigator (PI) may be designated if:
  - responsible for conducting the trial
  - access to and control over the data
  - right to publish the results of the trial
  - ability to meet all of the requirements
- PI serving as RP:
  - submits clinical trial information via the sponsor's PRS account
  - acknowledgement reflected by having PI list their name as the RP

See 42 CFR Part 11 Subpart A

Am I the RP?

- I recently took over sponsorship of an IND which includes several ACTs both ongoing and complete
- We recently acquired a small company that conducted clinical trials in an indication we are no longer going to pursue

YES

It is critical that you know the portfolio of studies under an IND/within a company's scope before assuming sponsorship/ownership – THIS INCLUDES knowing whether ACTs are in compliance!

Registration Requirements

- Required to register within 21 days of first human subject enrolled
- Registration data elements
  - Descriptive information
  - Recruitment information
  - Outcomes
  - Location and contact information
  - Administrative data

- Subject to NLM quality control - correct or address issues within 15 days

See 42 CFR 11 Subpart B

Reporting Requirements

- Required to report clinical trial information no later than 1 year after primary completion date
- Exceptions to deadline:
  - Certification for delayed submission
  - Extension requests for “good cause’
  - Waiver of the requirements for submission of results information

See 42 CFR 11 Subpart C

Reporting Requirements

- Submission of data in tabular format:
  - Participant flow
  - Demographics and baseline characteristics
  - Primary and secondary outcomes
- Full protocol
- Statistical analysis plan
- Subject to NLM quality control
  - correct or address issues within 30 days

See 42 CFR 11 Subpart C

Information Update Requirements

- At least every 12 months
- Certain data elements within 30 days
  - Expanded access information
  - Overall recruitment status
  - Study start date
  - Individual site status
  - Human Subjects Protection Review Board Status
  - Primary completion date
  - Responsible Party

See 42 CFR 11 Subpart D

Do I need to submit results?

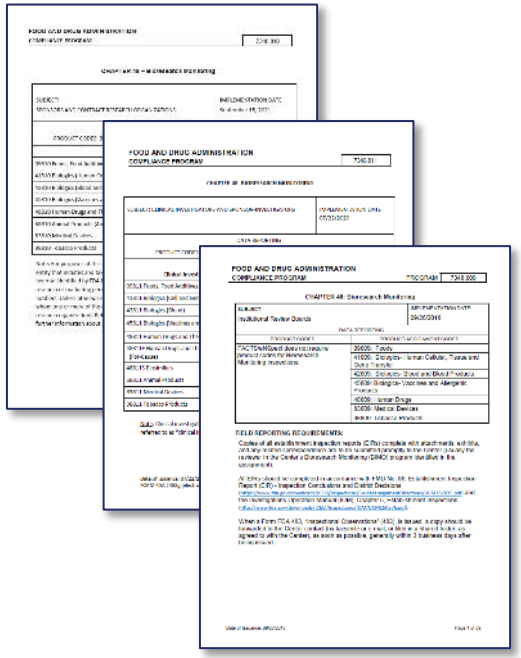
- We published our study results last year, so they are already publicly available.
- We terminated our study after only 6 patients enrolled.
- Our product was approved based on the study, so the information is in the label

YES

FDA Compliance & Enforcement Activities

BIMO Inspection Program

- ClinicalTrials.gov requirements addressed in BIMO compliance programs (CPs):
  - Institutional Review Boards
  - Sponsors and Contract Research Organizations
  - Clinical Investigators and Sponsor-Investigators
- CPs provide standard instructions for field investigators



[Bioresearch Monitoring Program (BIMO) Compliance Programs | FDA]

Complaint Evaluation

- Assessed on a case-by-case basis
- Information that may be evaluated to identify potential noncompliance includes:
  - ClinicalTrials.gov NCT records
  - Information collected as part of an FDA inspection
  - Related publications and media articles (e.g., journal articles, conference materials, trade press stories)

Surveillance Efforts

FDA prioritizes the following areas:

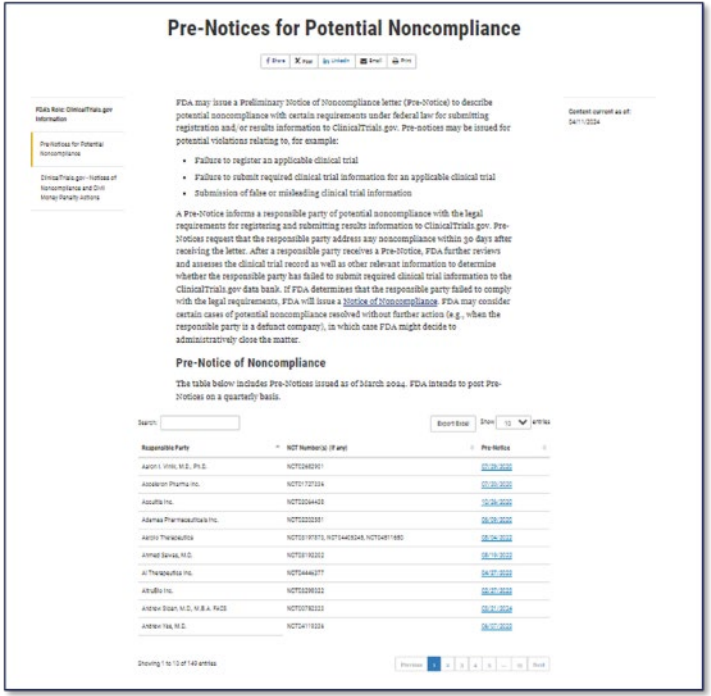
- ACTs of products that may pose a higher risk to human subjects or where violations are likely to have a high impact on public health
- Responsible parties/submitters with a pattern of previous noncompliance with the ClinicalTrials.gov requirements
- ACTs for which there is also noncompliance with other statutory and/or regulatory requirements pertaining to the conduct of the trial

Consequences of Noncompliance

- Preliminary Notice of Noncompliance Letter
- Notice of Noncompliance Letter
- Civil Money Penalties
- Grant funding actions
- Injunction and/or criminal prosecution

Preliminary Notice of Noncompliance Letter

- Identifies potential violation
- Provides opportunity to address potential violation
- Further assessment within 30 calendar days after receipt
- Posted on FDA's website



Pre-Notices for Potential Noncompliance

FDA may issue a Preliminary Notice of Noncompliance letter (Pre-Notice) to describe potential noncompliance with certain requirements under federal law for submitting registration and/or results information to ClinicalTrials.gov. Pre-notices may be issued for potential violations relating to, for example:

- Failure to register an applicable clinical trial
- Failure to submit required clinical trial information for an applicable clinical trial
- Submission of false or misleading clinical trial information

A Pre-Notice informs a responsible party of potential noncompliance with the legal requirements for registering and submitting results information to ClinicalTrials.gov. Pre-Notices request that the responsible party address any noncompliance within 30 days after receiving the letter. After a responsible party receives a Pre-Notice, FDA further reviews and assesses the clinical trial record as well as other relevant information to determine whether the responsible party has failed to submit required clinical trial information to the ClinicalTrials.gov data bank. If FDA determines that the responsible party failed to comply with the legal requirements, FDA will issue a Notice of Noncompliance. FDA may consider certain cases of potential noncompliance resolved without further action (e.g., when the responsible party is a defunct company), in which case FDA might decide to administratively close the matter.

Pre-Notice of Noncompliance

The table below includes Pre-Notices issued as of March 2024. FDA intends to post Pre-Notices on a quarterly basis.

Notice of Noncompliance Letter

- Notification of the Center's determination
- Opportunity to remedy no later than 30 calendar days after notification
- Included with record on ClinicalTrials.gov
- Posted on FDA's website

Notices of Noncompliance

ClinicalTrials.gov - Notices of Noncompliance and Civil Money Penalty Actions

Federal law requires responsible parties to submit registration and summary results information to the ClinicalTrials.gov data bank for certain applicable clinical trials. The law also requires a submitter of certain applications/submissions to FDA certify that all the above-referenced requirements have been met for applicable clinical trials referenced in such applications/submissions. FDA has the authority to issue a Notice of Noncompliance to a responsible party for failure to comply with certain requirements, including:

- Failing to submit required clinical trial information
- Submitting false or misleading clinical trial information

FDA also has the authority to issue a Notice of Noncompliance to a submitter who has failed to submit or knowingly submitted a false certification to FDA.

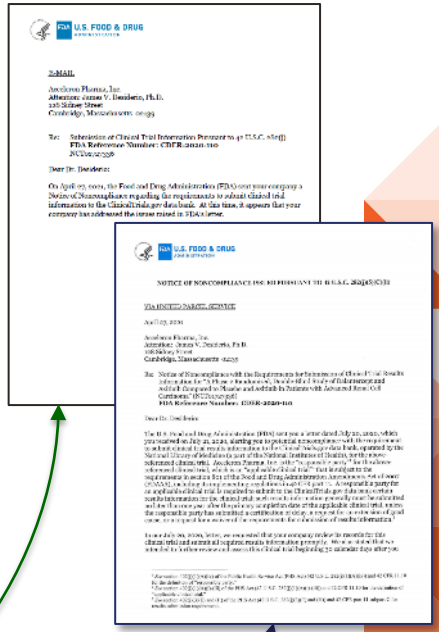
FDA has authority to assess civil money penalties for these violations. If a responsible party does not take adequate corrective action within 30 days after receiving a Notice of Noncompliance regarding failure to submit required information, that responsible party may be subject to additional civil money penalties.

FDA will take into consideration any corrective action that is taken by a responsible party after receiving a Notice of Noncompliance when considering civil money penalties. See Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank and 21 CFR part 17 for more information.

Notices of Noncompliance

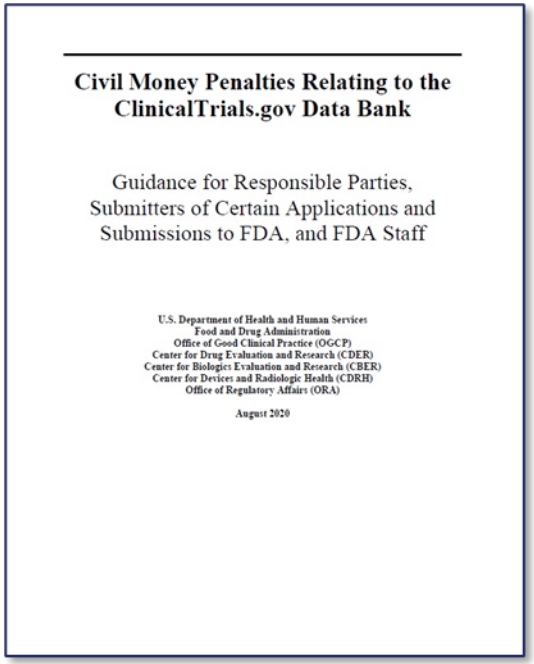
The table below lists the Notices of Noncompliance sent by FDA and the amount of civil money penalties assessed, if any, for each responsible party or submitter listed.

Responsible Party/Submitter	NCT Number	Notice of Noncompliance	Response Letter (if any)	Civil Money Penalty Amount (if any)
Dougan	NCT03785340	4/15/2022	08/01/2022	
Petrikovets, Andrey M.D.	NCT03052816	8/31/2021	12/20/2021	
Accuitis Inc.	NCT03064438	7/26/2021	09/26/2022	
Acceleron Pharma, Inc.	NCT01727336	4/27/2021	12/13/2021	



Civil Money Penalties

- Civil money penalties
  - Up to $10,000*
  - If a failure to register or failure to submit results information violation is not corrected within 30-day period following receipt of Notice of Noncompliance, up to $10,000 **per day** until violation corrected



Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank

Guidance for Responsible Parties, Submitters of Certain Applications and Submissions to FDA, and FDA Staff

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Good Clinical Practice (OGCP)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiologic Health (CDRH)
Office of Regulatory Affairs (ORA)

August 2020

*amounts adjusted annually; see 45 CFR 102.3

Challenge Question #1

When are results required to be submitted for ACTs?

A. There is no requirement to submit results information for ACTs

B. As soon as the last patient completes the study

C. Within 6 months of the primary completion date

D. No later than 1 year after the primary completion date unless qualifying for an exception

Challenge Question #2

Which of the following statements is NOT true?

A. ACTs are the subset of clinical studies required by regulation to register and report certain clinical trial information

B. The responsible party is required to register and report results information for ACTs.

C. All updates to the record in ClinicalTrials.gov must be made every 12 months

D. The IND holder is the responsible party for studies conducted under IND

Summary

- Clinical trial transparency is important
- NIH/NLM, FDA, and industry each have responsibilities related to ClinicalTrials.gov
- The sponsor or designee (responsible party) must ensure applicable trials are in compliance

Questions?

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