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

www.fda.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’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

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 those violations. If a responsible party does not take adequate corrective action within 90 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 11 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.

<table>
<thead>
<tr>
<th>Responsible Party/Submitter</th>
<th>NCT Number</th>
<th>Notice of Noncompliance</th>
<th>Hospital Letter (# if any)</th>
<th>Civil Money Penalty Amount (# if any)</th>
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<td>Parkyn, Arnold M.D.</td>
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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???*
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 Applicable Clinical Trial (ACT)
- ClinicalTrials.gov - Notices of Noncompliance and Civil Money Penalty Actions
- Frequently Asked Questions: ClinicalTrials.gov (National Institutes of Health)
Questions??