Dartmouth Health

OFFICE OF RESEARCH OPERATIONS
RESEARCH QUALITY & SAFETY
EDUCATION AND TRAINING

Sponsor-Investigator Handbook

Version 2.0, February 2025

Dartmouth Health

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This manual derives content directly from U.S. Food and Drug Administration (FDA) sources (federal regulations, guidance documents, and the Agency's website) and International Conference for Harmonisation Good Clinical Practice (ICH GCP).

Dartmouth-Hitchcock Office of Research Operations requires Sponsor-Investigators to have knowledge of the content and resources found on the FDA website, including, but not limited to, references to the Code of Federal Regulations and ICH GCP Guidance.

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Key Terms & Acronyms

Abbreviated IDE
IRB concurs with the non-significant risk assessment for the device and approves the study under 21 CRF 812.2

Actions indicated as result of FDA inspections
NAI = no action indicated OAI = official action indicated VAI = voluntary action indicated

ADR
adverse drug reaction

AE
adverse event

ALCOA+CCEA
attributable, legible, contemporaneous, original, accurate and complete, consistent, enduring, and available

CFR
Code of Federal Regulations

CITI Training: Collaborative Institutional Training Initiative
the CITI program provides foundational knowledge and training in the protection of human subjects, compliance with regulatory standards, and ethical conduct of research for research communities worldwide.

CRO
contract research organization

FDA
United States Food and Drug Administration

FDF
financial disclosure form

GMP
good manufacturing practice

IB
investigator's brochure

ICH GCP
International Conference on Harmonisation – Good Clinical Practice
Practice: GCP is the international ethical and scientific quality standard for designing, conducting, and recording trials that involve the participation of human subjects.

IDE
investigational device exemption

IND
investigational new drug

Key Terms & Acronyms continued

Investigator
an individual responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Source: https://www.fda.gov/media/93884/download

IO
institutional official

IP
investigational product (such as drug or biologic)

IRB
institutional review board

NSR
non-significant risk (such as device)

RNI
reportable new information; *A one size fits all submission to let the D-H IRB know of events that are "new" to the study. These new events might be a new risk that was identified, protocol violation, or a monitor's report, among other things.*

RP
research pharmacy (also referred to as investigational pharmacy)

Significant Risk Device
device that must have an IDE application approved by the FDA.

Sponsor
an individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Source: https://www.fda.gov/media/93884/download

Sponsor-Investigator
an individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a Sponsor-Investigator include both those of a sponsor and those of an investigator.

Source: https://www.fda.gov/media/93884/download

= relates to subject safety

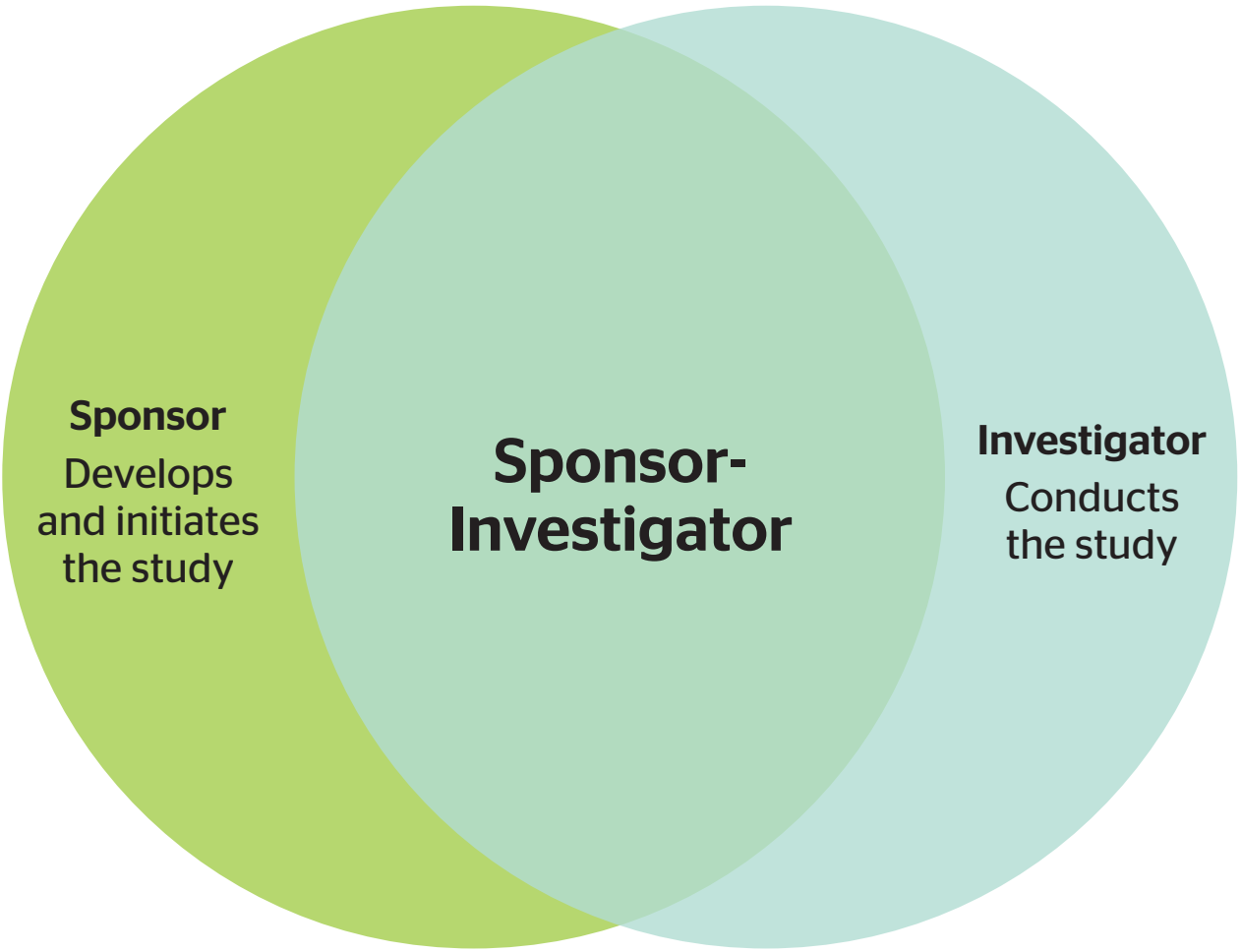
= relates to investigational drug

= relates to investigational device

= relates to areas of ORO support

= email ORO

= relates to approval prior to implementation



A Sponsor-Investigator is an investigator who takes on the roles of BOTH the sponsor and investigator in a clinical trial.

I.
Introduction

A. Overview

The role of Sponsor-Investigator in clinical research conduct is an extensive responsibility encompassing a broad range of accountability for human subjects, and to both institutional and regulatory authorities. In addition, the Sponsor-Investigator is accountable for all study processes and procedures, medical oversight, personnel training, and ultimately, the integrity of the study data and clinical conclusions.

B. Objective

The Declaration of Helsinki, International Council for Harmonisation, and Code of Federal Regulations provide the broad ethical and regulatory framework for the conduct of research in human participants. Institutional policy, in conjunction with the federal regulations, provide researchers the parameters, expectations, and rules by which to conduct clinical research.

Clinical research, in particular interventional clinical trials investigating drugs, biologics, and devices, has led to important revision and critical innovation in clinical standard of care over time. With the inherent objective of protecting human participants in research and ultimate goal of optimizing clinical care through a rigorous institutional research initiative, this handbook seeks to emphasize and make accessible both the regulations and institutional policy applicable to investigators who take on the role of Sponsor-Investigator.

II.

D-H Requirements for Sponsor-Investigators

A. D-H Sponsor-Investigator Requirements

In order to conduct FDA regulated research at Dartmouth-Hitchcock (D-H), Sponsor-Investigators are required to complete and remain current on required institutional training. Specific requirements for Sponsor-Investigators include:

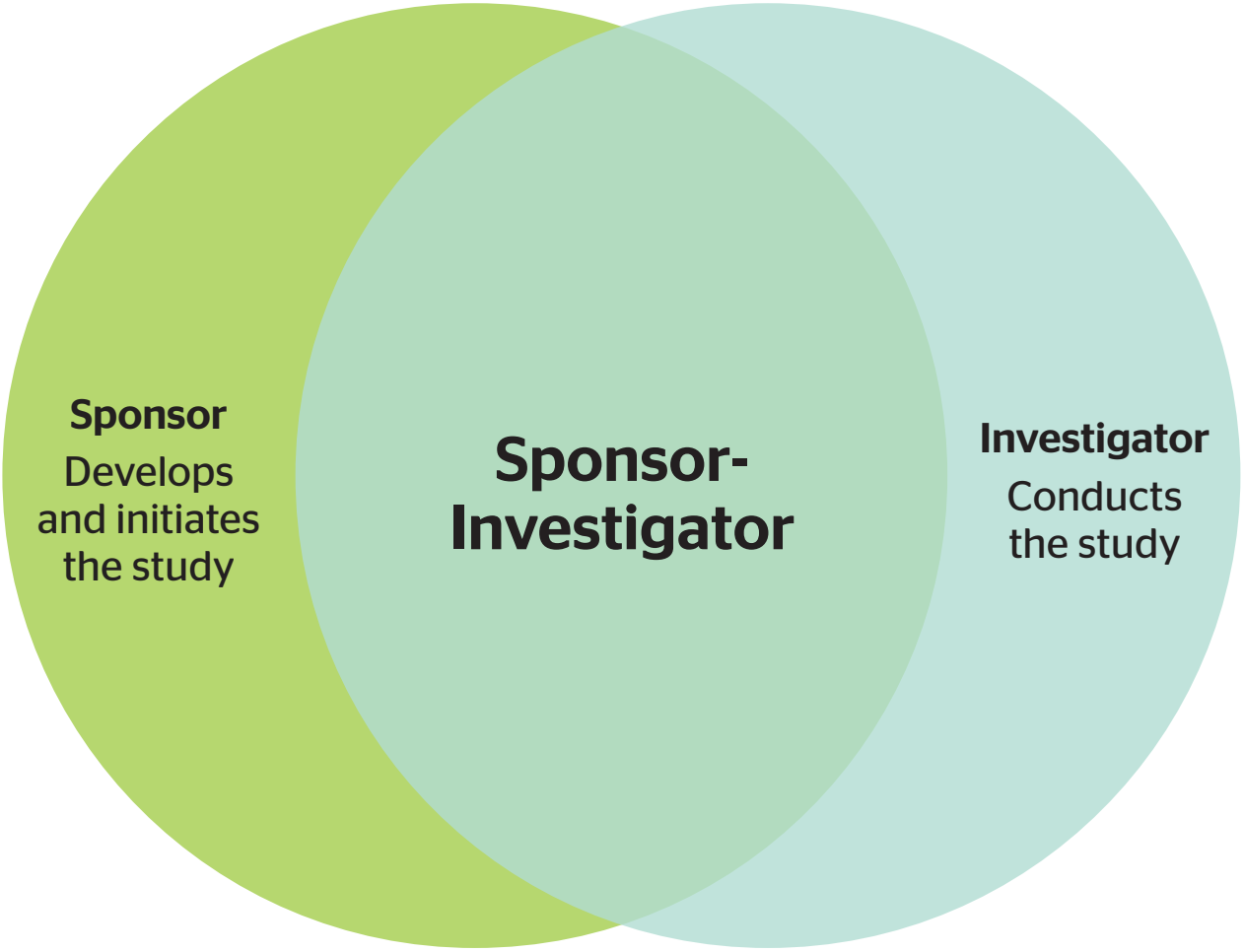
- ✓ Acknowledgment of reading and understanding current D-H Sponsor-Investigator handbook
- ✓ Completion of applicable institutional training via Halogen
- ✓ Fulfillment of institutional PI requirements per DH policy ID: 26012
- ✓ Fulfillment of CITI training requirements for researchers per DH policy ID: 23146

III.

Sponsor-Investigator Responsibilities

A. Overview Sponsor-Investigator Role

A Sponsor-Investigator is an investigator who takes on the roles of BOTH the sponsor and investigator in a clinical trial.



According to the International Conference for Harmonisation Good Clinical Practice (ICH GCP), a Sponsor-Investigator is an individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (such as it does not include a corporation or an agency). The obligations of a Sponsor-Investigator include both those of a sponsor and those of an investigator.

Source: **https://www.ich.org/page/ich-guidelines**

The Sponsor-Investigator role includes the responsibilities of BOTH sponsor and investigator in FULL.

A **sponsor** may be a pharmaceutical company, governmental agency, academic institution, cooperative group, or other private organization or individual.

B. Overview Sponsor Role

- Initiates clinical investigation
- Designs trial and develops the clinical protocol
- Selects qualified investigators to conduct trial
- Oversees all quality management activities to include:
  - » Monitoring
  - » Auditing
  - » Quality assurance and quality control

Note: ORO will provide quality management services to Sponsor-Investigators of IND or IDE studies.

- Works with the ORO to prepare and submit FDA submissions
- Manages the trial
- Establishes and oversees the data coordination
- Provides subject or investigator compensation (if applicable)
- Finances the trial (if applicable)
- Manufactures, packages, labels, and codes investigational product (IP)
- Oversees the ongoing safety evaluation of the IP
- Reports AEs to investigators/institutions/IRBs (as applicable)
- Reports premature termination or suspension of the trial to the appropriate governing bodies (as applicable)
- Develops applicable clinical trial reports

Drugs and Biologics

§312.50: General responsibilities of sponsors (IND)

Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND, maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug. Additional specific responsibilities of sponsors are described elsewhere in this part.

Significant Risk Devices

§812.40: Responsibilities of sponsors for Significant Risk Device Studies (requiring IDE)

Sponsors are responsible for selecting qualified investigators and providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, ensuring that IRB review and approval are obtained, submitting an IDE application to FDA, and ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation.

C. Overview Investigator Role

- Responsible for study conduct at the study site they oversee
- Accountable for clinical investigation including medical oversight
- Oversees subject eligibility and data integrity
- Ensures accountability of investigational product or device
- Ensures the protection of subject rights and safety, including obtaining informed consent and safety reporting
- Secures resources to conduct the investigation
- Communicates and complies with the IRB
- Complies with the protocol
- Maintains adequate source documents and essential regulatory documentation
- Reports premature termination or suspension of the study to subjects and to governing bodies (as applicable)
- Prepares applicable study reports

Traditionally, an **investigator** is a medical doctor at a private, public, or governmental organization.

Drugs and Biologics

§312.60: General responsibilities of investigators (IND)

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

An investigator shall obtain the informed consent of each human subject to whom the drug is administered, in accordance with part 50 of this chapter. Additional specific responsibilities of clinical investigators are set forth in this part and in parts 50 and 56 of this chapter.

Significant Risk Device

§812.100: Responsibilities of investigators for Significant Risk Device Studies (requiring IDE)

An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation. An investigator also is responsible for ensuring that informed consent is obtained in accordance with part 50 of this chapter.

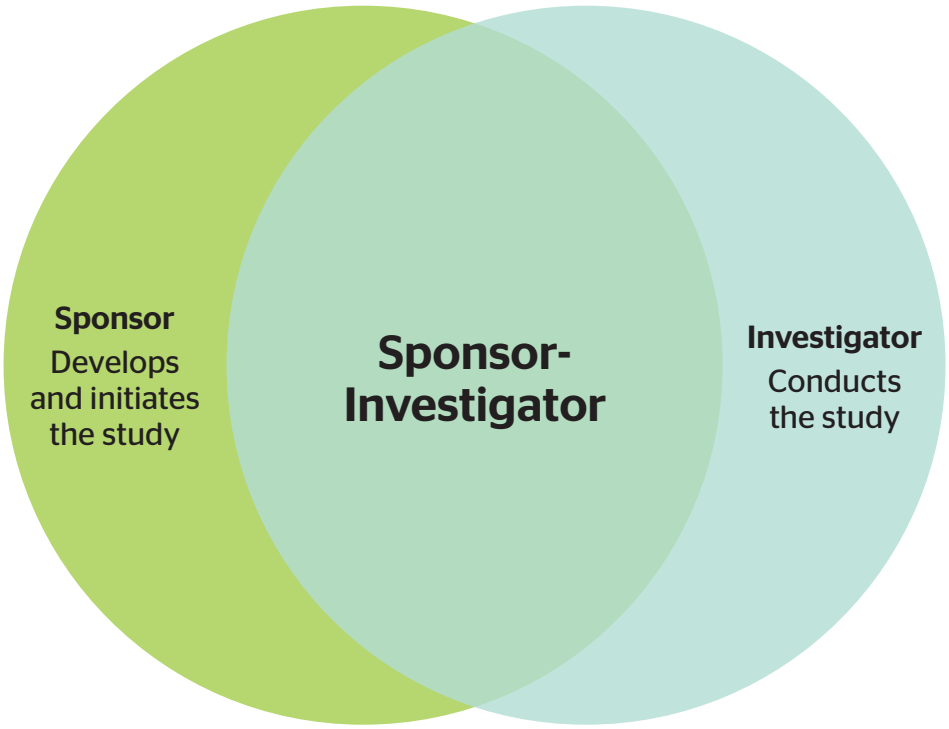
IV.

IND (Investigational New Drug) Studies

A. What is an IND?

An Investigational New Drug (IND) application is a request from a sponsor (such as an industry sponsor or Sponsor-Investigator) to obtain authorization from the FDA to administer an investigational drug or biological product to humans and to allow an experimental drug to be shipped across state lines.

In summary, an IND is a regulatory submission with subsequent approval from the FDA that permits clinical investigation of unapproved drugs or use of approved drugs in an investigational manner.



B. Sponsor-Investigator Responsibilities

The FDA regulations describe responsibilities of both sponsors and investigators in a variety of sections. The general responsibilities of each role are included below; please refer to the Sponsor-Investigator Responsibilities section of the Handbook for complete details.

§312.50 - General responsibilities of sponsors (IND)

Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND, maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug. Additional specific responsibilities of sponsors are described elsewhere in this part.

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An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

An investigator shall obtain the informed consent of each human subject to whom the drug is administered, in accordance with part 50 of this chapter. Additional specific responsibilities of clinical investigators are set forth in this part and in parts 50 and 56 of this chapter.

C. IND Categories

Commercial IND

- Traditionally filed with the intent of New Drug Application (NDA) seeking to commercialize drug
- Typically a corporate entity

Research IND (or non-commercial IND)

- Traditionally filed to contribute to generalizable knowledge (with no intention to commercialize)
  - » Use of a drug or biologic that is not approved by the FDA for the use to be studied or tested
  - » Use of an FDA approved drug in an investigational manner

All regulations are equally applicable to both commercial/ industry sponsors and academic researchers.

Other INDs

- **Emergency Use IND** allows the use of an investigational drug or biological product for a patient in an emergent life-threatening situation in which no acceptable treatment (standard or investigational) is available

Source: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-investigational-drug-or-biologic

- **Expanded Access IND** allows the use of an investigational drug or biologic for a patient in a serious or life-threatening situation in which no acceptable treatment (standard or investigational) is available

Source: https://www.fda.gov/news-events/public-health-focus/expanded-access

D. Regulatory Overview

Who files an application for an IND?

The Sponsor-Investigator is responsible for submitting an IND application to the FDA prior to seeking IRB approval.

When do I need to file an IND for an FDA approved drug?

The need for an IND is dependent on both the intent of an investigation and the degree of risk associated with the use of the drug.

A study may require an IND if the approved drug is being studied...

- In a different patient population
- For a new indication
- Via a different route of administration
- In a different dose
- Or considering other factors that would increase the risk, or decrease the acceptability of risk, associated with the use of the drug product

Does the protocol involve drugs that are NOT approved by the FDA?

YES

File an IND application with the FDA

NO

Does the study meet ALL of the following criteria?

1. Trial not intended to support a new indication or change the labeling of a drug
2. Trial is not intended to support a change in advertising
3. Trial does not involve route of administration, dose level, use in different patient population, or other factors that may significantly increase the risk to subjects
4. Trial is conducted in compliance with the IRB
5. Trial is conducted in compliance with informed consent
6. Trial is conducted by a qualified investigator
7. Trial is conducted in compliance with the drug promotion and sale requirements

YES

File an IND exemption request with the FDA

NO

File an IND application with the FDA

IND exemption requests should be submitted to the FDA by the Sponsor-Investigator prior to IRB submission. The exemption rationale along with the results of the FDA's determination should be included in the initial IRB application.

IND applications must be submitted to the FDA before submission to the IRB. The FDA's approval should be secured before the initial IRB application is submitted.

ORO will support your FDA submission process. Please contact ORO prior to filing an IND application or an IND exemption request.

E. Reporting Requirements

FDA reporting requirements (Sponsor responsibility)

Initial IND application (§312.23)

- Cover letter with submission identifier, brief explanation of investigation, investigational drug product name and proposed formulation, disease or condition under investigation, product manufacturer name and contact information, reference to existing IND application (if applicable)
- Form FDA 1571: IND application
- Form FDA 1572: Statement of the investigator
- Form FDA 3674: Certification requirement and mandatory registration and reporting of results for applicable clinical trials through ClinicalTrials.gov
- Form FDA 3792: Biosimilar user fee cover sheet (if applicable)
- Table of contents
- Introductory statement
- General investigational plan
- Investigator's Brochure (if applicable)
- Protocol
- Chemistry, manufacturing, and control information
- Pharmacology toxicology information
- Previous human experience
- Additional information, such as:
  - » Drug dependence and abuse potential
  - » Radioactive drugs
  - » Pediatric studies
  - » Other Information

Regulatory binder

- Form FDA 3454: Certification: Financial Interest and Arrangements of Clinical Investigators
- Form FDA 3455: Disclosure: Financial Interest and Arrangements of Clinical Investigators

All investigators named on the submission to FDA per §812.20(b)(5) and §812(b)(4) must provide the sponsor with a signed financial disclosure form (FDF). This disclosure informs the sponsor's completion of FDA 3454 and/or 3455 as applicable.

Updated FDFs must be provided to the sponsor throughout the course of the investigation and for 1 year after completion of the study, per §54.4(b).

The 3454 and 3455 need to be kept current and on file in the regulatory binder, but do not need to be submitted to FDA.

Note: D-H expects the use of the FDA electronic submission process (CDER NextGen portal) for all regulatory submissions related to investigational drugs.

FDA considers the IND to be effective, per §312.40(b), 30 days after FDA acknowledges receipt of the IND application, unless the Agency notifies the sponsor that the IND has been placed on clinical hold.

IND applications with a letter of cross reference

- An existing IND application may be cross referenced by a Sponsor-Investigator, provided a letter of authorization is issued by the holder of the IND for the investigational product
- This allows the Sponsor-Investigator to cite the referenced IND in several application sections, such as:
  - » Investigator's Brochure (if applicable)
  - » Chemistry, manufacturing, and control information
  - » Pharmacology and toxicology information

Protocol amendments (§312.30(b))

- Certain protocol amendments must be submitted prior to implementing the changes

- Protocol amendments must be submitted to FDA in the following cases:
  - Phase 1 studies: changes that significantly affect safety of the subjects
  - Phase 2 or 3 studies: changes that significantly affect the safety of the subjects, scope of the investigation, or scientific quality of the study
    - Any increase in drug dosage or duration of exposure to the drug beyond that described in the current protocol, or any significant increase in the number of subjects
    - Any significant change in the design of a protocol
    - Addition of a new test or procedure intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or elimination of a test to monitor safety
- Some protocol amendments may be implemented before notifying FDA, such as:
  - Addition of a new lead investigator
    - PI may begin work, but amendment must be submitted within 30 days of IRB approval to add PI and institution as an external site
    - A 1572 signed by the lead investigator and their CV must accompany the amendment
    - A protocol change intended to eliminate an apparent immediate hazard to human subjects may be implemented immediately, provided FDA and IRB are subsequently notified

Information amendments (§312.31)

Information essential to the IP that is not within the scope of a protocol amendment, IND safety report, or annual report, such as:

- New toxicology
- Chemistry
- Other technical information
- Report regarding discontinuance of a clinical investigation

Safety reports

Sponsor-Investigators are responsible for all safety reporting to include:

- Any adverse event associated with the use of the drug that is both serious and unexpected

OR

- Any findings from tests in laboratory animals that suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, and carcinogenicity

Every submission to FDA includes a Form 1571, serial numbered consecutively to reflect the sequence of the submission to FDA.

Annual reports (§312.33)

- Submitted within 60 days of the anniversary date the IND went into effect every year for each reporting period
- Brief report on progress of investigation to include:
  - » Total number of subjects to date tabulated by age group, gender, race
  - » Number of subjects to complete study
  - » Number who dropped out
  - » Brief description of any available study results
  - » Narrative or tabular summary showing the most frequent and most serious adverse experiences by body system
  - » Summary of IND safety reports submitted during the past year
  - » A list of subjects who died during participation in the investigation with the cause of death for each subject
  - » A list of subjects who dropped out during the course of the investigation in association with an adverse experience, whether or not thought to be drug related
  - » A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, bioavailability, or relevant information from controlled trials
  - » A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings
  - » A summary of any significant manufacturing or microbiological changes made during the past year
  - » Update to the general investigational plan for the coming year
  - » Updated Investigator's Brochure (if applicable), including a description of the revisions and copy of the revised version (if an LOA was submitted to cross-reference an existing IND, information on the IB is not applicable)
  - » Any significant protocol modifications during the year not previously reported in an IND protocol amendment
  - » A brief summary of significant foreign marketing developments with the drug during the past year, such as approval or withdrawal of marketing in any country

Adverse Event	FDA Reporting Timeframe	Type of Report	Recipient
Serious[1] AND Unexpected[2] AND Suspected to be related to the investigational product[3] *even if considered a component of a study endpoint	No later than 15 calendar days after the sponsor's initial receipt of information	FDA Form 3500A (MEDWATCH)	FDA[4] AND Participating investigators AND IRB (per DH IRB policy for reporting)
Fatal OR Life threatening[5] AND Unexpected[2] AND Suspected to be related to the investigational product[3] *even if considered a component of a study endpoint	No later than 7 calendar days after the sponsor's initial receipt of information[6]	FDA Form 3500A (MEDWATCH)	
Events occurring at a higher rate than anticipated (that meet the following criteria): Serious[1] AND Expected[7] AND Suspected to be related to the investigational product[8]	No later than 15 calendar days after the sponsor determines the results from the aggregate analysis of the specific events qualifies for reporting[9]	Narrative format (aggregate analysis) AND Individual MEDWATCH reports for the cases analyzed	
Findings from: Animal / in vitro / epidemiological studies that suggest a significant risk to human subjects	No later than 15 calendar days after the sponsor's initial receipt of information	Narrative format	

Safety Reports — Footnotes

[1] Death, life threatening adverse drug experience, inpatient/prolonged hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, medical event jeopardizing the patient and may require medical/surgical intervention.

[2] An adverse event or suspected adverse reaction that is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. This also includes events that are anticipated within the drug class but not specifically mentioned as occurring with the particular drug under investigation.

[3] A subset of all adverse events for which there is a **reasonable possibility that the drug caused the event.**

[4] All IND Safety Reports (narratives / MEDWATCH reports) must be submitted to the appropriate CDER review division that has responsibility for review of the IND.

[5] Immediate risk of death (based upon the investigator's judgment).

[6] FDA recommends these 7-day reports are submitted electronically via the CDER NextGen portal. Other means of rapid communication (such as email) with the respective review division's Regulatory Project Manager may also be used.

[7] Known consequences of the disease under investigation, commonly known events that occur in the study population, or are listed in the protocol or investigator's brochure.

[8] A subset of all adverse events for which there is a **reasonable possibility that the drug caused the event.**

[9] FDA considers an aggregate analysis of specific safety events reportable if the results of the analysis indicate the events are occurring more frequently in the drug treatment group than in the control group. (If the study does not contain a control group, historical controls maybe referenced).

Final Report and Withdrawal – All INDs should have a final report and a request to withdraw submitted to FDA.

§312.38 Withdrawal of an IND

(a) At any time a sponsor may withdraw an effective IND without prejudice.

(b) If an IND is withdrawn, FDA shall be so notified, all clinical investigations conducted under the IND shall be ended, all current investigators notified, and all stocks of the drug returned to the sponsor or otherwise disposed of at the request of the sponsor in accordance with §312.59.

(c) If an IND is withdrawn because of a safety reason, the sponsor shall promptly so inform FDA, all participating investigators, and all reviewing Institutional Review Boards, together with the reasons for such withdrawal.

ORO will support your IND withdrawal process. Please contact ORO in regard to withdrawal.

ClinicalTrials.gov reporting requirements

The Sponsor-Investigator of an FDA-regulated applicable clinical trial is required to register and report results of the study on the ClinicalTrials.gov website.

Refer to D-H policy ID: 22264, Registration and Results Reporting of Clinical Research in ClinicalTrials.gov

ORO provides support and guidance for ClinicalTrials.gov reporting. Please contact the D-H Protocol Registrations and Results Reporting System (PRS) Administrator for more information.

See ORO ClinicalTrials.gov guidance on the ORO intranet page

D-H IRB reporting requirements overview

- Initial application
- Modifications (amendments to the protocol including addition of a new investigator)
- Continuing review
- Safety reports
- Withdrawal or discontinuation
- Closure report

Refer to D-H IRB HRP-103 - Investigator Manual for comprehensive IRB reporting requirements

Record Retention

§312.57(c) - Recordkeeping and record retention

A **sponsor** shall retain the records and reports required by this part for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.

§312.62(c) - Investigator recordkeeping and record retention

Record retention. An **investigator** shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

V.

IDE (Investigational Device Exemption) Studies

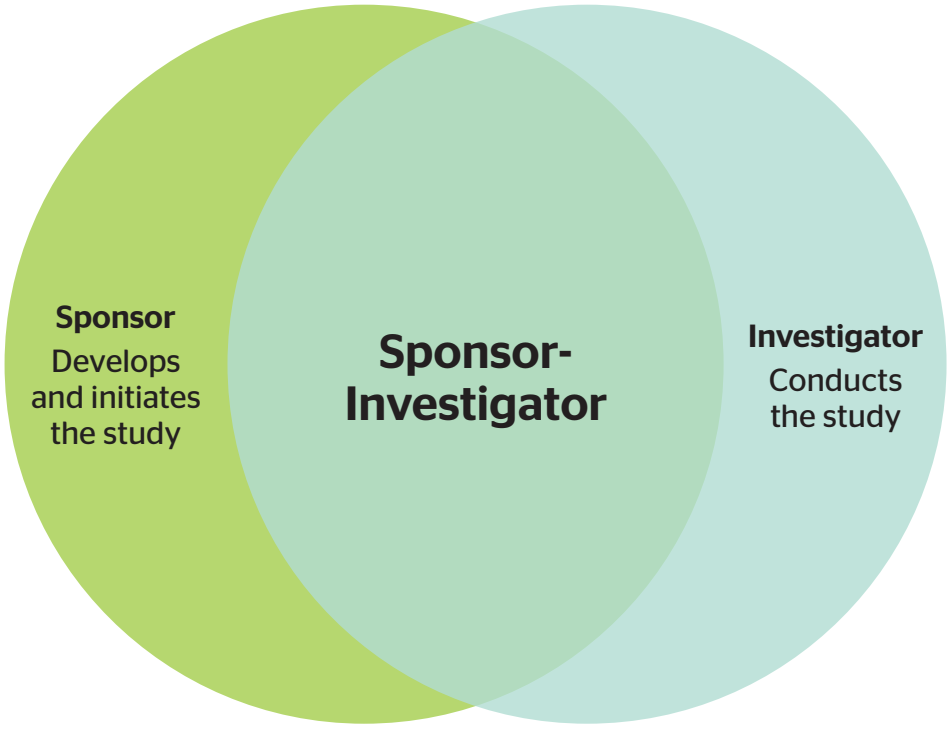
A. What is an IDE?

An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data.

An approved investigational device exemption (IDE) permits a device (that otherwise would be required to comply with a performance standard or to have premarket approval) to be shipped lawfully for the purpose of conducting investigations of that device.

In summary, an IDE is a regulatory submission with subsequent approval from the FDA permitting clinical investigation of a device that poses a certain degree of risk to subjects.

Note: Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices.



B. Sponsor-Investigator Responsibilities

The FDA regulations describe responsibilities of both sponsors and investigators in a variety of sections. The general responsibilities of each role are included below; please refer to the Sponsor-Investigator Responsibilities section of the Handbook for complete details.

§812.40: General responsibilities of sponsors for Significant Risk Device Studies (requiring IDE)

Sponsors are responsible for selecting qualified investigators and providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, ensuring that IRB review and approval are obtained, submitting an IDE application to FDA, and ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation.

§812.100: General responsibilities of investigators for Significant Risk Device Studies (requiring IDE)

An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation. An investigator also is responsible for ensuring that informed consent is obtained in accordance with part 50 of this chapter.

C. IDE Categories

- **IDE**—FDA approval required and IRB approval of the study
  - » Use of a **significant risk device** within the context of an investigation, where compliance with §812 is required
- **Abbreviated IDE**—IRB concurrence with NSR and approval of the study required
  - » Use of a **non-significant risk device** within the context of an investigation where compliance with certain elements of §812 is required
- **Compassionate Use—Emergency Use IDE**—FDA and IRB notification required
  - » Use of an investigational device when an **individual patient is in a life-threatening situation and needs immediate treatment** (there are no alternative options and no time to use existing procedures to get FDA approval for the use)
- **Compassionate Use—Non-Emergency Use IDE**—FDA and IRB chair concurrence required
  - » Use of an investigational device to **treat or diagnose an individual patient or a small group of patients** with a serious disease or condition when there are no available alternative options

- **Treatment IDE**—FDA and IRB approval required
  - » During the course of the clinical trial, if the data suggest that the device is effective, then the trial may be expanded under a new IDE to include additional patients with life-threatening or serious diseases. This is called a treatment IDE.

Source: https://www.fda.gov/medical-devices/investigational-device-exemption-ide/expanded-access-medical-devices

D. Regulatory Overview

Who files an application for an IDE?

The Sponsor-Investigator is responsible for submitting an IDE application to the FDA prior to seeking IRB approval.

When is a traditional IDE submission to the FDA required?

When the device is new (not yet FDA approved or cleared) and **poses significant risk** to potential subjects.

OR

When the device is FDA approved or cleared and the clinical evaluation includes certain modifications or a new intended use.

Note: FDA and IRB approval are BOTH required in order to proceed with study.

Are some device studies fully Exempt from §812?

Yes, under the following criteria:

- In commercial distribution before May 28, 1976
- Commercially available (approved or cleared) device that is used or investigated in accordance with the indications on the labeling
- A non-invasive diagnostic device
- Veterinary devices or research on/with laboratory animals
- Custom devices as defined in §812.3(b)

Additional exemption criteria:
Testing of consumer preference
Testing of a minor modification
Testing of a combination of approved devices

Note: If the testing is not for the purpose of determining safety or effectiveness, and does not put subjects at risk.

ORO will support your FDA submission process. Please contact ORO prior to filing an IDE application or for a risk determination/exemption consultation request.

E. Reporting Requirements

Sponsor reporting requirements
Initial IDE application (§812.20)

- Name and address of sponsor
- Report of prior investigations:
  - » Background (including a summary of other unpublished information)
  - » Prior animal testing
  - » Prior laboratory testing
  - » Prior clinical testing (specifying whether conducted within or outside the United States)
- Investigational plan:
  - » Purpose of the study (including name, intended use, objectives, duration)
  - » Protocol (including rationale, endpoints, design, population, assessments)
  - » Risk analysis (specifying related risks, mitigation, justification for the investigation)
  - » Description of the device (including its components, properties, principle of operation)
- Monitoring procedures
- Additional records and reports
- Methods, facilities, and control data (including manufacturing, processing, packaging, storage, and installation)
- Investigator information (including each investigator's CV)
- Certification of investigator agreement for each investigator
- IRB name, address, and chairperson name
- Name and address of other participating institutions

- Amount charged for device and why the sale doesn't constitute commercialization (if applicable)
- Labeling
- Consent materials
- FDA Form 3674 certifying registration with ClinicalTrials.gov
- Other relevant information
- Bibliography

FDA considers the IDE to be approved under §812.30(a):
30 days after FDA acknowledges the IDE application, unless the Agency notifies the sponsor that the IDE has been disapproved

OR

Upon earlier notification by FDA that the IDE has been approved.

IDE supplements (§812.35):

Protocol changes require reporting to FDA before or after implementation, according to whether they are significant or minor.

Protocol Amendment—Changes in Investigational Plan

Report to FDA after IRB approval, but before implementation

- Significant changes to the protocol that affect:
  - Data validity
  - Scientific soundness
  - Rights, safety, and welfare of participants

Protocol Amendment—Notice of IDE Change: 5-day Notice

Report to FDA within 5 working days of implementation

- Changes to the protocol that include developmental or manufacturing changes, along with supporting data

Protocol Amendment—Approval for New Facilities

Report to FDA with certification of IRB approval, and before implementation

- Identification of the investigational site

- Certification of IRB approval
- Information updating the initial IDE application
- Modifications required by IRB

Protocol changes submitted with a progress report

Report minor changes to FDA with Progress Report

- Purpose of the study
- Risk analysis
- Monitoring procedures
- Labeling
- Informed consent materials
- IRB information

IDE reports (§812.150):

- List of investigators
  - » Current list of names and addresses of all participating investigators in the IDE—**Report to FDA every 6 months, or with annual progress report by FDA waiver**
- Progress Reports (at least annually or semi-annually)
  - » Basic elements
  - » Study progress (data from the beginning of the study, unless otherwise indicated)
    - » Brief summary of the study progress in relation to the investigational plan/purpose of study
    - » Number of investigators/investigational sites (attach list of investigators)
    - » Number of subjects enrolled
    - » Number of devices received
    - » Brief summary of results
    - » Summary of anticipated and unanticipated adverse effects
    - » Description of any deviations from the investigational plan by investigators (since last progress report)
  - » Risk analysis (new adverse events, reprints, new risk analysis)
  - » Other changes (manufacturing, monitoring, labeling, informed consent, IRB)
  - » Future plans
    - » Progress toward product approval/clearance with projected date of PMA or 510(k) submission
    - » Any plans to change the investigation, such as to expand the study size

or indications, to discontinue portions of the investigation, or to change manufacturing practices (Note: Actual proposals for these changes should be made in a separate IDE supplement)

Source: https://www.fda.gov/medical-devices/investigational-device-exemption-ide/ide-reports

Safety reports

§ 812.3(s) Unanticipated adverse device effect:
Unanticipated adverse device effect is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Unanticipated adverse device effects (UADEs)—Leading to investigation termination
The sponsor's evaluation of the UADE must be reported to the FDA, all reviewing IRBs, and participating investigators within **10 working days** after the sponsor receives notice of the effect. Additional reports may be required as per FDA.

If the sponsor determines that the adverse device effect presents an unreasonable risk to subjects, the ***investigation shall be terminated*** as soon as possible.

Termination shall occur no later than **5 working days** after the determination, and no later than **15 working days** after the sponsor first receives notification of the effect. Reporting of termination to FDA shall occur no later than **5 working days** of receipt of withdrawal of IRB approval, and within **30 working days** of termination of the study. FDA and IRB must approve resuming a terminated significant risk device investigation.

- Investigation completion or termination—**submit to the FDA within 30 working days of the completion or termination of the investigation.**
- Final report (follows a format similar to the progress report)—**submit a final report to FDA within 6 months after the completion or termination of the investigation.**
  - » Basic elements
  - » Study progress
  - » Risk analysis
  - » Other changes
  - » Marketing application or future plans

The IDE regulations require the sponsor ensure all reviewing IRBs/ investigators are informed of the following:

- Unanticipated Adverse Device Effects—**within 10 working days after the sponsor first receives notice of the adverse effect**
- Progress reports—**at least annually** (excludes investigator notification)
- Withdrawal of FDA approval—**within 5 working days after receipt of notice**
- Any request that an investigator return, repair, or dispose of any unit of an investigational device—**within 30 days of the request** (excludes investigator notification)
- Withdrawal of IRB approval—**within 5 working days of receipt of the withdrawal of approval**
- Completion or termination of the investigation—**within 30 working days**
- Final report—**within 6 months after the completion or termination of the investigation**

- Withdrawal of IRB Approval—**submit to FDA within 5 working days after receipt of notice**
- Recalls and Device Disposition—**submit to FDA within 30 working days after request is made by the sponsor**
- Failure to Obtain Informed Consent—**submit to FDA within 5 working days after receipt of notice of use of a device without first obtaining consent**
- Significant Risk Determination—**submit to FDA within 5 working days after the sponsor learns the IRB has disagreed with the sponsor's non-significant risk determination**

- Other—submit to FDA or IRB accurate, complete, and current information about any aspect of the investigation—**submit as per FDA/IRB guidance**

Regulatory binder

- Form FDA 3454: Certification: Financial Interest and Arrangements of Clinical Investigators
- Form FDA 3455: Disclosure: Financial Interest and Arrangements of Clinical Investigators

All investigators named on the submission to FDA per §812.20(b)(5) and §812(b)(4) must provide the sponsor with a signed financial disclosure form (FDF). This disclosure informs the sponsor's completion of FDA 3454 and/or 3455 as applicable.

Updated FDFs must be provided to the sponsor throughout the course of the investigation and for 1 year after completion of the study, per §54.4(b).

The 3454 and 3455 need to be kept current and on file in the regulatory binder, but do not need to be submitted to FDA.

D-H expects the use of the CDRH Customer Collaboration Portal for all regulatory submissions related to devices.

Contact the IND/IDE Research Regulatory Affairs Specialist for support.

Each IDE application, supplement, or report will include FDA Form 3514 clearly categorizing the submission type.

Investigator Reporting Requirements

Report	Recipient	Timeframe
Unanticipated Adverse Device Effects	Sponsor and IRB	**As soon as possible, but in no event later than 10 working days** after the investigator first learns of the effect
Withdrawal of IRB Approval	Sponsor	Within **5 working days** after the approval is withdrawn
Progress Reports	Sponsor, Monitor, and IRB	Regular intervals but no less than on a **yearly** basis
Deviations from the Investigational Plan	Sponsor and IRB	**Emergency: as soon as possible but no later than 5 working days** after the emergency occurred **Non-Emergency: prior approval from the sponsor** is required for changes in or deviations from the investigational plan—**FDA and IRB approval are required** if the change or deviation may affect the scientific soundness of the investigational plan or the rights, safety, or welfare of the subject
Informed Consent	Sponsor and IRB	**5 working days** after the device was used without consent
Final Report	Sponsor and IRB	**Within 3 months** after termination or completion of the investigation

Note: These timelines are derived from the federal guidance; please defer to IRB guidance specific to your study (such as the IRB of record) for IRB timelines.

F. Abbreviated IDE

A non-significant risk (NSR) device is one that poses a moderate risk to the human subjects. Examples include, most daily-wear contact lenses and lens solutions, ultrasonic dental scalers, and Foley catheters.

- IRB submission AND approval are required
- FDA submission is NOT required

Note: FDA considers an investigation of a non-significant risk device to have an abbreviated IDE when the IRB concurs with the NSR determination and approves the study

Source: https://www.fda.gov/medical-devices/investigational-device-exemption-ide/ide-approval-process

If a device is determined to be non-significant risk (NSR), an IDE submission to the FDA is not required; however, the device is then regulated under an Abbreviated IDE and must still adhere to certain regulatory requirements.

Abbreviated IDE (§812.2(b)): Regulatory key points

- The investigational device cannot be banned under §895
- The use of the device in the investigation poses a moderate risk; **IDE application is NOT required**
- **IRB approval is required** prior to the initiation of the clinical study; the IRB should officially concur with the sponsor's proposed non-significant risk device determination with sufficient documentation
- The device must be labeled in accordance with the labeling provisions of IDE regulations and bear the statement: *"CAUTION-Investigational Device. Limited by Federal Law (or United States) to Investigational Use" and "The device may not be promoted as safe and effective for the use for which it is being investigated."*
- Informed consent must be obtained from each subject unless documentation is waived by the IRB
- The investigation must be monitored to protect subjects and assure protocol compliance
- The investigation must maintain proper records and reports according to §812.140
- The investigation must be conducted in compliance with required investigator required reporting §812.150

- The investigation must be conducted in compliance with required sponsor required reporting §812.150
- The investigation must be conducted in compliance with prohibitions in §812.7 against promotion and other practices

Source: https://static1.squarespace.com/static/55ba3377e4b065cd994470b8/t/627d56730a153d76ae79597a/1652381299768/Abbreviated+IDE+Requirements-v+1.pdf

Abbreviated IDE: Sponsor Reporting Requirements

Report	Recipient	Timeframe
Unanticipated Adverse Device Effects	FDA and IRB	**10 working days** after the sponsor first receives notice of the effect
Withdrawal of IRB Approval	FDA, IRB, and Investigators	Within **5 working days** after the approval is withdrawn
Withdrawal of FDA Approval	IRB and Investigators	Within **5 working days** after receipt of notice of the withdrawal of approval
Progress Reports	IRB	Regular intervals but no less than on a **yearly** basis
Recalls and Device Disposition	FDA and IRB	**30 working days** after the request is made
Informed Consent	FDA	**5 working days** after the device was used without consent
Significant Risk Determination	FDA	**Within 5 working days** after the sponsor learns the IRB has disagreed with the sponsor's non-significant risk determination
Final Report	IRB	**Within 6 months** after termination or completion of the investigation
Other	FDA	As per IRB or FDA request

Note: These timelines are derived from the federal guidance; please defer to IRB guidance specific to your study (such as the IRB of record) for IRB timelines.

Abbreviated IDE: Investigator Reporting Requirements

Report	Recipient	Timeframe
Unanticipated Adverse Device Effects	Sponsor and IRB	**As soon as possible, but in no event later than 10 working days** after the investigator first learns of the effect
Withdrawal of IRB Approval	IRB	Within **5 working days** after the approval is withdrawn
Informed Consent	Sponsor and IRB	**5 working days** after the device was used without consent
Other	FDA	As per IRB or FDA request

Note: These timelines are derived from the federal guidance; please defer to IRB guidance specific to your study (such as the IRB of record) for IRB timelines.

ClinicalTrials.gov reporting requirements

As the Sponsor-Investigator of an FDA regulated applicable clinical trial, you are deemed the responsible party for the study. As such, the Sponsor-Investigator is responsible for and required to register and report results of the study on ClinicalTrials.gov.

Refer to D-H policy ID: 22264, Registration and Results Reporting of Clinical Research in ClinicalTrials.gov

ORO provides support and guidance for ClinicalTrials.gov reporting. Please contact the D-H Protocol Registrations and Results Reporting System (PRS) Administrator for more information.

If you are a Sponsor-Investigator for an IDE, you are required to report the study on ClincalTrials.gov

See ORO ClinicalTrials.gov guidance on the ORO intranet page

D-H IRB reporting requirements

- Initial application
- Modifications (amendments to the protocol including addition of a new investigator)
- Continuing review
- Safety repots
- Withdrawal or discontinuation
- Closure report

Refer to D-H IRB HRP-103 - Investigator Manual for comprehensive IRB reporting requirements

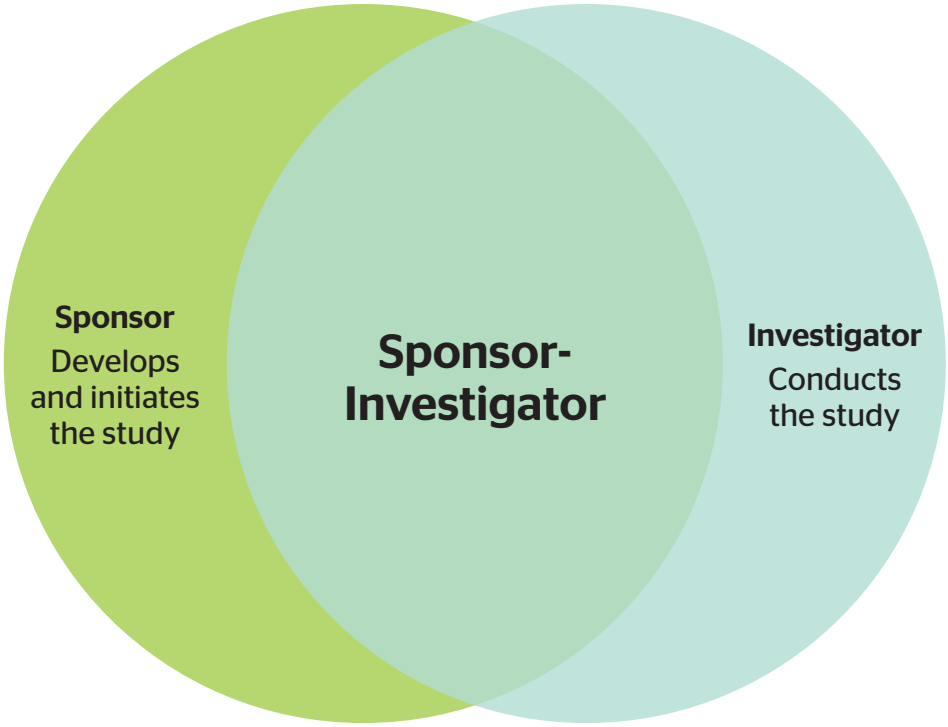
Record Retention

§812.140(d) - Records

Retention period. An **investigator** or **sponsor** shall maintain the records required by this subpart during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application, a notice of completion of a product development protocol, a humanitarian device exemption application, a premarket notification submission, or a request for De Novo classification.

VI.

Good Clinical Practice (GCP)



A. ICH GCP E6 Overview

This handbook is not intended to be inclusive of all applicable GCP ICH E6 standards. This section highlights the key aspects relating to Sponsor-Investigators and their role and responsibilities in clinical research.

This handbook will also address the D-H specific policies, procedures, and resources designed to meet GCP standards and facilitate implementation of Good Clinical Practice across all clinical trials conducted at D-H.

A full list of regulatory obligations set forth by ICH GCP E6 can be found on the ICH website at: https://www.ich.org/page/ich-guidelines

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve human subjects. Among other things, compliance with GCP helps assure that the rights, safety, and well-being of trial subjects are protected and that the clinical trial data are credible. This International Conference for Harmonisation (ICH) guidance provides a unified standard applicable to the European Union, Japan, and the United States to facilitate the mutual and reciprocal acceptance of clinical data by the regulatory authorities in those jurisdictions. The ICH industry standard is endorsed by regulatory bodies, such as FDA, who share the aim of harmonizing regulatory expectations globally. Specifically, FDA has adopted ICH as guidance incumbent upon all those conducting clinical research activity.

What is the aim of GCP?

Implementing GCP in clinical trial conduct aims to ensure:

- The rights, safety, and well-being of human subjects are protected
- The trial is conducted with rigor and integrity, and in accordance with the approved study plan and protocol
- The data derived from the clinical trial are reliable

Why use Good Clinical Practice?

GCP training aims to ensure:

- D-H expects all clinical trials are conducted under GCP
- NIH funded clinical investigators and clinical trial staff are expected to be trained in GCP
- GCP is the industry "gold standard" for clinical trial conduct

Source: **https://www.ich.org/page/ich-guidelines**

Does D-H Expect Compliance with Good Clinical Practice?

Yes.

- GCP standards are binding, regardless if cited
- D-H expects Sponsor-Investigators to apply the “how to” details set forth in GCP to secure compliance with the various requirements of the applicable governing bodies
- Sponsor-Investigators are expected to review the most current version(s) of ICH GCP E6 in its entirety before leading a clinical trial that involves an IND or IDE

B. Investigator Responsibilities

Core responsibilities under ICH GCP:

- The investigator may delegate trial-specific activities to other persons or parties. The investigator may be supported by the sponsor to identify a suitable service provider(s); however, the investigator is responsible for making the final decision on whether the service provider intended to support the investigator is appropriate based on information provided by the sponsor.
- The investigator bears the ultimate responsibility for maintaining 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.
- The investigator should ensure that persons or parties to whom the investigator has delegated trial-specific activities are appropriately qualified and supervised, and are adequately informed about the protocol and that the investigational product(s) and their assigned trial activities (including activities conducted by staff provided by other parties, for example home nurses arranged by the sponsor).
  - » Trial-related training offered to persons assisting in the trial should include those topics and training necessary to enable them to fulfil delegated trial activities in excess of their usual training and experience.
- The investigator should ensure a record is maintained of the persons and parties to whom the investigator has delegated significant trial-related activities. In situations where the clinical trial activities are performed in accordance with routine clinical care, delegation documentation may not be required.
  - **See the eReg User Guide for how to generate and complete an electronic delegation of authority log (DH Intranet > Office of Research Operations > eReg Resources > eReg User Guide)**
  - » Refer to Delegation of Authority - D-H Investigational Drug Services (Policy ID: 17725)
  - **Refer to Delegation of Authority - ORO Centralized Research Processing Lab (Policy ID: 21125)**
- Agreements made by the investigator/institution with service providers for trial-related activities should be documented.
  - **Refer to the Clinical Trial Office (CTO) for support (DH intranet > Office of Research Operations > Clinical Trials Office)**
- The investigator/institution should permit monitoring and auditing by the sponsor and inspection by the appropriate regulatory authorities.

Investigator Qualifications and Training

Investigators must:

- Be qualified by education, training, and experience to assume responsibility for proper trial conduct
- Provide evidence of such qualifications through up-to-date curriculum vitae and other relevant documentation requested by the sponsor, the IRB, and the regulatory authorities
  - » Refer to the D-H Policy for PI Eligibility Requirements (Policy ID: 26012)
  - » Refer to the D-H Policy for Conflicts of Interest in Research (Policy ID: 2870)
  - » Refer to the D-H Policy for Human Subjects Research Training (Policy ID: 23146)
- Be thoroughly familiar with the appropriate use of the investigational product(s) as described in the protocol, current Investigator's Brochure, product information, and other information sources provided by the sponsor

Resources

Investigators are expected to:

- Demonstrate ability, based upon retrospective or currently available data, to meet the expected recruitment goal (number of eligible subjects within a specific timeframe) as defined by the sponsor
- Have the following for the duration of the trial:
  - » Sufficient time (protected time for research is essential)
  - » Adequate number of staff who are properly qualified
  - » The investigator's team should collectively have expertise including but not limited to: subject management, regulatory affairs, investigational product, and clinical research nursing

    The ORO provides support for investigators by way of the Clinical Trial Unit (CRU) and the ORO Lab (see ORO Intranet Page>Research Support Services)
- Ensure adequate facilities

Communication with the IRB

- An investigator should communicate with IRB including obtaining approval for the protocol, informed consent form, consent form updates, subject recruitment procedures, and any other written materials provided to subjects. This includes:
  - » Before initiating a trial, obtain a documented and dated approval/favorable opinion from the IRB for the informed consent form, protocol, recruitment materials, and other materials provided to participants
  - » Ensure the IRB is provided current copy of the Investigator's Brochure or basic product information brochure
  - » Follow the IRB and sponsor requirements with respect to trial summaries (such as continuing reviews)
  - » Ensure the information provided to participants is kept up to date and approved by the IRB
  - » Promptly communicate to the IRB and, when applicable, the institution about any changes significantly affecting the conduct of the trial and/or increasing the risk to participants

Refer to the D-H IRB Intranet page

- Refer to HRP-103 Investigator Manual
- To access the D-H eIRB system: **https://dhirb.huronresearchsuite.com/**

Compliance with Protocol

Investigators must:

- Comply with the protocol, GCP, and applicable regulatory requirements, and sign the protocol (or an alternative contract) to confirm agreement with the sponsor
- Conduct trial according the IRB approved protocol and any regulatory requirements
- Not deviate from the approved protocol unless such changes are IRB approved (unless when necessary to eliminate hazards to trial subjects)
  - » Promptly reports deviations necessary to eliminate hazards to subjects to the IRB and/or other regulatory authorities
  - » Report information on the immediate hazard, the implemented change, and the subsequent proposed protocol amendment to the IRB and/or regulatory authorities
- Document all protocol deviations and reviews deviations communicated to them by the sponsor

- Ensure personnel delegated by the investigator are complying with the protocol
- Develop Corrective and Preventative Action (CAPA) Plans for important deviations

The ORO Research Quality and Safety Team has developed a CAPA Toolkit (see ORO Intranet Page>Research Quality and Safety>Quality and Safety Research Resources)

Premature Termination or Suspension of a Trial

- An investigator is responsible for promptly notifying:
  - Participants (including providing appropriate therapy and follow up)
  - IRB
  - Sponsor
  - Applicable regulatory authorities

Depending on who initiates termination of a trial, there are different reporting requirements.

See GCP guidance for details.

Note: The institution may also place a hold on a trial. See ORO Voluntary Hold Policy (Policy ID: 23656)

Participant Medical Care and Safety Reporting

Medical Care

The investigator:

- **Is responsible for the trial-related medical care and decisions (qualified physician, dentist, or healthcare professional – in accordance with local regulatory requirements)**
  - » Other healthcare professionals may be involved in medical care to participants (as per local regulatory requirements)
- Informs the participant's primary physician about the participant's involvement in the trial if the participant has a primary physician and agrees to the primary physician being informed
- Ensures adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the trial (during and following participation in the trial)
- Informs a participant when medical care is needed for intercurrent illness(es) of which the investigator becomes aware

Safety Reporting

- AEs and/or clinically significant laboratory abnormalities for safety evaluations should be reported to the IRB as per pertinent policy and sponsor according to the protocol
- All SAEs should be reported immediately (after the investigator reasonably becomes aware of the event) to the sponsor. In accordance with applicable regulatory requirements, the protocol may identify SAEs not requiring immediate reporting, for example, death or other events that are endpoints
- SAEs that qualify as unanticipated problems should be reported to the IRB
  - » Subsequent information should be submitted as a follow-up report, as necessary
  - » For reported deaths, supply the sponsor, the IRB, and, when applicable, the

regulatory authority with any additional requested information (for example, autopsy reports and terminal medical reports) when they become available. This information maybe be required to make the final determination regarding the attribution of the event

» The Sponsor-Investigator may delegate activities for safety reporting to qualified investigator site staff but retains the overall responsibility for safety of participants under their responsibility and is ultimately responsible for compliance with the reporting requirements

The investigator or qualified sub-investigator is responsible for assigning the attribution of adverse events, including serious adverse events, experienced by participants during conduct of the trial.

- Refer to Investigator Review of External IND Safety Reports Policy (Policy ID: 21732) for details regarding the investigator's review of events that are pertinent to the trial that the investigator oversees at D-H but occur at an external location for which the investigator is not directly responsible
- If the study is conducted at D-H, safety information should be reported as per D-H IRB's New Information SOP (D-H eIRB system>Library>Standard Operating Procedures>HRP-024)

Informed Consent

In obtaining and documenting informed consent (paper or electronic format), the investigator should comply with the applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki

- Prior to consenting and enrolling participants, the investigator should have IRB documented approval/favorable opinion of the informed consent materials and process
- The information should be as clear and concise as possible, use simple language, and avoid unnecessary volume and complexity
- Varied approaches (such as text, images, videos, and other interactive methods) may be used in the informed consent process including for providing

information to the participant. Obtaining consent remotely may be considered where appropriate

- The participant or the participant's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue trial participation (document the willingness to continue participation)
- Neither the investigator nor the investigator site staff should coerce or unduly influence a participant to participate or to continue their participation in the trial
- None of the information provided to the participant during the informed consent process should contain any language that causes the participant or the participant's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their service providers from liability for negligence
- The informed consent process should be conducted by the investigator or other investigator site staff delegated by the investigator, in accordance with applicable regulatory requirements. If the participant is unable to provide consent themselves, the participant's legally acceptable representative should provide their consent on behalf of the participant
- The information provided during the informed consent process and translations should be relevant, clear, simple, concise, and understandable to the participant or the participant's legally acceptable representative and the impartial witness (when applicable)
- Before informed consent may be obtained, provide the participant or the participant's legally acceptable representative ample time unless justified (such as in an emergency situation) an opportunity to enquire about trial details and to decide whether or not to participate in the trial. Questions about the trial should be answered the satisfaction of the participant or the participant's legally acceptable representative
- Prior to trial participation, the informed consent form should be signed and dated by the participant or by the participant's legally acceptable representative and, when appropriate, impartial witness and by the investigator or delegated investigator site staff who conducted the informed consent discussion. The informed consent process may involve a physical signature or an electronic signature

Exceptional circumstances, emergency situations, or situations when a participant/LAR is unable to read, or when the participant is a minor require specific provisions.

See GCP guidance for details.

- The informed consent discussion should explain applicable elements of the clinical investigation
- Prior to participation, the participant or the participant's legally acceptable representative should receive a copy (paper or electronic) of the signed informed consent form and any other informed consent materials provided to the participants

New information regarding the study, the study drug or device, or other study related events that may impact a participant's willingness to continue participation, should be assessed to determine of if reconsent is needed. Prior to use, any revised consent materials or informed consent forms must receive IRB approval or favorable opinion.

ORO provides training on conducting the informed consent conversation and process with research participants – please refer to the Research Informed Consent Training Intranet page (DH Intranet > Office of Research Operations > Education and Training > Research Informed Consent Training)

- Refer to the Informed Consent Process for Research Studies Policy (Policy ID: 28975)
- Refer to the Informed Consent D-H IRB Policies (D-H eIRB system>Library>Standard Operating Procedures>HRP-090 and HRP-091)
- Refer to the D-H IRB Consent Templates (D-H eIRB system>Library>Templates>HRP-502, HRP-506, and HRP-507)

Investigational Product Management

The investigator accounts for investigational product(s)

- The Research Pharmacy must be used to manage the accountability of investigational drugs regulated under an IND

  Institutional requirements (IP management) align GCP with guidance:

  » The investigator/institution and/or a pharmacist or other appropriate

individual should maintain records of the product delivery, the inventory, the use by each participant (including documenting that the participants were provided the doses specified by the protocol), and the return to the sponsor and destruction or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial participants
    - » The investigational product(s) should be stored as specified by the sponsor and in accordance with applicable regulatory requirement(s)
- The investigator ensures that the investigational product(s) are used only in accordance with the approved protocol
- When applicable, the investigator or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each participant and should check, at intervals appropriate for the trial, that each participant is following the instructions properly
- Refer to the Research Pharmacy Intranet Page (ORO Intranet Page>Research Support Services>Investigational-Pharmacy)
- Refer to the following relevant D-H Policies
    - » Investigational Drugs Policy (Policy ID: 2091)
    - » Delegation of Authority - D-H Investigational Drug Services (Policy ID: 17725)
    - » Investigational Product Storage and Quarantine (Policy ID: 12149)
    - » Inpatient Use of Patient's Own Supply of Investigational Schedule I Controlled Substance Procedure (Policy ID: 20235)
    - » Study Drug Returns Procedure (Policy ID: 2763)
    - » Medication Storage and Handling Policy (Policy ID: 6823)
    - » Safe Handling of Hazardous Drugs Policy (Policy ID: 2176)
    - » Subject-Administered Investigational Product: Documentation and Operational Procedures (Policy ID: 24413)

ALCOA+CCEA

All study records and documentation should follow the basic principles of **ALCOA+CCEA**

- **A**ttributable
- **L**egible
- **C**ontemporaneous
- **O**riginal
- **A**ccurate

+

- **C**omplete
- **C**onsistent
- **E**nduring
- **A**vailable

Records

Investigators are expected to:

- Maintain adequate and accurate source documents and trial records (as per ALCOA); data reported on case report forms must be consistent with source data and any discrepancies should be explained; any changes made should be dated, initialed, and explained appropriately
  - » Refer to Documentation of Clinical Research in the Dartmouth Hitchcock Clinical Trial Management System (CTMS) and the Electronic Medical Record (eDH) Policy (Policy ID: 4856)
- Review data in a timely manner, including relevant data from external sources (such as central laboratory data, centrally read imaging data, other institution's records and, if appropriate, electronic patient-reported outcome (ePRO) data) which can have an impact on, for example, participant eligibility, treatment or safety
- Ensure that data acquisition tools (such as CRFs) and other systems deployed by the sponsor for clinical trial purposes are used as specified in the protocol or trial-related instructions
  - » Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs/reports completed by the investigator site
- Implement appropriate measures to protect the privacy and confidentiality of personal information of trial participants in accordance with applicable regulatory requirements on personal data protection. Data reported to the sponsor should be identified by an unique participant code that can be traced back to the identity of the participant by the investigator/institution
- For systems deployed by the investigator/institution that maintain and retain trial data/information, the investigator/institution should ensure that such data are protected from unauthorized access, disclosure, dissemination, or alteration and from inappropriate destruction or accidental loss
  - » Refer to the following policies (required to ensure the data and regulatory documentation pertinent to a Sponsor-Investigator IND/IDE trials are 21 CFR Part 11 compliant – and therefore meet the requirements set forth in section G)

    EDC™

    Electronic Data Capture System: Use Requirements for Human Subjects Research (Policy ID: 30116)

    eREG™

eRegulatory Management System: Use Requirements for Human Subjects Research Policy (Policy ID: 24815)

Utilizing computerized systems in clinical trials involves specific provisions.

See CGP guidance for details.

OnCore

Refer to the OnCore Intranet page for details regarding D-H's Clinical Trial Management System (DH Intranet>Office of Research Operations>OnCore Resources)

- Maintain the trial records as specified in GCP - Essential Records for the Conduct of a Clinical Trial and as required by the applicable regulatory requirement(s)

See D-H eReg User guide for DH expectations regarding essential documentation filing expectations (DH Intranet > Office of Research Operations > eReg Resources > eReg User Guide)

Maintenance of essential records for the conduct of a clinical trial entails specific provisions.

See GCP guidance for details.

- The investigator/institution should have control of all essential records generated by the investigator/institution before, during and after the trial
- Maintain records per sponsor, regulatory requirements, and institutional standards
  - » Refer to the Health Record Retention Policy (Policy ID: 20413)
- Make available for direct access all requested trial- related records (upon request of the monitor/auditor/IRB/regulatory authority)

Clinical Trial/Study Reports

Investigators are required to:

- Provide the IRB with a summary of the trial outcome and, if applicable, provide the regulatory authorities with any required reports

When a coordinating investigator is involved in a trial, consideration should be given to them being a signatory on the clinical trial report.

See ICH E3 Structure and Content of Clinical Study Reports.

C. Sponsor Responsibilities

Core responsibilities of the sponsor under ICH GCP:

- Ensure that the trial design and trial conduct, the processes undertaken and the information generated are of sufficient quality to ensure reliable trial results, trial participant's safety, and appropriate decision making
- Ensure that trial processes are conducted in compliance with the trial protocol and related documents as well as with applicable regulatory requirements and ethical standards
- Determine in advance necessary trial-specific criteria for classifying protocol deviations as important (including those that impact the rights, safety and well-being of trial participants and the reliability of results)
- Ensure decisions related to the trial are appropriately assessed for their impact on participant rights, safety, and well-being and the reliability of trial results. Risks related to such decisions should be suitably managed throughout the planning, conduct, and reporting of the trial
- The range and extent of oversight measures should be commensurate with the complexity of and risks associated with the trial. The selection and oversight of investigators and service providers are fundamental features of the oversight process. Oversight by the sponsor includes both quality assurance and quality control processes relating to the trial-related activities of investigators and service providers
- Ensure appropriate and timely escalation and follow-up of issues to allow the implementation of appropriate actions in a timely manner
- May consider establishing an Independent Data Monitoring Committee (IDMC) to assess the progress of a clinical trial including the safety data and the efficacy endpoints at intervals and to recommend to the sponsor whether to continue, modify, or stop a trial
- When appropriate, sponsors may also establish an endpoint assessment/adjudication committee in certain trials to review important endpoints reported by investigators to determine whether the endpoints meet protocol-specified

criteria. Such committees should typically be blinded to the assigned treatments when performing their assessments, regardless of whether the trial itself is conducted in a blinded manner, to ensure that the data reviewed by committee are as free of bias as possible

- Committees established for purposes that could impact participant safety or the reliability of trial results should include members with relevant expertise and with managed conflicts of interest, have written operating procedures (such as charters) and document their decisions

Trial Design

Sponsors are expected to:

- Ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials and/or real-world data are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied
- Incorporate quality into the design of the clinical trial by identifying factors that are critical to the quality of the trial and by managing risks to those factors
- Consider inputs from various stakeholders such as the institution, health care professionals, and patients
- Ensure the all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures, and data collection. Protocols, data acquisition tools, and other operational documents should be fit for purpose, clear, concise, and consistent, when applicable

The ORO can provide support to sponsors in their design of the trial by way of connecting them to various institutional resources (such as biostatisticians, clinical pharmacologists, and physicians); contact **OfficeofResearchOperations@hitchcock.org**

Resources

Sponsors are expected to:

- Ensure sufficient resources are available to conduct the trial – this includes but is not limited to: investigator/statistical/pharmacology expertise, quality assurance staff, study staff, electronic systems (such as 21 CFR 11 compliant data capture), and funding.

The ORO provides support for investigators by way of the Clinical Research Unit (CRU) and the ORO Lab (see ORO Intranet Page>Research Support Services)

» See Study Specific Processing Training Checklist - ORO Centralized Processing Laboratory (Policy ID: 21757)
» See Start of Study Checklist - ORO Centralized Research Processing Laboratory (Policy ID: 21835)
» See Sample Processing Log - ORO Centralized Research Processing Lab (Policy ID: 20158)

Qualification and Training

Sponsors are required to ensure appropriately qualified personnel are contributing to their assigned duties, including:

- The delegated investigators (such as PIs)
- Biostatisticians, data scientists/data managers, auditors/monitors, clinical pharmacologists, laboratory personnel, regulatory support
- Ensure appropriately qualified medical personnel are available to support the sponsor in trial-related medical questions or issues
- Lead and conduct the site initiation visit
- Provide training materials for all aspects of the trial
- Ensure investigator and their delegated team are adequately trained

Financing

- Sponsors ensure financial aspects of the trial are documented in an agreement between the sponsor and the investigator/institution

Refer to the CTO and/or Grants intranet pages for support services

» DH Intranet Page > Office of Research Operations>Clinical Trials Office (CTO)
» DH Intranet Page > Office of Research Operations>Grants
» DH Intranet Page > Office of Research Operations>Research Operations Finance

Agreements

Sponsors are expected to obtain the investigator's/institution's/service provider's agreement to:

- Conduct the trial in accordance with the approved protocol and in compliance with GCP and applicable regulatory requirement(s);
- Comply with procedures for data recording/reporting;
- Retain the trial-related essential records for the required retention period

in accordance with applicable regulatory requirements or until the sponsor informs the investigator/institution or, where applicable, the service provider, that these documents are no longer needed, whichever is longer;

- Permit monitoring, auditing, and inspections by sponsors, IRBs, internal monitors, and regulatory authorities (domestic and foreign) including providing direct access to source records and facilities, including to those of service providers.
- Document the responsibilities of coordinating investigator(s) and the other participating investigators prior to the start of the trial
  - » This is traditionally accomplished by ensuring the delegation of authority log is fully executed before the trial is activated

  See the eReg User Guide for how to generate and complete an electronic delegation of authority log (DH Intranet > Office of Research Operations > eReg Resources > eReg User Guide)

  - » Refer to Delegation of Authority - D-H Investigational Drug Services (Policy ID: 17725)
- Transfer their particular trial-related activities to another service provider – this must be documented in an agreement. The sponsor remains ultimately responsible for the execution of these transferred trial-related activities
- Have access to relevant information (for example SOPs and performance metrics) for selection and oversight of service providers
- Be responsible for assessing the suitability of and selecting the service provider to ensure that they can adequately undertake the activities transferred to them. The sponsor should provide the service providers with the protocol where necessary as well as any other documents required for them to perform their activities
- Sponsors may transfer investigator trial-related activities to another service provider – this must be documented in an agreement. The investigator remains ultimately responsible for the execution of these transferred trial-related activities

  Refer to the CTO and/or Grants ORO intranet pages for support services

Investigator Selection

Sponsors are responsible for:

- Selection of qualified and appropriately resourced investigators who agree to conduct trial and are knowledgeable of the protocol and Investigator's Brochure (IB)
- Assessment of qualification based upon: education, training, and experience
- Providing the investigator with the protocol and up-to-date IB, giving them adequate time to review the material
- Refer to the D-H Policy for PI Eligibility Requirements (Policy ID: 26012)

Communication with IRB and Regulatory Authorities

- Regulatory Authority (such as FDA)
  - » In accordance with applicable regulatory requirements, before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator) should submit any required application(s) to the appropriate regulatory authorities for review, acceptance and/or permission to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol
    - ✉ The ORO facilitates all FDA submissions for Sponsor-Investigators of IND/IDE trials – email **OfficeofResearchOperations@hitchcock.org** for support
- IRB

  For each investigator, the sponsor is responsible for obtaining the following:
  - » Name/address of the investigator's/institution's IRB
  - » A statement from the IRB to confirm it is organized and operates according to GCP and applicable laws and regulations
  - » Documented IRB initial and subsequent IRB approval as well as any termination of the trial or suspension of approval

Quality Management

Sponsors are expected to:

- Implement an appropriate system to manage quality throughout all stages of the trial process
- Institute quality management that should include the design and implementation of efficient protocols, tools, and procedures for data collection and processing – including collection of information essential to decision making

- Focus on ensuring human subject protection and reliability of trial results
- Apply a risk-based approach / quality by design:
  - » The sponsor should adopt a proportionate and risk-based approach to quality management that involves incorporating quality into the design of the clinical trial (quality by design) and identifying those factors that are likely to have a meaningful impact on participants' rights, safety, and well-being, and the reliability of the results (such as critical to quality factors as described in ICH E8(R1)).
- Describe the quality management approach implemented in the trial in the clinical trial report

Risk management may require specific provisions including identification, evaluation, control, communication, review, and reporting.

See GCP guidance for details.

The ORO Research Quality and Safety Team will support the Sponsor-Investigator in the development of the quality management system – the assigned ORO monitor for the trial will coordinate/lead this effort

Quality Assurance and Quality Control

- Sponsors are required to ensure implementation and maintenance of quality assurance and quality control systems with written SOPs to secure compliance with GCP, protocol, applicability regulatory requirements
  - » Apply quality assurance activities throughout the course of the trial and appropriately implement strategies to identity potential/actual serious non-compliance. This approach aims to support effective development of Corrective and Preventative Action Plans (CAPAs).
    - **The ORO Research Quality and Safety Team has developed a CAPA Toolkit (see ORO Intranet Page>Research Quality and Safety>Quality and Safety Research Resources)**
- Audit
  - » The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, is to evaluate whether the processes put in place to manage and conduct the trial are effective and compliant

  - The sponsor should appoint individuals who are independent of the clinical trial being audited
    - ✉ The ORO Research Quality and Safety Team provides auditing services for Sponsor-Investigators of IND/IDEs – email **OfficeofResearchOperations@hitchcock.org** for support
- The audit plan should be guided by the level of importance of trial submissions to regulatory authorities (such as the FDA), the number of subjects, the type and complexity of the trial, the level of risk to the trial subjects, and identified problems

Auditing the trial involves specific provisions including selection of qualified auditors and auditing procedures.

See GCP guidance for details.

  - The aim of monitoring is to ensure the participants' rights, safety, and well-being and the reliability of trial results as the trial progresses. Monitoring is one of the principal quality control activities
- Monitoring involves a broad range of activities including, but not limited to, communication with investigator sites, verification of the investigator and investigator site staff qualifications and site resources, training and review of trial documents and information using a range of approaches including source data review, source data verification, data analytics, and visits to institutional facilities undertaking trial-related activities.
- Monitoring should be performed by persons not involved in the clinical conduct of the trial being monitored
  - ✉ The ORO Research Quality and Safety Team provides auditing services for Sponsor-Investigators of IND/IDEs – email **OfficeofResearchOperations@hitchcock.org** for support
- Monitoring activities should include:
  - Verification of IP
  - Review of protocol adherence
  - Verification of informed consent documentation
  - Verification of eligibility and source documents
  - Ensuring investigators/study team members are appropriately trained
  - Verification of sources documents and trial records

  - » Review of adverse events, concomitant medication, and intercurrent illness reporting; determine whether adverse events are being reported within required time frames
- Sponsors are expected to establish an independent data monitoring board to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial

Monitoring the trial involves specific provisions including investigator site monitoring, centralized monitoring, and monitoring plans, procedures, activities, and reporting.

See GCP guidance for details.

Quality Control is applied to each stage of data handling; data **must** be reliable

Noncompliance

- Noncompliance with the protocol, SOPs, GCP, IRB and/or regulatory requirements by an investigator or any members of the sponsor's research staff should lead to appropriate and proportionate action by the sponsor to secure compliance
- If noncompliance significantly impacts participant rights, safety, and well-being or the reliability of trial results, the sponsor should:
  - » Perform a root cause analysis and implement corrective or preventive actions
  - » Notify the regulatory authority (such as FDA) and/or ensure reporting to the FDA in line with applicable regulatory requirements
  - » Ensure the investigator reports noncompliance as per the applicable requirements
    - » If the study is conducted at D-H, noncompliance must be reported as per D-H IRB's Reportable New Information SOP – (D-H eIRB system>Library>Standard Operating Procedures>HRP-024)

- If the monitoring or auditing identifies serious and/or persistent noncompliance on the part of an investigator, the sponsor should terminate the investigator's participation in the study and regulatory authorities should be notified
  - When an investigator's/institution's participation is terminated because of noncompliance, the sponsor should promptly notify the regulatory authorities and IRB as appropriate

Safety Assessment and Reporting

Sponsors are responsible for:

- Managing immediate hazards, the ongoing safety evaluation of IP, and notifying investigators of findings that would adversely affect the safety of subjects, impact the conduct of study, or alter the IRB approval to continue the study
  - The Investigator's Brochure or, where applicable, the current scientific information such as a basic product information brochure, forms the basis of safety assessment and reporting for the clinical trial
- Conducting Safety Assessments
  - The sponsor should aggregate, as appropriate, and periodically review relevant safety information. This may result in the update of the protocol, Investigator's Brochure, informed consent materials and related documents
  - The sponsor should review the available emerging safety information to assess whether there is any new data that may affect the participant's willingness to continue in the trial, impact the conduct of the trial, or alter the approval of the IRB and/or regulatory authorities, as applicable. Any information of this nature should be communicated to the participants, investigator, IRB, and regulatory authorities, as applicable, in a timely manner
- Submitting Safety Reporting
  - Submit to regulatory authorities safety updates and periodic reports, including changes to the Investigator's Brochure, as required by applicable regulatory requirements
  - Expediting the reporting to the regulatory authorities of all adverse events that meet ALL three criteria:
    1. **Suspected:** there is a reasonable possibility that the drug/device caused the event
    2. **Unexpected:** not listed in the investigator brochure/alternative document or is not listed at the specificity or severity that has been observed
    3. **Serious:** death, life threatening adverse drug experience, inpatient/prolonged hospitalization, a persistent or significant disability/incapacity,

or a congenital anomaly/birth defect, medical event jeopardizing the patient and may require medical/surgical intervention

  - » Ensuring the investigator reports adverse events in line with the applicable IRB requirements
  - » If the study is conducted at D-H, specific adverse events must be reported as per the D-H IRB New Information SOP (D-H eIRB system>Library>Standard Operating Procedures>HRP-024)

Safety reporting requires specific provisions.

See GCP guidance for details.

Insurance/Indemnification/Compensation to Participants and Investigators

- If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial except for claims that arise from malpractice and/or negligence
- The sponsor's policies and procedures should address the costs of treatment of trial participants in the event of trial-related injuries in accordance with the applicable regulatory requirement(s)
- The approach to compensating trial participants should comply with applicable regulatory requirement(s)

Investigational Product(s) (IP)

Sponsors are required to:

- Ensure that sufficient safety and efficacy data from non-clinical studies and/or clinical trials are available to support human exposure by the route, at the dosage, for the duration, and in the trial population being studied
- The IB should be updated when new information becomes available
- **Manufacturing, Packaging, Labeling, and Coding IP—there are specific provisions related to blinded trials - see GCP guidance for details**
  - » Ensure investigational product is characterized as appropriate to the stage of development of products, is manufactured in accordance with applicable GMP, and is coded and labelled in manner that protects blinding if applicable; labelling should comply with regulatory requirements
  - » Determine acceptable storage parameters, including temperature, storage

conditions such as protection from light, storage times, reconstitution fluids, procedures, and devices for product infusion if any
  - Packaging should be such to prevent contamination or unacceptable deterioration during transport and storage

> If the product is manufactured and supplied by an external entity (such as a pharmaceutical company), the D-H sponsor is still ultimately responsible for the IP management/oversight as per GCP.

Supplying and Handling IP

Sponsors are expected to:

- Be responsible for supplying the investigator with the IP once the necessary approvals are in place, such as IRB and other regulatory authority approval
- Ensure written procedures include instructions that the investigator should follow regarding handling and storage of IP; this includes adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of any IP to the sponsor or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirements
- Ensure the following:
  - Timely delivery of investigational product(s) to the investigator(s) or, where appropriate, to trial participants in accordance with applicable regulatory requirements to avoid any interruption to the trial as well as for the continuation of treatment for participants
  - Maintenance of records that document the identity, shipment, receipt, return, and destruction, or alternative disposition of the investigational product(s)
  - Maintenance of a system for retrieving investigational products and documenting this retrieval such as for deficient product recall, return, and destruction, or alternative disposition after trial completion, or expired product reclaim
  - Maintenance of a system for the disposition of unused investigational product(s) and for the documentation of this disposition
  - Steps are taken to ensure that the investigational products are stable over

the period of use and only used within the current shelf-life
    - » Maintenance of sufficient quantities of the investigational products used in the trials to reconfirm specifications should this become necessary, and maintain records of batch sample analyses and characteristics
- Refer to the Research Pharmacy Intranet Page (ORO Intranet Page>Research Support Services>Investigational-Pharmacy
- Refer to the following relevant D-H Policies
    - » Investigational Drugs Policy (Policy ID: 2091)
    - » Investigational Product Storage and Quarantine (Policy ID: 12149)
    - » Inpatient Use of Patient's Own Supply of Investigational Schedule I Controlled Substance Procedure (Policy ID: 20235)
    - » Study Drug Returns Procedure (Policy ID: 2763)
    - » Medication Storage and Handling Policy (Policy ID: 6823)
    - » Safe Handling of Hazardous Drugs Policy (Policy ID: 2176)
    - » Subject-Administered Investigational Product: Documentation and Operational Procedures (Policy ID: 24413)

Data and Records

Data

The sponsor should:

- Ensure the integrity and confidentiality of data generated and managed
- Apply quality control to the relevant stages of data handling to ensure that the data are of sufficient quality to generate reliable results. The sponsor should focus their quality assurance and quality control activities and data review on critical data, including its relevant metadata
- Pre-specify data to be collected and the method of its collection in the protocol
- Ensure that data acquisition tools are fit for purpose and designed to capture the information required by the protocol. They should be validated and ready for use prior to their required use in the trial
    - » D-H requires Sponsor-Investigators of IND/IDEs capture

      Trial data within the D-H instance of EDC (D-H Validated and 21 CRF 11 compliant system). See Policy ID: 30116 for details

Regulatory documentation within the D-H instance of eReg (D-H Validated and 21 CRF 11 compliant system). See Policy ID: 24815 for details

- Ensure that documented processes are implemented to ensure the data integrity for the full data life cycle
- Provide guidance to investigators/institutions, service providers and trial participants, where relevant, on the expectations for data capture, data changes, data retention, and data disposal
- Not make changes to data entered by the investigator or trial participants unless justified and documented by the sponsor and agreed upon by the investigator
- Allow correction of errors to data, including data entered by participants, where requested by the investigators/participants. Such data corrections should be justified and supported by source records around the time of original entry
- Ensure that the investigator has access to data collected in accordance with the protocol during the course of the trial including relevant data from external sources, for example, central laboratory data, centrally read imaging data and, if appropriate, ePRO data that are necessary to enable the investigators to make decisions (such as regarding eligibility, treatment, continuing participation in the trial, and care for the safety of the individual
  trial participants).
- Not have exclusive control of data captured in data acquisition tools
- Ensure that the investigator has access to the required data for retention purposes
- Ensure that the investigator receives instructions on how to navigate systems, data, and relevant metadata for the trial participants under their responsibility

The D-H EDC team will support the sponsor in the development of such materials – see EDC and eReg Intranet Pages for details

» DH Intranet>Office of Research Operations>EDC Resources
» DH Intranet>Office of Research Operations>eReg Resources

- Seek investigator endorsement of their data at predetermined milestones
- Document the data management steps to be undertaken prior to data analysis. These steps may vary depending on the purpose of the analysis to be conducted

The ORO Research Quality and Safety Team will support the sponsor in the development of the Data Management Plan; the assigned ORO monitor for the trial will coordinate/lead this effort

Electronic records used in clinical investigations that fall under the scope of Part 11 requirements include:

- Records needed for FDA to reconstruct a clinical investigation that are maintained and retained under predicate rules in electronic form in place of paper form or where the record is relied upon to perform regulated activities
- Records submitted to FDA in electronic form under predicate rules, even if such records are not specifically identified in FDA regulations

- Prior to provision of the data for analysis, edit access to the data acquisition tools should be restricted as appropriate to the purpose of the analysis. For example, at interim analysis, the restriction may only be temporary or managed differently compared to the final analysis
- Use a unique trial participant identification code that allows identification of all the data reported for each participant

  OnCore™

  Participant IDs are generated by the D-H instance of OnCore. See Policy ID: 4856 for trial/participant registration requirements.
- In accordance with applicable regulatory requirements, the sponsor should document what happens to data when a participant withdraws or discontinues from the trial
- Ensure that trial data are protected from unauthorized access, disclosure, dissemination, or alteration and from inappropriate destruction or accidental loss
- Hve processes and procedures in place for reporting incidents (including security breaches) that have a significant impact on the trial data to relevant parties, including regulatory authorities, where relevant

  Refer to the Research Data Handbook for details regarding D-H knowledge about the acquisition and use of data for research purposes (synergy.dartmouth.edu > Data and Informatics > SYNERGY Research Data Handbook)

  Refer to the OnCore Intranet page for details regarding D-H Clinical Trial Management System (DH Intranet>Office of Research Operations>OnCore Resources)

The sponsor's responsibilities related to the use of computerized systems, design of blinded trials, and statistical programming and data analysis entail specific provisions.

See GCP guidance for details.

Record Keeping and Retention

The sponsor should:

- Retain all of the sponsor-specific essential records pertaining to the trial in conformance with the applicable regulatory requirements (or subsequent owners of the data)

See D-H eReg User guide for D-H expectations regarding essential documentation filing expectations (DH Intranet > Office of Research Operations > eReg Resources > eReg User Guide)

Maintenance and retention of essential records for the conduct of a clinical trial involves specific provisions.

See GCP guidance for details.

» Refer to the Health Record Retention Policy (ID: 20413) for institutional expectations regarding research record retention.

- Inform the investigator(s)/institution(s) and service providers in writing, when appropriate, of the need for essential records retention and should notify the investigator(s)/institution(s) and service providers in writing, when appropriate, when the trial-related records are no longer needed
- Report any transfer of ownership of the essential records to the appropriate authorities as required by the applicable regulatory requirements
- Ensure that it is specified in the protocol or other documented agreement that the investigator(s)/institution(s) provide direct access to source records for trial-related monitoring, audits, IRB review, and regulatory inspection
- Ensure that trial participants have consented to direct access to their original medical records and other participant-related trial documents for trial-related monitoring, audit, IRB review, and regulator inspection as part of the informed consent

In general, electronic signatures and their associated electronic records that meet all applicable requirements under Part 11 will be considered equivalent to handwritten signatures. Part 11 specifies that signed electronic records must contain the printed name of the signer, the date and time when the signature was executed, and the meaning associated with the signature.

Reports

- If a trial is prematurely terminated or suspended, the sponsor should promptly inform the investigators/institutions and the regulatory authorities of the termination or suspension and the reasons for the termination or suspension. The IRB should also be informed promptly and provided with the reasons for the termination or suspension by the sponsor or by the investigator/institution, in accordance with applicable regulatory requirements
- Ensure that the clinical trial reports, including interim reports, are prepared and provided to the regulatory agencies as required by the applicable regulatory requirements. The sponsor should also ensure that the clinical trial reports in marketing applications meet the standards of ICH E3 or are otherwise in accordance with applicable regulatory requirements.
- Investigators should be provided with a summary of the trial results

Blinded trials entail specific provisions.

See GCP guidance for details.

VII.

Study Close Out Procedures

Study Close Out Procedures

When the clinical investigation concludes, including both subject involvement and data analysis, it is the Sponsor-Investigator responsibility to perform proper study close out procedures. Check in with the study monitor(s) to ensure all queries are resolved. Close out procedures include the following:

- Return IP to the manufacturer or destroy the product/device(s) per institutional policy
- Complete final IP/device accountability monitoring
- Ensure accountability documentation is incorporated into the regulatory files
- Lock the database
- Certify the CRFs (PI responsibility)
- Resolve all queries
- Complete data analyses
- Post results on ClinicalTrials.gov
- Submit manuscript (if applicable)
- Close study with the IRB (after all identifiable data have been analyzed; de-identified data can still be analyzed after IRB closure)
- Withdraw the IND/IDE with FDA (include IRB closure memo)
- Collect financial disclosure forms (FDFs) from all investigators listed on a 1572 (IND)/investigator agreement (IDE) throughout the course of the study and one year after the investigation is completed
- Retain study records as per **D-H Health Record Retention Policy, ID: 20413** and applicable regulations

The designated ORO monitor will support the Sponsor-Investigator with the operational study close out activities.

VIII.

FDA Inspections

FDA inspections may be conducted for a variety of reasons, including but not limited to, for-cause and surveillance inspections. Sponsors, investigators, Sponsor-Investigators, and IRBs and their staffs are each directly involved these inspections. If you or anyone on your study team receives notice of an FDA bioresearch inspection, you must contact the institutional official (IO) immediately and work with the ORO to prepare for the inspection.

A. Types of FDA Inspections

- Surveillance inspections
- For-cause inspections
- Application-based inspections
- Reliability/integrity/compliance based inspections

B. What to Expect from an FDA Sponsor-Investigator Inspection

- Advance notice of inspection typically 3 business days
- Inspection duration typically 3 to 5 business days
- Interviews of the Sponsor-Investigator and key research personnel
- Review of all study records, databases, and/or data systems relevant to the IND or IDE
- Assessment of investigational product and/or device accountability

C. How to Prepare for an FDA Inspection

- You should promptly inform the IO upon receiving notice from the FDA regarding the agency's intention to inspect
  - » IO will inform the appropriate D-H personnel

ORO will support and guide the Sponsor-Investigator and study team in preparation for and during the inspection

The ORO will guide the **Sponsor-Investigator** and study team through the inspection readiness process:

- Space reservation
- Encrypted USB request
- ClinicalTrials.gov review
- Equipment and access to systems plan
- Documentation preparation
- Pre-inspection quality assurance assessment

The ORO will support the Sponsor-Investigator and study team throughout the course of the inspection, which will likely include review of the following:

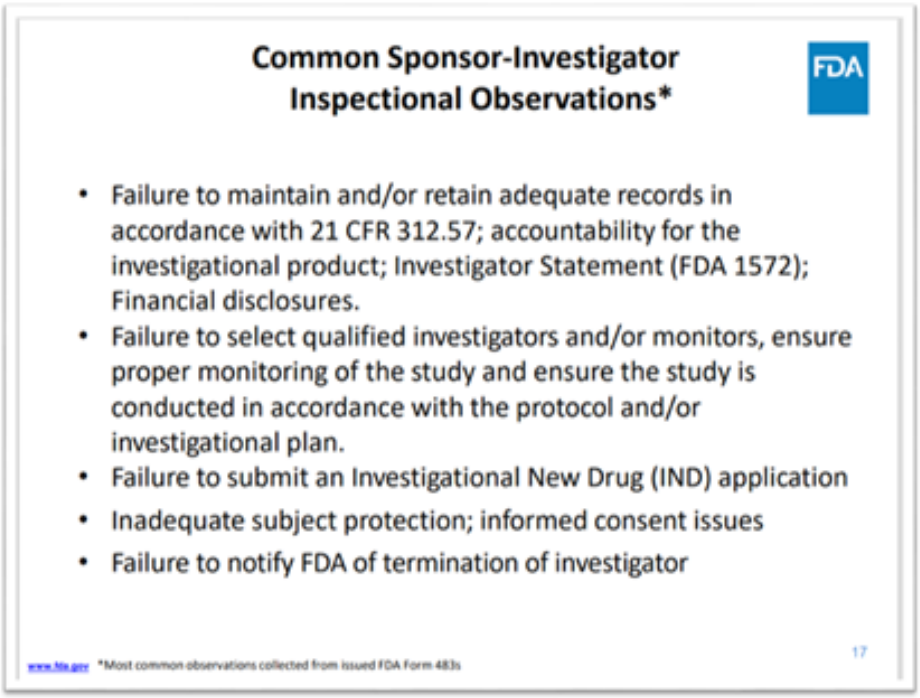
- Protocol and protocol amendments
- Consent forms
- IRB submissions and approvals
- Screening and eligibility logs
- Case report forms and source documentation – including relevant electronic systems (such as electronic medical record and data acquisition system)
- Safety reports
- Laboratory certifications
- Staff training logs and delegation of authority

Following an FDA inspection, areas of inspection are evaluated for compliance and determined as one of 3 classifications:

- **NAI = no action indicated**
- **VAI = voluntary action indicated**
- **OAI = official action indicated**

D. Common Clinical Investigator Inspectional Observations

These observations are taken directly from FDA inspection reports and are helpful to understand the depth of a bioresearch inspection.



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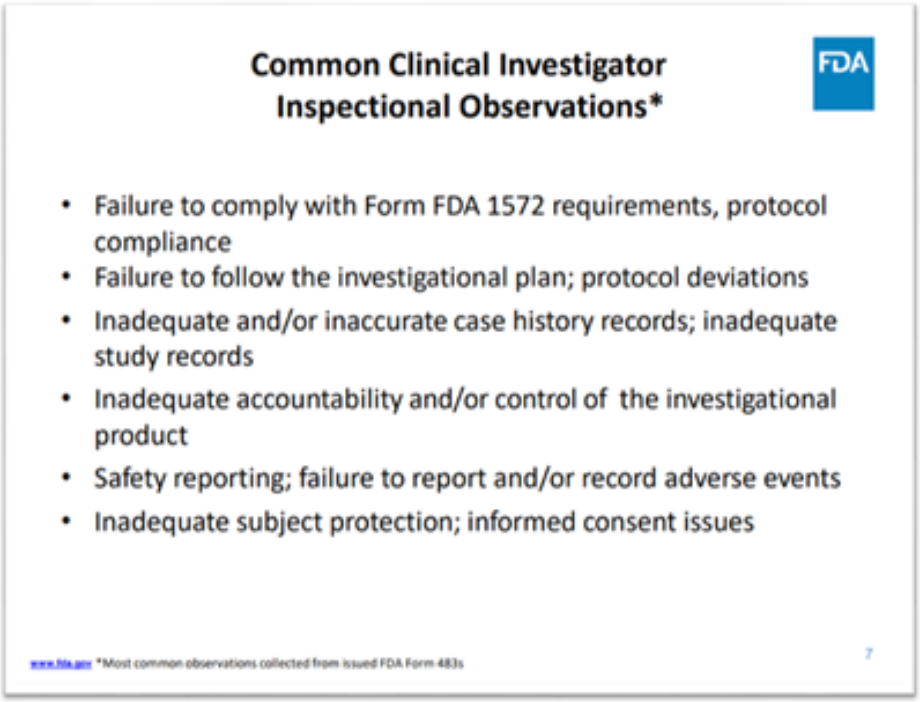

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E. FDA Warning Letters

The FDA may, after consideration of a 483 letter (letter issued following an inspection) and investigator's rebuttal, issue a warning letter. Warning letters identify the specific violation/problem, and direct the recipient to correct it. Warning letters are publicly-available upon issue.

The following are examples of real-life warning letters from the FDA to Sponsor-Investigators following bioresearch inspections:

You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].
As a clinical investigator, you are required to ensure that your clinical studies are conducted in accordance with the investigational plan. The investigational plan for Protocol (b)(4) requires that you omit certain (b)(4) treatments for subjects randomized into the (b)(4). In addition, the investigational plan for Protocol (b)(4) requires you to ensure that subjects meet certain treatment eligibility criteria before each treatment cycle. You failed to adhere to these requirements.

Failure to submit an Investigational New Drug application (IND) for the conduct of a clinical investigation with investigational new drugs that is subject to 21 CFR 312.2(a) [21 CFR 312.20(a), 312.20(b), and 312.40(a)].

You failed to maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug (21 CFR 312.57(a)).
As a sponsor, XX was required to maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug (b)(4). These records were required to include, as appropriate, the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each shipment. XX failed to maintain adequate records with respect to the investigational drug (b)(4).

You failed to obtain informed consent in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60 and 21 CFR 50.20].

You failed to retain records required to be maintained under 21 CFR part 312 for a period of two years following the date a marketing application is approved for the drug for the indication for which the drug is being investigated; or, if no application is filed or if the application is not approved for such indication, until two years after the investigation is discontinued [21 CFR 312.62(c)]

Additionally, we note that the sponsor, not the IRB, is responsible for compliance with IND regulations, including the requirements at 21 CFR 312.2, and that the sponsor is responsible for being aware of and following all applicable FDA regulations.

F. Penalties and Prosecution

Violations of FDA regulations and other unsafe practices may result in civil or criminal penalties to the Sponsor-Investigator and other sanctions to the institution.

The following are examples of investigators subject to potential debarment, civil monetary penalties, and other sanctions as a result of an FDA inspection and enforcement process:

"Because failure to submit clinical trial information required under section 402(j) of the PHS Act (42 U.S.C. 282(j)), including its implementing regulations in 42 CFR part 11, is a prohibited act under section 301(jj)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 331(jj)(2)), FDA may initiate an administrative action seeking a **civil money penalty against your company.**"

"In addition to civil money penalties, violations of section 301(jj) of the FD&C Act (21 U.S.C. 331(jj)) could result in other regulatory action, **such as injunction and/or criminal prosecution, without further notice.**"

Source: https://www.ecfr.gov/current/title-42/chapter-I/subchapter-A/part-11/subpart-E

G. Other Penalties of Non-Compliance

Institutional penalties may include:

- Suspension of clinical research privileges (indefinite or defined period)
- Restriction of clinical research privileges

Penalties imposed by industry sponsors may include:

- Disinclination to collaborate on future clinical research protocols

Other potential consequences or penalties of non-compliance:

- Disqualification as clinical investigator
- Civil money penalties
- Grant funding actions
- Suspension or restriction of clinical research privileges (indefinite or defined period)
- Disinclination of industry sponsors to collaborate on future clinical research protocols
- Injunction or criminal prosecution

IX.

Research Misconduct

A. Overview

Research misconduct refers to fabrication, falsification, and/or plagiarism in proposing, performing, or reviewing research, or in reporting research results. The Office of Research Integrity (ORI) oversees and directs the research activities of the Public Health Service (PHS), which notably includes within it the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the Food and Drug Administration (FDA) on behalf of the Secretary of Health and Human Services, with some small exceptions. Other federal agencies have adopted their own research misconduct policies governing research activities performed by contractors and grant recipients, such as the National Science Foundation (NSF) and the National Aeronautics Space Administration (NASA), adopting guidance largely consistent with ORI's expectations of grant recipients.

D-H has its own Research Misconduct Policy (Research-Related Fabrication, Falsification, and Plagiarism, Policy ID: 16861) setting forth its expectations and requirements consistent with federal obligations. Research misconduct is different from, but can overlap with, other concerns about research integrity and regulatory compliance. Resolution of non-misconduct compliance concerns will not resolve good faith allegations of research misconduct, and vice versa.

According to the D-H the policy, all research within D-H shall be conducted with the highest standards of professional conduct, integrity, and ethical behavior. It is the shared responsibility of all members of our institution to ensure integrity in the design, conduct and reporting of research, and to ensure that misconduct in research endeavors is dealt with in a timely and effective manner and that the reputation for D-H high standards of research integrity it preserved.

All concerns about potential misconduct should be promptly reported to the D-H Research Integrity Officer.

Source: **https://ori.hhs.gov/definition-research-misconduct**

Refer to the D-H Policy for Research Misconduct (Policy ID: 16861)
Refer to the D-H Policy Code of Ethical Conduct (Policy ID: 2347)

B. ORI Oversight and HHS' Administrative Actions and Sanctions

1. All concerns of potential research misconduct are taken seriously, and first reviewed, by D-H. For extramurally sponsored research, such as PHS- or NIH-funded studies, ORI is also responsible for assessing concerns for research misconduct relating to sponsored research. While ORI relies heavily on the recipient institutions to carry out an internal proceeding under their own policies (which include an inquiry and full investigation) to determine whether research misconduct occurred, ORI independently reviews any reported findings of misconduct within its jurisdiction and renders an independent charge and/or findings to the respondent.

2. Where ORI makes findings of misconduct, it will recommend HHS impose administrative actions based on the circumstances and severity of the misconduct. Administrative actions range from letters of reprimand, suspension/termination of PHS grants or cooperative agreements, imposition of supervision requirements on PHS funding, to exclusion/debarment from certain federal programs or transactions, including federal grants and contracts.

3. Findings of misconduct made by ORI are public. They are recorded as case summaries published on ORI's website and noted in the Federal Register, along with any administrative actions imposed. HHS may take action directly against an institution showing a disregard or unwillingness to implement and follow ORI's regulatory requirements and can, for example, require a return of research funds expended on activities involved in research misconduct. Note that ORI does not have the statutory authority to issue subpoenas or to prosecute respondents, either civilly or criminally. However, if ORI believes that a criminal or civil fraud violation may have occurred, ORI must refer the matter to the appropriate office (the Department of Justice or the HHS Office of the Inspector General) for further consideration.

X.

Key Points

A. Regulatory Requirements

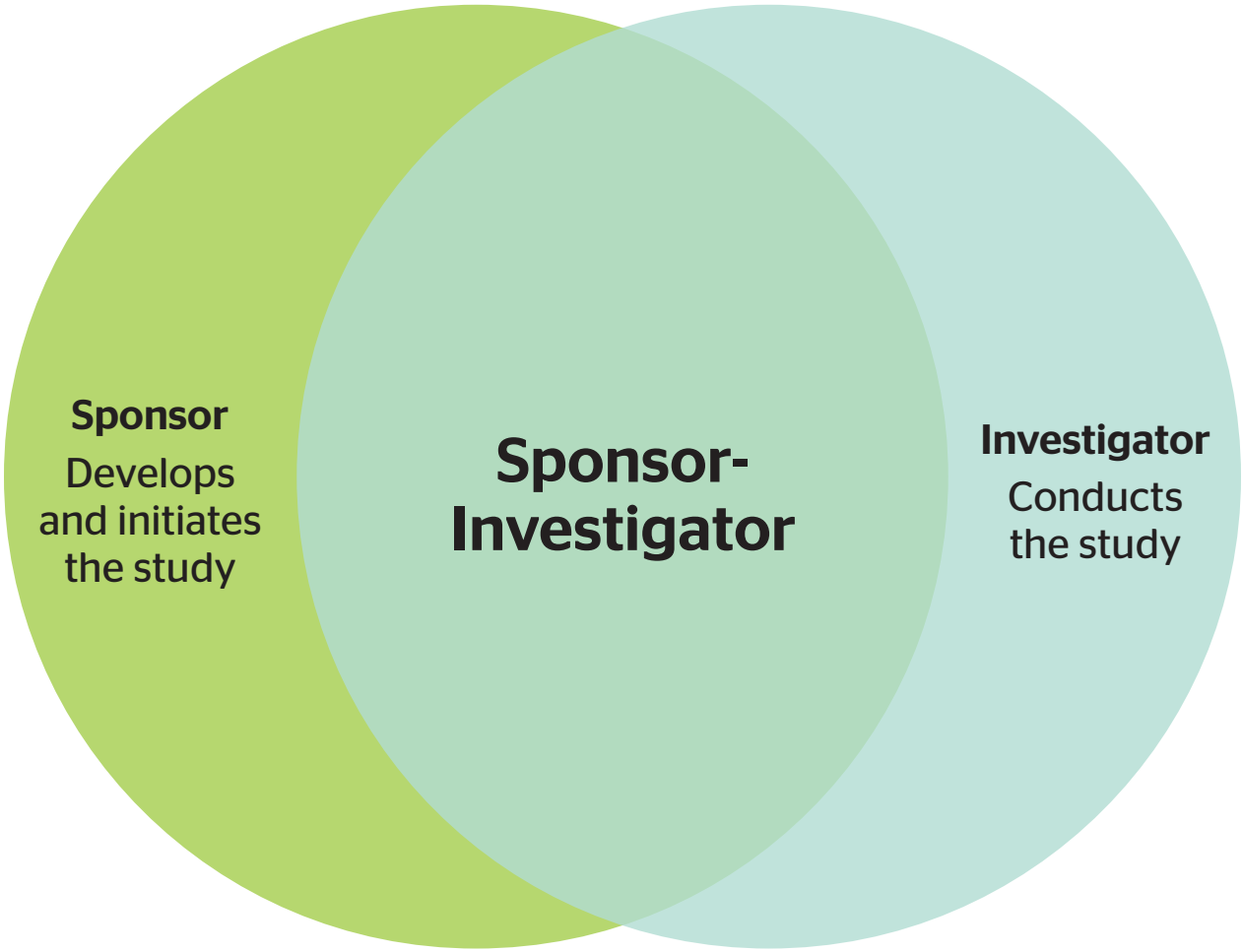
As a reminder, oversight of the following regulatory requirements and institutional policies are the responsibility of IND/IDE Sponsor-Investigators:

- Adherence to CFR, Section 21, Part 11 (Electronic Records, Electronic Signatures)
- Adherence to CFR, Section 21, Part 50 (Protection of Human Subjects)
- Adherence to CFR, Section 21, Part 54 (Financial Disclosure by Clinical Investigators)
- Compliance with CFR, Section 21, Part 56 (Institutional Review Boards)
- Adherence to CFR, Section 21, Part 312 (Investigational New Drug Application)
- Adherence to CFR, Section 21, Part 812 (Investigational Device Exemptions)
- Adherence to CFR, Section 42, Part 93 (Public Health Service Policies on Research Misconduct)
- Compliance with CFR, Section 45, Part 46 (Common Rule) - if applicable
- Adherence to ClinicalTrials.gov guidelines and applicable regulations
- Knowledge and compliance with Clinical Investigator responsibilities
- Knowledge and compliance with Sponsor responsibilities
- Adherence to ICH Good Clinical Practice (GCP)
- Adherence to D-H IRB Policies/Procedures
- Adherence to Institutional Policies- see D-H policies specific to Sponsor-Investigators in the last section of the Handbook

B. Conclusion

The role of Sponsor-Investigator in clinical research conduct is an extensive responsibility encompassing a broad range of accountability for human subjects, and reporting to both institutional and regulatory authorities. In addition, the Sponsor-Investigator is responsible for all study processes and procedures, medical oversight, personnel training, and ultimately, the integrity of the study data and clinical conclusions.

Please contact the Dartmouth Health Office of Research Operations for assistance and support with your federally regulated drug and device studies. More information and resources for IND and IDE studies are available on the ORO Sponsor-Investigator Resource intranet page.



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- Delegation of Authority - D-H Investigational Drug Services (ID: 17725)
  - » https://dh.navexone.com/content/docview/?docid=26566
- Delegation of Authority - ORO Centralized Research Processing Lab (ID: 20272)
  - » https://dh.navexone.com/content/docview/?docid=39095
- PI Eligibility Policy (ID: 26012)
  - » https://dh.navexone.com/content/docview/?docid=50715
- Conflicts of Interest (COI) in Research Policy (ID: 2870)
  - » https://dh.navexone.com/content/docview/?docid=43410
- Human Subjects Research Training (ID: 23146)
  - » https://dh.navexone.com/content/docview/?docid=57814
- Required Review of Imaging Exams Performed for Human Subjects Research Protocols (ID: 25166)
  - » https://dh.navexone.com/content/docview/?docid=47734
- Office of Research Operations Voluntary Hold Process (ID: 23656)
  - » https://dh.navexone.com/content/docview/?docid=41722
- Investigator Review of External IND Safety Reports Policy (ID: 21732)
  - » https://dh.navexone.com/content/docview/?docid=35822
- Informed Consent Process for Research Studies Policy (ID: 28975)
  - » https://dh.navexone.com/content/docview/?docid=59595
- Investigational Drugs Policy (ID: 2091)
  - » https://dh.navexone.com/content/docview/?docid=53786
- Investigational Product Storage and Quarantine (ID: 12149)
  - » https://dh.navexone.com/content/docview/?docid=56949
- Study Drug Returns Procedure (ID: 2763)
  - » https://dh.navexone.com/content/docview/?docid=2950
- Medication Storage and Handling Policy (ID: 6823)
  - » https://dh.navexone.com/content/docview/?docid=14344
- Safe Handling of Hazardous Drugs Policy (ID: 2176)
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D-H Resources continued

- Subject-Administered Investigational Product: Documentation and Operational Procedures (ID: 24413)
  - » https://dh.navexone.com/content/docview/?docid=48717
- Documentation of Clinical Research in the Dartmouth Hitchcock Clinical Trial Management System (CTMS) and the Electronic Medical Record (eDH) Policy (ID: 4856)
  - » https://dh.navexone.com/content/docview/?docid=56990
- Electronic Data Capture System: Use Requirements for Human Subjects Research (ID: 30116)
  - » https://dh.navexone.com/content/docview/?docid=61812
- eRegulatory Management System: Use Requirements for Human Subjects Research Policy (ID: 24815)
  - » https://dh.navexone.com/content/docview/?docid=48722
- Study Specific Processing Training Checklist - ORO Centralized Processing Laboratory (ID: 21757)
  - » https://dh.navexone.com/content/docview/?docid=39451
- Start of Study Checklist - ORO Centralized Research Processing Laboratory (ID: 21835)
  - » https://dh.navexone.com/content/docview/?docid=36067
- Sample Processing Log - ORO Centralized Research Processing Lab (ID: 20158)
  - » https://dh.navexone.com/content/docview/?docid=39446
- Health Record Retention Policy (ID: 20413)
  - » https://dh.navexone.com/content/docview/?docid=33204
- Research Misconduct Policy and Procedure (ID: 16861)
  - » https://dh.navexone.com/content/docview/?docid=52244
- Registration and Results Reporting of Clinical Research on Clinicaltrials.gov Procedure (ID: 22264)
  - » https://dh.navexone.com/content/docview/?docid=40226
- Code of Ethical Conduct-D-H (ID: 2347)
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