

Investigator Responsibilities

Regulations and FDA Expectations for the Conduct of Clinical Trials

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Learning Objectives

- ❖ Discuss good clinical practice standards and FDA regulations governing clinical trials.
- ❖ Review clinical investigator responsibilities for clinical trial conduct and clinical trial quality
- ❖ Discuss ClinicalTrials.gov requirements, who is the responsible party, and when registration and results information submission are required.
- ❖ Understand how risk proportionality applies to investigator oversight of clinical trial conduct, including in trials incorporating decentralized and/or pragmatic elements.



Clinical Investigator

- An individual who conducts a clinical investigation (i.e., under whose immediate direction the drug is dispensed to a subject)
- In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team.

[21 CFR 312.3]



Sponsor Investigator

- An individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed.
- The requirements applicable to a sponsor-investigator include both those applicable to an investigator and those applicable to a sponsor.

[21 CFR 312.3]



Clinical Investigator Network



Investigator Responsibilities

Legal Framework



Federal Food, Drug, and Cosmetic Act (FD&C Act)

Section 505(i) is the statutory authority for FDA's oversight of clinical investigations to test safety and effectiveness of investigational drugs

Code of Federal Regulations (CFR)

Regulations promulgated under Section 505(i) describing FDA's authority over the conduct of clinical investigations

Guidances

Advisory only, to assist regulated entities in complying with the regulations

FDA resource for regulatory information including 21 CFR Database and FDA guidance documents (<https://www.fda.gov/regulatory-information>)



Regulations Relating to GCP and Clinical Trials

These regulations are intended to ensure the integrity of clinical data on which product approvals are based and to help protect the rights, safety, and welfare of human subjects.

- ❖ 21 CFR 312 - Investigational New Drug (IND)
- ❖ 21 CFR 50 - Protection of Human Subjects
- ❖ 21 CFR 54 - Financial Disclosure by Investigators
- ❖ 21 CFR 56 - Institutional Review Boards
- ❖ 21 CFR 11 - Electronic Records, Electronic Signatures
- ❖ 21 CFR 314 - New Drug Applications
- ❖ 21 CFR 320 - Bioavailability & Bioequivalence
- ❖ 21 CFR 601 - Biologic License Applications
- ❖ 21 CFR 812 - Investigational Device Exemptions
- ❖ 21 CFR 814 - Premarket Approval of Medical Devices
- ❖ 42 CFR 11 - ClinicalTrials.gov Registration and Results Information Reporting Requirements



Responsibilities & Relevant 21 CFR Regulations

- ❖ General responsibilities; Personally conduct and supervise the investigation (312.60)
- ❖ Conduct investigation in accordance with investigator statement, protocol, and applicable regulations (312.60)
- ❖ Protect the rights, safety, and welfare of study subjects (312.60)
- ❖ Assurance of IRB review and approval (312.66)
- ❖ Protect human subjects: ensuring informed consent is adequately obtained (50, 312.60)
- ❖ Submission of required reports to sponsor (312.64)
- ❖ Maintain adequate records of the disposition of the investigational drug (312.62(a))
- ❖ Recordkeeping and retention
 - ❖ Maintain adequate and accurate case histories for each subject's participation on the clinical investigation (312.62(b))
 - ❖ Retain records for 2 years after marketing or 2 years after investigational use is discontinued and FDA notified (312.62(c))
- ❖ Employ procedures and controls (particularly for validation, audit trails, record retention, and record copying) on electronic systems, electronic records, and electronic signature (11)
- ❖ Control and accountability of investigational drug
- ❖ Ensure control of the investigational drug (312.61)
- ❖ Handling of controlled substances (312.69)



*Not all inclusive

Risk Proportionality Expectations

- Ensure a comprehensive and shared understanding of the study's critical to quality (CTQ) factors and potential risks to those CTQ factors
- Focus resources and investigator oversight on critical data points and high-risk areas (i.e., data and processes deemed CTQ)
- Assess risks throughout the study, adapting practices as necessary to respond to new information or unforeseen challenges that may arise in study conduct



Statement of Investigator, Form FDA 1572

| | | |
|--|-----------------------|--|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION | | Form Approved: OMB No. 0910-0014 Expiration Date: March 31, 2025 See OMB Statement on Reverse. |
| STATEMENT OF INVESTIGATOR <i>(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)</i> (See instructions on reverse side.) | | |
| 1. NAME AND ADDRESS OF INVESTIGATOR Name of Clinical Investigator | | |
| Address 1 | | Address 2 |
| City | State/Province/Region | Country |
| ZIP or Postal Code | | |
| 2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFY THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS PROVIDED (Select one of the following.) | | |
| <input type="checkbox"/> Curriculum Vitae | | <input type="checkbox"/> Other Statement of Qualifications |
| 3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED | | |
| CONTINUATION PAGE for Item 3 | | |
| Name of Medical School, Hospital, or Other Research Facility | | |
| Address 1 | | Address 2 |
| City | State/Province/Region | Country |
| ZIP or Postal Code | | |
| 4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY | | |
| CONTINUATION PAGE for Item 4 | | |
| Name of Clinical Laboratory Facility | | |
| Address 1 | | Address 2 |
| City | State/Province/Region | Country |
| ZIP or Postal Code | | |
| 5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES) | | |
| CONTINUATION PAGE for Item 5 | | |
| Name of IRB | | |
| Address 1 | | Address 2 |

No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572

[21 CFR 312.53(c)]



Investigator Oversight Responsibilities

- ✓ Retains the ultimate responsibility and maintains appropriate supervision of the persons or parties undertaking the activities delegated to ensure the rights, safety and well-being of the trial participants and data reliability
- ✓ May delegate trial-related activities to other persons or parties
- ✓ Supervise a clinical study in which some study tasks are delegated to employees or colleagues of the investigator or other service providers



Investigator Oversight Responsibilities

- Maintain record of delegated trial-related activities, as appropriate, proportionate to significance of the trial-related activities
- Ensure persons or parties to whom trial-related activities are delegated are **appropriately qualified** and **adequately informed** about relevant aspects of the protocol, the investigational product(s) and their assigned trial activities
- Trial-related training to persons assisting in the trial should correspond to what is necessary to enable them to fulfill their delegated trial activities that go beyond their usual training and experience



Investigator Responsibilities Guidance

Guidance for Industry

Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

Procedural
October 2009

Overview of the responsibilities of a person who conducts a clinical investigation of a drug, biological product, or medical device [an investigator as defined in 21 CFR 312.3(b) and 21 CFR 812.3(i)]

<https://www.fda.gov/media/77765/download>



IRB Review and Approval



- ✓ Assure that an institutional review board (IRB) that complies with the requirements set forth in part 56 will be responsible for the **initial and continuing review and approval** of the proposed clinical study

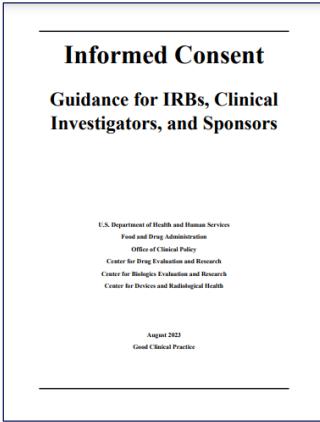


Informed Consent Requirements

- ✓ Investigator must obtain **legally effective informed consent** of each human subject to whom the drug is administered, except as provided in 21 CFR 50.23 or 50.24 [21 CFR 312.60; 21 CFR 312.50.20]
- ✓ Study participants must be given **opportunity to ask questions** and receive answers to those questions (21 CFR 50.20)
- ✓ Informed consent shall be **documented by the use of a written consent form approved by the IRB** and signed and dated by the subject or the subject's legally authorized representative at the time of consent (21 CFR 50.27)



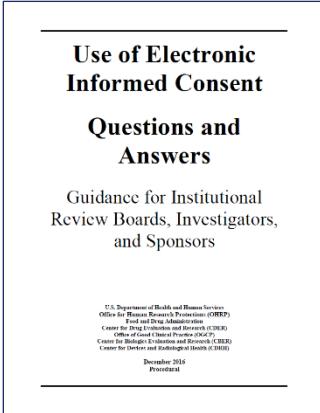
Informed Consent Guidance Documents



General guidance on FDA's regulatory requirements for informed consent

- Discussion of the roles of IRBs, clinical investigators, sponsors, and FDA related to informed consent,
- Frequently asked questions

<https://www.fda.gov/media/88915/download>



Promotes and permits the use of various electronic media (e.g., text, graphics, audio, video, podcasts and interactive Web sites) to obtain and document informed consent

<https://www.fda.gov/media/116850/download>



Study Conduct

- ✓ Ensure that an investigation is conducted according to the signed **investigator statement, the investigational plan, and applicable regulations**
- ✓ Protect the **rights, safety, and welfare of subjects** under the investigator's care; and for the **control of drugs** under investigation
- ✓ Implement processes, measures and approaches in a way that is **proportionate to the risks to participants and to the importance of the data collected**



Data Management Responsibilities

Such that data submitted to the Agency can be verified for purpose of reconstructing the study (e.g., **complete, consistent, accurate**) –

- ✓ **Maintain adequate records of the disposition of the drug** (21 CFR 312.62(a))
- ✓ **Prepare and maintain adequate and accurate case histories** that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation; **Document informed consent was obtained prior to study participation** (21 CFR 312.62(b))
- ✓ **Retain records** per 21 CFR 312.62(c)



Challenge Question #1

Who is responsible for compliance with recordkeeping and record retention requirements for electronic data remotely collected for a clinical trial?

- A. Sponsor
- B. Clinical investigator**
- C. Local healthcare provider
- D. Data storage service provider



IND Safety Reporting Responsibilities

- ✓ Determine if the adverse event (AE) is serious
- ✓ Report serious AEs (SAEs) to the sponsor immediately (21 CFR 312.64) regardless of whether the investigator believes the SAEs are related to the drug
- ✓ Record non-serious adverse events and report them to the sponsor as specified in the protocol
- ✓ FDA generally considers a serious and unexpected adverse event that meets the criteria for an IND safety report to be an unanticipated problem involving risk to human subjects or others that therefore must be reported to the IRB by the investigator
 - Review IND safety reports; Submit to the IRB (21 CFR 312.66)

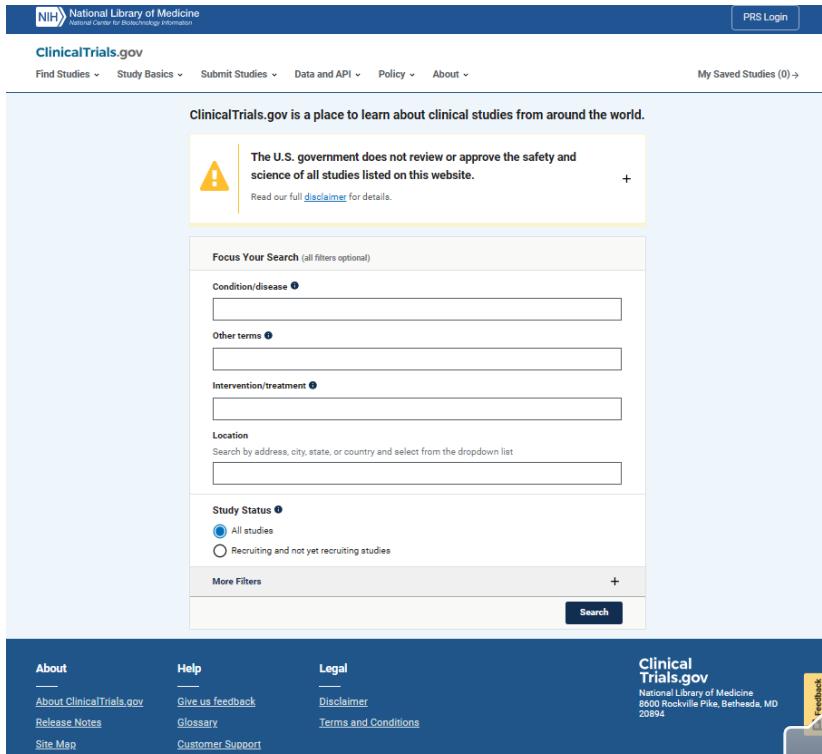


ClinicalTrials.gov

Registration and

Results Information

Requirements



The screenshot shows the ClinicalTrials.gov homepage. At the top, the NIH National Library of Medicine logo is on the left, and a PRS Login button is on the right. Below the header, there are navigation links: Find Studies, Study Basics, Submit Studies, Data and API, Policy, and About. A link to 'My Saved Studies (0) →' is also present. The main content area features a yellow warning box stating: 'The U.S. government does not review or approve the safety and science of all studies listed on this website.' It also includes a link to the full [disclaimer](#). Below this, there is a search form titled 'Focus Your Search (all filters optional)'. It includes fields for 'Condition/disease', 'Other terms', 'Intervention/treatment', and 'Location'. Under 'Study Status', there are radio buttons for 'All studies' (selected) and 'Recruiting and not yet recruiting studies'. A 'More Filters' button is available, and a 'Search' button is at the bottom right. At the very bottom of the page is a dark blue footer with links for 'About', 'Help', and 'Legal', along with the ClinicalTrials.gov logo and contact information.

Responsibilities for ClinicalTrials.gov



- NIH/NLM: Implementation responsibilities
- FDA: 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]



National Institutes of Health (NIH) - National Library of Medicine (NLM)

fda.gov/cdersbia

Applicable Clinical Trials (ACTs)



Subset of clinical studies required by regulation to register and report clinical trial information



Controlled clinical investigation



Not all studies are applicable clinical trials (e.g., observational studies)



Registration Requirements

- Required to register within 21 days of first human subject enrolled

Registration of Data Elements

- Descriptive information (e.g., phase, study design, interventions and controls, eligibility criteria)
- Recruitment information (e.g., not yet recruiting, enrolling)
- Outcomes (e.g., primary, secondary outcomes)
- Location and contact information (e.g., where the study will be conducted and sites' contact information)
- Administrative data (e.g., POC and address for the sponsor)

Quality Control (QC)

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



Reporting Requirements

- Required to report clinical trial information no later than 1 year after primary completion date
 - Exceptions to deadline (i.e., certification for delayed submission, extension requests for 'good cause', and waiver of the requirements for submission of results information)
- Updates at least every 12 months
- Certain data elements within 30 days (e.g., expanded access information, overall recruitment status, study start date, individual site status, IRB status, primary completion date, RP)

Data Submission in Tabular Format

- Participant flow (describes summary of the progress of participants in the trial by study arm/group/cohort and includes the number of participants enrolled, completed, and withdrawn)
- Demographics and baseline characteristics
- Primary and secondary outcomes
- Full protocol
- Statistical analysis plan

Subject to NLM QC

- Correct or address issues within 30 days



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



Designating an 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 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  RP

Challenge Question #2

Who is responsible for ClinicalTrials.gov registration and results information submission?

- A. Study sponsor
- B. Principal investigator of an investigator-initiated study
- C. Individual designated by a sponsor, grantee, contractor, or awardee
- D. All of the above.



Conclusion



- Clinical investigators are ultimately responsible for oversight of the conduct of a clinical investigation, compliance with federal law and FDA regulations, upholding good clinical practice, and assuring human participant protection and data integrity.



Resources



Regulatory Information

Search for FDA guidance documents, learn about the laws enforced by FDA, and more.

Search for FDA Guidance Documents

Search for official FDA guidance documents and other regulatory guidance for all types.

Learn More

NAVIGATE THE REGULATORY INFORMATION SECTION

Rules & Regulations

Summary of the FDA's process for rulemaking.

Laws Enforced by FDA

The Federal Food, Drug, and Cosmetic Act and other congressional milestones are presented in this section.

Standards

FDA participates in the development of standards and uses standards to fulfill its regulatory responsibilities.

Freedom of Information

Electronic reading room contains publicly releasable agency records and other information routinely made available.

Dockets Management

Docket management serves as the official repository for the administrative proceedings and rule-making documents for FDA.

Food and Drug Administration Safety and Innovation Act

FDASIA gives FDA the authority to collect user fees and review of innovator drugs, medical devices, generic drugs and biosimilar products.

How to Make a FOIA Request

Guidelines for making a Freedom of Information Act request for public information.

Federal Food, Drug, and Cosmetic Act

Online access to the FDA's principal authorizing legislation.

Search for FDA guidance documents, learn about the laws enforced by FDA, and more:

<https://www.fda.gov/regulatory-information>

