ClinicalTrials.gov: The FDA's Role in Registration and Results Information Reporting

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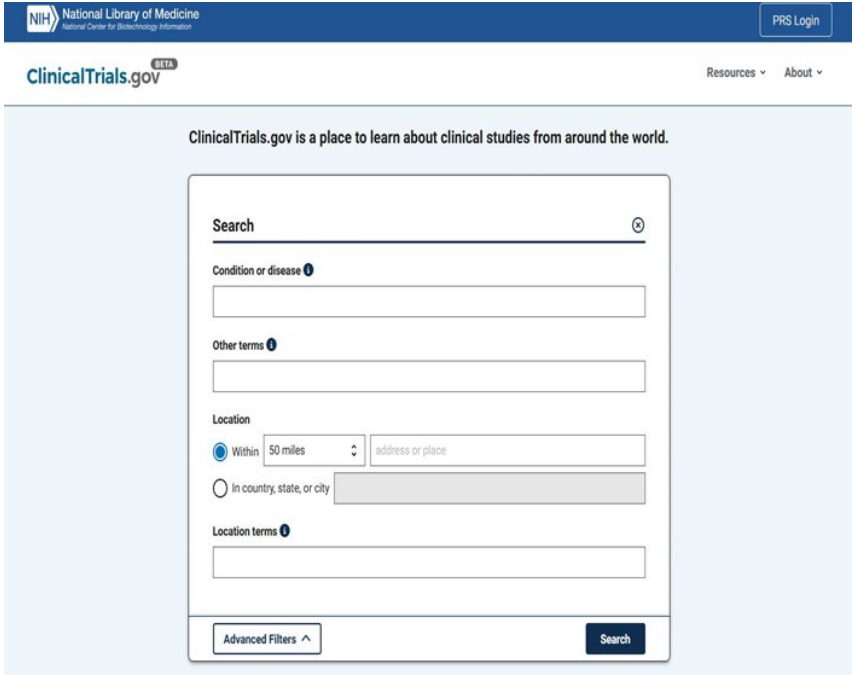
Learning Objectives

- Understand the roles and responsibilities related to ClinicalTrials.gov
- Understand CDER's approach to conducting its compliance activities related to ClinicalTrials.gov
- Recognize the potential consequences of noncompliance with the ClinicalTrials.gov requirements
- Increase awareness of ClinicalTrials.gov registration and reporting requirements

ClinicalTrials.gov

- 1997: NIH required to create clinical trial database (FDAMA)
- 2000: ClinicalTrials.gov launched
- 2007: Expansion of ClinicalTrials.gov requirements (FDAAA)
- 2017: Final rule issued clarifying and expanding requirements (42 CFR Part 11)



Responsibilities for ClinicalTrials.gov

- **NIH/NLM: Implementation responsibilities**
- FDA: Compliance and enforcement
- Study sponsors or investigators: provide study registration and results information

NLM: Role Related to ClinicalTrials.gov

- Maintaining and updating the website
- Processing and posting registration and results information
- Reviewing submitted study information for apparent errors, deficiencies, or inconsistencies.
  - Major issues
  - Advisory issues
- Oversight of NIH funded studies

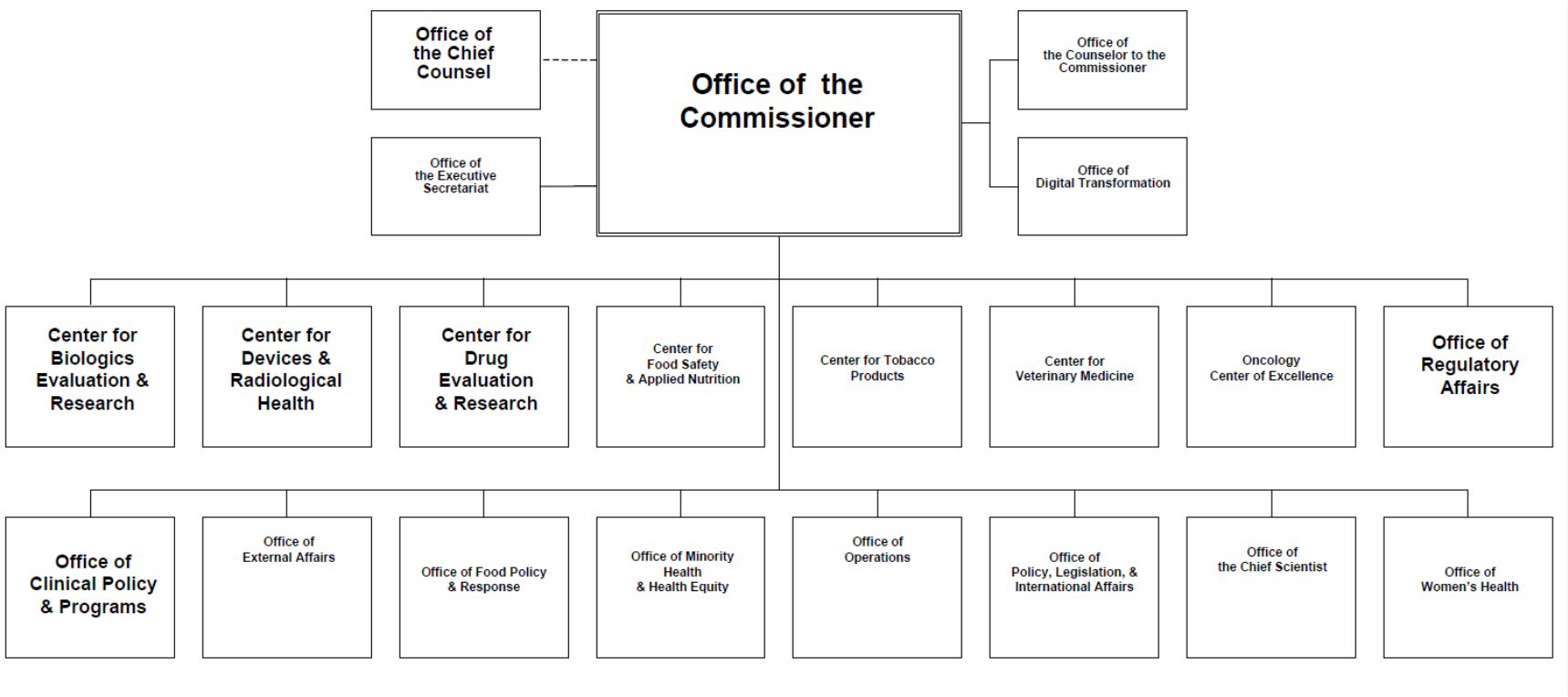
Responsibilities for ClinicalTrials.gov

- NIH/NLM: Implementation responsibilities
- **FDA: Compliance and enforcement**
- Study sponsors or investigators: provide study registration and results information

FDA: Role Related to ClinicalTrials.gov

- Compliance and enforcement
  - Informed consent statement regarding ClinicalTrials.gov [21 CFR 50.25(c)]
  - Certification of Compliance (Form FDA 3674)
  - Clinical trial registration and results information submission requirements [42 CFR Part 11]
- Encourage voluntary compliance
  - Outreach, collaboration

FDA: Role Related to ClinicalTrials.gov



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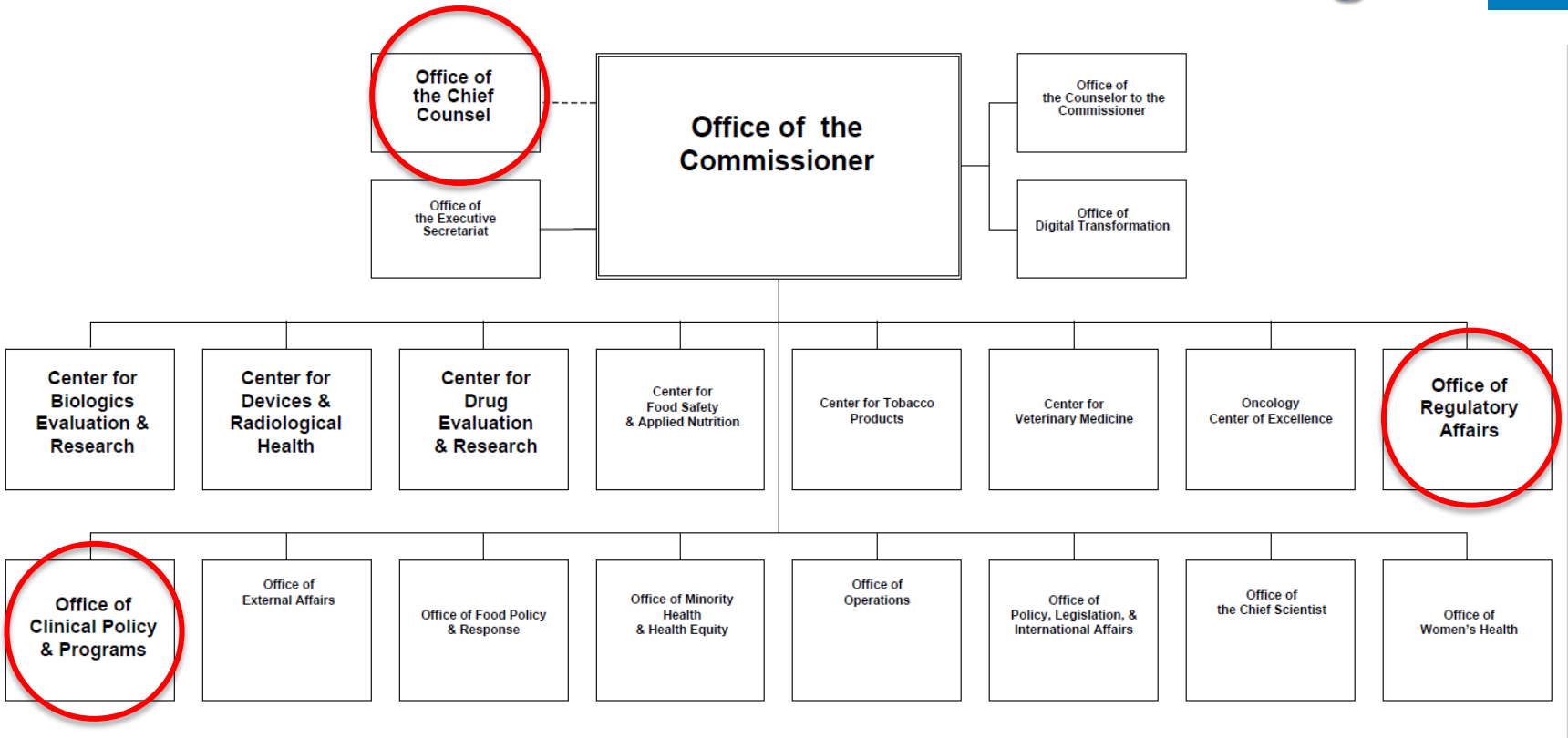

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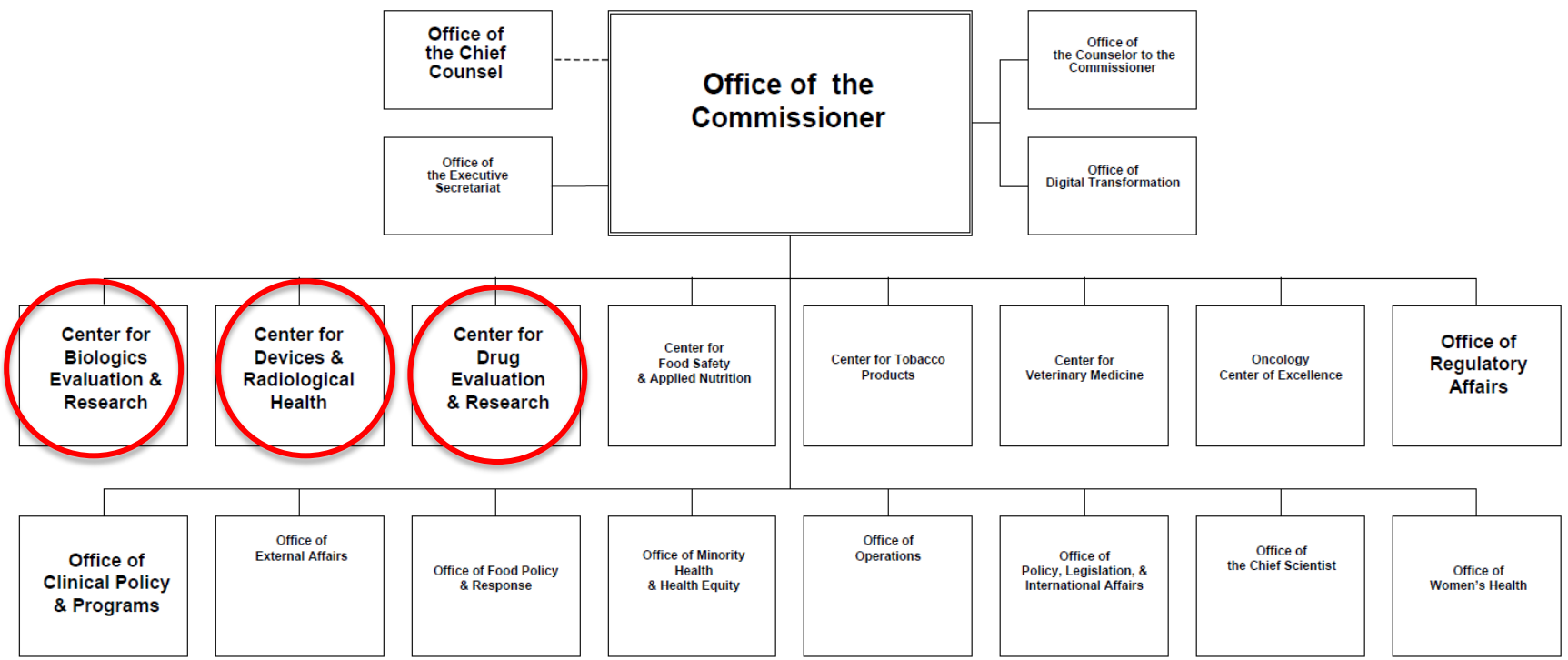
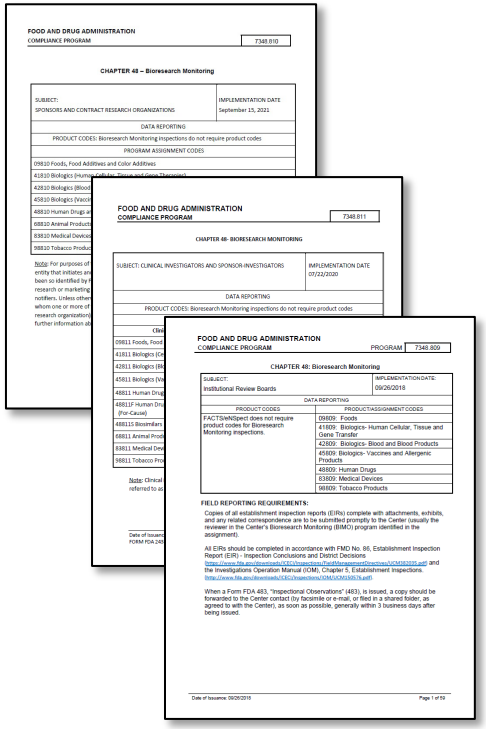


FDA's Compliance & Enforcement Activities

- Compliance activities related to ClinicalTrials.gov are incorporated into FDA's Bioresearch Monitoring (BIMO) program
  - Inspection program
  - Complaint evaluations
  - Surveillance efforts

BIMO Inspection Program

- ClinicalTrials.gov requirements addressed in following BIMO compliance programs (CPs):
  - Institutional Review Boards CP 7348.809
  - Sponsors and Contract Research Organizations CP 7348.810
  - Clinical Investigators and Sponsor-Investigators CP 7348.811
- The CPs provide standard instructions for field investigators



Complaint Evaluation

- Potential noncompliance is assessed on a case-by-case basis
- Information that may be evaluated to identify potential noncompliance includes:
  - ClinicalTrials.gov records, FDA 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: Risk-Based Compliance Approach

FDA intends to focus its attention in the following areas:

- Applicable clinical trials of products that potentially may pose a higher risk to human subjects or that are intended to address a significant public health need
- Responsible parties/submitters with a pattern of previous noncompliance with the ClinicalTrials.gov requirements
- Applicable clinical trials for which noncompliance exists in conjunction with noncompliance with other statutory and/or regulatory requirements pertaining to the conduct of the trial

Preliminary Notice of Noncompliance Letter

- Identifies potential violation
- Provides recipient an opportunity to address potential violation
- Further assessment by FDA beginning 30 calendar days after the Preliminary Notice (Pre-Notice) of Noncompliance Letter's receipt
- CDER has issued over 50 Pre-Notices of Noncompliance in last two calendar years

Notice of Noncompliance Letter

- Notifies the recipient of the Center's determination
- Gives an opportunity to remedy noncompliance not later than 30 calendar days after the notification.
- Posted on FDA's website
- Linked to record on ClinicalTrials.gov
- Five Notices of Noncompliance issued and posted on FDA.gov

Additional Consequences of Noncompliance

- Civil money penalties (amounts adjusted annually; see 45 CFR 102.3)
  - Up to $10,000 for all violations adjudicated in a single proceeding
  - 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
  - No CMPs issued to date
- Grant funding actions
- Injunction and/or criminal prosecution

Notices of Noncompliance and Civil Money Penalty Actions

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.

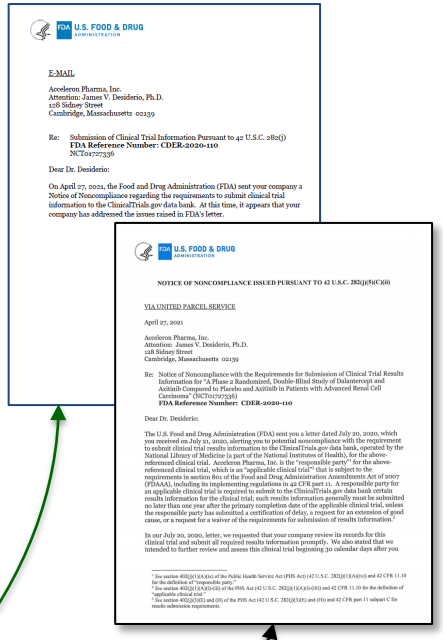
FDA has authority to assess civil money penalties for these violations. If a responsible party does not take adequate corrective action within 30 days after receiving a Notice of Noncompliance regarding failure to submit required information, that responsible party may be subject to additional civil 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	08/26/2022	
Acceleron Pharma, Inc.	NCT01727336	4/27/2021	12/13/2021	



U.S. FOOD & DRUG ADMINISTRATION

E-MAIL

Acceleron Pharma, Inc.
Attention: James V. Desiderio, Ph.D.
128 Sidney Street
Cambridge, Massachusetts 02139

Re: Submission of Clinical Trial Information Pursuant to 42 U.S.C. 282(j)
FDA Reference Number: CDER-2020-110
NCT01727336

Dear Dr. Desiderio:

On April 27, 2021, the Food and Drug Administration (FDA) sent your company a Notice of Noncompliance regarding the requirements to submit clinical trial information to the ClinicalTrials.gov data bank. At this time, it appears that your company has addressed the issues raised in FDA's letter.

U.S. FOOD & DRUG ADMINISTRATION

NOTICE OF NONCOMPLIANCE ISSUED PURSUANT TO 42 U.S.C. 282(j)(5)(C)(ii)

VIA UNITED PARCEL SERVICE

April 27, 2021

Acceleron Pharma, Inc.
Attention: James V. Desiderio, Ph.D.
128 Sidney Street
Cambridge, Massachusetts 02139

Re: Notice of Noncompliance with the Requirements for Submission of Clinical Trial Results Information for "A Phase 2 Randomized, Double-Blind Study of Dalantercept and Axitinib Compared to Placebo and Axitinib in Patients with Advanced Renal Cell Carcinoma" (NCT01727336)
FDA Reference Number: CDER-2020-110

Dear Dr. Desiderio:

The U.S. Food and Drug Administration (FDA) sent you a letter dated July 20, 2020, which you received on July 21, 2020, alerting you to potential noncompliance with the requirement to submit clinical trial results information to the ClinicalTrials.gov data bank, operated by the National Library of Medicine (a part of the National Institutes of Health), for the above-referenced clinical trial. Acceleron Pharma, Inc. is the "responsible party"[1] for the above-referenced clinical trial, which is an "applicable clinical trial"[2] that is subject to the requirements in section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), including its implementing regulations in 42 CFR part 11. A responsible party for an applicable clinical trial is required to submit to the ClinicalTrials.gov data bank certain results information for the clinical trial; such results information generally must be submitted no later than one year after the primary completion date of the applicable clinical trial, unless the responsible party has submitted a certification of delay, a request for an extension of good cause, or a request for a waiver of the requirements for submission of results information.[3]

In our July 20, 2020, letter, we requested that your company review its records for this clinical trial and submit all required results information promptly. We also stated that we intended to further review and assess this clinical trial beginning 30 calendar days after you

[1] See section 402(j)(1)(A)(ix) of the Public Health Service Act (PHS Act) (42 U.S.C. 282(j)(1)(A)(ix)) and 42 CFR 11.10 for the definition of "responsible party."
[2] See section 402(j)(1)(A)(i)–(iii) of the PHS Act (42 U.S.C. 282(j)(1)(A)(i)–(iii)) and 42 CFR 11.10 for the definition of "applicable clinical trial."
[3] See section 402(j)(3)(I) and (D) of the PHS Act (42 U.S.C. 282(j)(3)(I) and (D)) and 42 CFR part 11 subpart C for results submission requirements.

Responsibilities for ClinicalTrials.gov

- NIH/NLM: Implementation responsibilities
- FDA: Compliance and enforcement
- **Study sponsors or investigators: provide study registration and results information**

Study Sponsor or Investigator: Role Related to ClinicalTrials.gov

- Submit the study information on ClinicalTrials.gov
  - Submit complete, accurate, and up-to-date information about their study

- Ensure that their studies follow all applicable laws and regulations
  - Serve as the responsible party for applicable clinical trials (ACTs)

Who is the Responsible Party?

- Each ACT must have one *(and only one)* responsible party
- The sponsor will be considered the responsible party unless and until a principal investigator has been designated

So who is the sponsor???

eCFR : 42 CFR Part 11 -- Clinical Trials Registration and Results Information Submission

Who is the Sponsor?

- 21 CFR 50.3:
  - **Sponsor:** Person who initiates a clinical investigation, but who does not actually conduct the investigation
  - **Sponsor-investigator:** an individual who both initiates and actually conducts, alone or with others, a clinical investigation.

- 42 CFR 11.4(c)(1)
  - When the ACT is conducted under IND or IDE, the IND/IDE holder will be considered the sponsor
  - When an ACT is 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.

Who is the Sponsor?

- **Grants:** the funding recipient (grantee) generally is considered to be the initiator of the clinical trial, and therefore, the sponsor.
  - *This is because, as a general rule, when a clinical trial is funded in this manner, the funding recipient "initiates" the clinical trial process by, for example, submitting a funding proposal and designing the clinical trial.*

- **Contracts:** the party obtaining the goods or services for its direct benefit or use (the funder) generally is considered to be the initiator of the trial, and therefore, the sponsor.
  - *This is because, as a general rule, when a clinical trial is funded in this manner, it is the funder of the clinical trial that initiates the clinical trial process by, for example, contracting with another entity for that entity to conduct a clinical trial meeting the specifications of the funder.*

Designating the Responsible Party

- The sponsor may designate the principal investigator if:
  - responsible for conducting the trial,
  - has access to and control over the data from the clinical trial,
  - has the right to publish the results of the trial, and
  - has the ability to meet all of the requirements under this subsection for the submission of clinical trial information
- Sponsor must provide an account for the principal investigator within the sponsor's PRS organizational account
- Format for designation:
  - the principal investigator submits clinical trial information via the sponsor's PRS organizational account
  - acknowledgement reflected by having the principal investigator list their name as the RP

Clinical Trial Registration Requirements [42 CR Part 11]

- Required to register within 21 days of first human subject enrolled
- Registration data elements [42 CFR 11.28]
  - Descriptive information – key words, inclusion/exclusion, phase, number of arms and descriptions, study design, interventions and controls
  - Recruitment information – e.g., not yet recruiting, enrolling, active, not recruiting, etc.
  - Outcomes – primary, secondary outcomes and timeframes
  - Location and contact information
  - Administrative data
- Subject to quality control [42 CFR 11.64(b)]
- Correct or address issues within 15 days of electronic notification

Clinical Trial Results Reporting Requirements [42 CFR Part 11]

- Responsible parties for ACTs subject to the final rule requirements are required to submit results information
- Standard submission deadline is 1 year after primary completion date
  - Partial results should be submitted, and remaining information submitted later, if applicable
- Exceptions to deadline:
  - Certification for delayed submission
  - Extension requests for “good cause’
  - Waiver of the requirements for submission of results information

Clinical Trial Results Reporting Requirements [42 CFR 11.48]

- Submission of data in tabular format:
  - Participant flow
  - Demographics and baseline characteristics
  - Primary and secondary outcomes
- Full protocol
- Statistical analysis plan
- Subject to NIH quality control review

Clinical Trial Updating Information Requirements [42 CFR 11.64]

- 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
- Certain data elements within 15 days
  - Device product not approved or cleared by U.S. FDA

Key Messages

- Clinical trial transparency is important
- NIH/NLM, FDA and sponsors/investigators each have responsibilities related to ClinicalTrials.gov
- The sponsor or designee (responsible party) must ensure applicable clinical trials are in compliance.
- Contact the NIH/NLM for questions related to submission of registration and results information.

Resources

- ClinicalTrials.gov – a Three-Part Series | FDA
- FDA's Role: ClinicalTrials.gov Information
- Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank – Draft Guidance for FDA Staff, Responsible Parties, and Submitters of Certain Applications and Submissions to FDA September 2018
- Form FDA 3674 - Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions Guidance to Industry
- Questions and Answers on Informed Consent Elements, 21 CFR 50.25(c) Guidance to Industry
- 42 CFR Part 11
- ClinicalTrials.gov – NIH/NLM
- NIH Checklist for Evaluating Whether a Clinical Trials is an Appliable Clinical Trial (ACT)
- ClinicalTrials.gov - Notices of Noncompliance and Civil Money Penalty Actions
- Frequently Asked Questions: ClinicalTrials.gov (National Institutes of Health)

U.S. FOOD & DRUG ADMINISTRATION

Questions??