VCU
Office of the Vice President
for Research and Innovation

Investigational New Drug (IND): Sponsor and Investigator Responsibilities

A sponsor-investigator assumes BOTH investigator and sponsor responsibilities as outlined in the FDA Code of Federal Regulations 21 CFR 312. This means that such investigators have additional responsibilities.

All VCU/VCUHS faculty/employees who apply for an IND must abide by all relevant federal, state, and VCU/VCUHS policies. The Sponsor and Investigator or the Sponsor- Investigator (if the same individual) must understand and agree to abide by all responsibilities. This document outlines Federal Regulations regarding responsibilities of Sponsors and Investigators for an IND.

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IND Sponsor Responsibilities

The FDA regulations (21 CFR 312.3) define the "Sponsor" of the IND application as "the person who takes responsibility for and initiates a clinical investigation. The Sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The Sponsor does not actually conduct the investigation unless the Sponsor is the Sponsor-Investigator of the IND application."

A. General responsibilities of the Sponsor of an IND application [21 CFR 312.50]

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 below.

B. Specific responsibilities of the Sponsor of an IND application

1. **Selecting Investigators** [21 CFR 312.53]
   The Sponsor of the IND application shall select only Investigators (i.e., study site principal investigators) qualified by training and experience as appropriate experts to study the investigational drug.

2. **Obtaining Information from the Investigator** [21 CFR 312.53]

   a. **A signed Investigator's Statement** (i.e., FDA Form 1572)
   b. **A Curriculum Vitae** or other statement of the qualifications of the Investigator that includes the education, training, and experience that qualifies the Investigator as an expert to study the investigational drug for the use specified in the clinical study
   c. **Financial disclosure information** [21 CFR 54 and 21 CFR 312.53]
      Sufficient accurate financial information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. The sponsor shall obtain a commitment from the clinical investigator to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

      The Sponsor shall describe (i.e., in a written document attached to the applicable Disclosure of Financial Interest of Clinical Investigators) any steps taken to minimize the potential for bias resulting from any of the disclosed reportable financial interests.

For VCU affiliated investigators the COI committee will review for COI and establish a mitigation plan as needed. See *VCU Faculty Held IND and IDE Procedure Handbook*, VCU COI for IND/IDE instructions, and VCU Policy on COI.

3. **Informing Investigators [**21 CFR 312.55]

   a. Before a clinical investigation begins, the Sponsor of the IND application shall provide each Investigator (i.e., study site principal investigator) with an Investigator's Brochure.

      An Investigator's Brochure is not required if the clinical study (studies) being conducted under the Sponsor-Investigator IND application is (are) limited to VCU/VCUHS sites. However, drug biologic information is required in the IND application and must be made available to the investigational pharmacy and any VCUHS site as required by *Conduct of Clinical Research in Patient Care Areas* (PC.CP.004) policy. An Investigator's Brochure is required if the clinical study will be conducted at external, multicenter study sites.

   b. The Sponsor shall, at a minimum, ensure that each participating Investigator and/or substantially involved Sub-Investigators (i.e., Sub- investigators who will be involved in the treatment and evaluation of the research subjects) are provided with a current version of the IRB- approved research protocol.

   c. The Sponsor of the IND application shall, as the overall investigation of the drug proceeds, keep each participating Investigator (i.e., study site principal investigator) informed of new observations regarding the drug that are discovered by or reported to the Sponsor; particularly with respect to serious and unexpected suspected adverse reactions and safe use of the drug.

   d. New drug safety information may be distributed to Investigators by means of a periodically revised Investigator Brochure, reprints of published studies, reports or letters directed to Investigators, or other appropriate means.

   e. IND Safety Reports are required to be copied to all participating Investigators.

4. **Assuring Compliance of Investigators [**21 CFR 312.56]

   A Sponsor who discovers that an Investigator (i.e., study site principal investigator) is not complying with the obligations addressed under the signed Statement of Investigator (i.e., FDA Form 1572), the general investigational plan, or applicable FDA regulations shall promptly either secure compliance or discontinue supplying the investigational drug to the Investigator and end the Investigator's participation in the clinical study.

   The Sponsor shall discontinue supplying the investigational drug to any Investigator who has failed to maintain required records or reports of the clinical study or who declines to make such records or reports available for FDA inspection. (*See Specific Responsibilities of Investigators*)

If the Investigator's participation in a clinical study is terminated, the Sponsor shall require that the Investigator dispose of or return the investigational drug to the Sponsor. (*See Investigational Drug Accountability*)

5. **Ensuring proper monitoring of the progress and conduct of the clinical investigation(s) at each of the involved study sites**;

    a. Ensuring that the clinical investigation(s) is (are) conducted in accordance with the general investigational plan and protocols contained in the IND application. This includes monitoring the progress and conduct of the clinical investigation(s) at each of the involved study sites.
    b. Complying with the Good Clinical Practice (GCP) guidelines for Sponsors of clinical investigations being conducted under an IND application. (See *Good Clinical Practice (GCP) Guidelines - Sponsor Responsibilities*)

6. **Maintaining an effective (i.e., up-to-date) IND** [21 CFR 312] with regard to information concerning the pharmacology and toxicology of the investigational drug, the manufacture of the investigational drug, and clinical investigations of the investigational drug;

    a. The Sponsor shall review and evaluate evidence relating to the safety and effectiveness of the investigational drug as it is being obtained from the Investigator(s).
    b. The Sponsor shall submit written IND Safety Reports to the FDA and participating Investigators. [21 CFR 312.32]
    c. The Sponsor shall submit Annual Reports to the FDA per 21 CFR 312.33.

7. **Ensuring that the FDA and all participating Investigators (i.e., study site principal investigators) are promptly informed of serious and unexpected, suspected adverse reactions and/or other newly identified, significant risks related to the investigational drug**.

    a. If it is determined that the investigational drug presents an unreasonable and significant risk to human subjects, the Sponsor shall
        1) Discontinue the clinical studies that present the risk,
        2) Notify the FDA
        3) Notify all involved institutional review boards (IRBs), and
        4) Notify all Investigators who have, at any time, participated in clinical studies of the drug. [21 CFR 312.56]

    The Sponsor shall discontinue the clinical study (studies) of the investigational drug as soon as possible, and in no event later than 5 days after making the determination that the clinical study (studies) should be discontinued. Upon request, the FDA will confer with the Sponsor regarding the need to discontinue a clinical study.

    If a clinical study is discontinued, the Sponsor shall require that involved

Investigators dispose of or return the investigational drug to the Sponsor. (See *Investigational Drug Accountability*)

8. **Record-keeping and record retention requirements** [21 CFR 312.57]

    a. **Investigational drug accountability**:
    The Sponsor of the IND application shall maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug.

        1) Investigational drug accountability records are required to include, as appropriate, the name of the Investigator (i.e., study site principal investigator) to whom the drug was shipped or otherwise provided and the date, quantity, and batch or lot number of each such shipment.
        2) The Sponsor shall assure that Investigators have in place adequate investigational drug accountability records and that Investigators are storing the drug in a secure manner and in accordance with the Sponsor's established storage parameters (e.g., temperature, humidity, avoidance of exposure to light, etc.) for the stability of drug.
        3) If the investigational drug is a controlled substance listed in any schedule of the Controlled Substances Act [21 CFR 1308], the Sponsor shall also assure that the drug is stored in a securely locked, substantially constructed cabinet or other enclosure; access to which is limited so as to prevent theft or diversion of the drug into illegal channels of distribution. [21 CFR 312.58] Records for these must also be available on request by the DEA. [21 CFR 312.59]

    b. **The Sponsor of the IND application shall retain records and reports required under the regulations governing IND applications for up to 2 years** after a marketing application is approved for the drug. If an application is not approved for the drug until 2 years after the investigation of the drug has been discontinued and the FDA has been so notified. See *VCU policy on record retention*.

9. **Disposition of unused supplies of the investigational drug** [21 CFR 312.59]

    The Sponsor shall assure the return of all unused supplies of the investigational drug from each Investigator whose participation in the investigation of the drug has been discontinued or terminated.

    The Sponsor may authorize alternative disposition (e.g., disposal) of unused supplies of the investigational drug provided that this alternative disposition does not expose humans to risks from the drug and is appropriately documented.

10. **Inspection of the Sponsor's records and reports [**21 CFR 312.58]

    a. **FDA inspection***:*

Upon request from any properly authorized officer or employee of the Food and Drug Administration and at reasonable times, permit such officer or employee to access, copy, and verify any records and reports relating to clinical studies being conducted under the IND.

Upon written request by the FDA, the Sponsor shall submit the records and reports (or copies the records or reports) to the FDA.

b. **DEA inspection of controlled substances**

If the investigational drug is a substance listed in any schedule of the Controlled Substances Act [21 CFR 1308], the Sponsor of the IND application shall, upon request from any properly authorized employee of the Drug Enforcement Administration, permit such employee to inspect and copy records concerning shipment, delivery, receipt, and disposition of the drug.

11. **Transfer of Sponsor responsibilities to a Contract Research Organization [**21 CFR 312.52]

The Sponsor of an IND application may transfer some of all of the Sponsor's responsibilities to a Contract Research Organization (CRO) or a similar entity.

a. The Sponsor retains overall responsibility and liability for any responsibilities transferred to a CRO and therefore should conduct strict oversight of all delegated CRO activities.
b. The assumption of Sponsor responsibilities by a CRO shall be described in writing in the IND application.

- If only certain of the Sponsor's responsibilities are being transferred to the CRO, the written statement shall describe specifically each of these responsibilities being assumed by the CRO.
- If all of the Sponsor's responsibilities are being transferred to the CRO, the written statement shall specify that all of these responsibilities are being assumed by the CRO.
- Any of the Sponsor's responsibilities not covered in the written statement addressing the transfer of responsibilities to a CRO shall be deemed (i.e., by the FDA) to remain the responsibility of the Sponsor.
- NOTE: At VCU, this written agreement must be submitted to the VCU FDA Regulatory Resource Manager and must be institutionally agreed to by the Office of Sponsored Projects.

c. A CRO that assumes some or all of the Sponsor's responsibilities shall comply with the specific FDA requirements applicable to the respective responsibilities and shall be subject to the same regulatory action as a Sponsor for failure to comply with the respective FDA requirements.

IND Investigator Responsibilities

The FDA regulations (21 CFR Sec. 312.3) define an "Investigator" as "an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject. In the event that an investigation is conducted by a team of individuals, the Investigator is the responsible leader of the team. 'Sub-investigator' includes any other individual member of that team." The Investigator has overall responsibility for ensuring 1) the appropriate conduct of clinical studies conducted under an IND, including their initial and continuing IRB approval; 2) the appropriate informed consent of subjects prior to their participation in a clinical study; 3) compliance with all reporting requirements; 4) investigational drug accountability, and 5) proper record-keeping and record retention.

A. General Responsibilities of Investigators [21 CFR 312.60]

Investigators (i.e., study site principal investigators) of clinical studies being conducted under an IND application are generally responsible for:

1. **Ensuring that the clinical study is being conducted according to the terms of the signed Investigator's Statement (FDA Form 1572), the investigational plan, and the FDA regulations governing IND applications**;

Investigator Commitments from the FORM FDA 1572

- I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- I agree to personally conduct or supervise the described investigation(s).
- I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.
- I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64. I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.
- I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical

investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

- I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

2. **Comply with the Good Clinical Practice (GCP) guidelines for clinical safety Investigators**. (See *Good Clinical Practice (GCP) Guidelines - Investigator Responsibilities*);
3. **Protecting the rights, safety, and welfare of research subjects under the Investigator's care**
4. **Controlling access to, and use of, the drug under investigation**.

B. Specific Responsibilities of Investigators (i.e., study site principal investigators)

1. **Protection of the rights, safety, and welfare of research subjects**.

    a. **Assurance of IRB review** [21 CFR 312.66]

        The Investigator shall assure that an Institutional Review Board (IRB) that complies with the requirements set forth at 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study in which the Investigator is involved.

    b. **An Investigator shall not, in the absence of prior IRB approval, make any changes to an IRB- approved clinical study except where necessary to eliminate apparent immediate hazard(s) to human subjects**.

    c. **An Investigator shall promptly report all changes in the research activity (e.g., protocol deviations) and all unanticipated problems involving risks to human subjects or others to the reviewing IRB**.

    d. **Consent of human subjects** [21 CFR 312.60]

        The Investigator shall, in accordance with 21 CFR Part 50, obtain prospectively the informed consent of each human subject to whom the investigational drug is administered (except as provided in 21 CFR Sec. 50.23, Exception from general requirements, or 21 CFR Sec. 50.24, Exception from informed consent requirements for emergency research).

        The case history of each human subject shall document that informed consent was obtained prior to the subject's participation in the clinical study. [21 CFR 312.62]

2. **Control of the investigational drug** [21 CFR 312.61]

    The Investigator shall administer the investigational drug only to research subjects who are under the Investigator's personal supervision or under the supervision of a Sub-investigator who is responsible to the Investigator.

    The Investigator shall not supply the investigational drug to any person who is not authorized to receive the drug.

    If the investigational drug is a controlled substance listed in any schedule of the Controlled

Substances Act (21 CFR Part 1308), the Investigator shall ensure that the drug is stored in a securely locked, substantially constructed cabinet or other enclosure; access to which is limited so as to prevent theft or diversion of the drug into illegal channels of distribution.

3. **Investigator Reports** [21 CFR 312.64]

   a. **Financial interest disclosure reports [**21 CFR 312.64]
   The Investigator shall provide the Sponsor of the IND application with completed *Certifications of Financial Interest of Clinical Investigators* and, when applicable, *Disclosures of Financial Interest of Clinical Investigators for clinical investigators* who are substantially involved in the conduct of the clinical study.

   The Investigator shall promptly update this information with the Sponsor if any relevant changes occur during the course of the Investigator's or applicable Sub- Investigators' participation in the clinical study and for 1 year following completion of the study.

   b. **Progress Reports**
   The Investigator shall provide, in a timely manner, all periodic reports requested by the Sponsor of the IND application. (Note that the Sponsor of the IND application is responsible for collecting and evaluating the clinical trial data and for submitting annual progress reports to the FDA.)

   c. **Safety Reports [**21 CFR 312.64]
   The Investigator must immediately report to the Sponsor of the IND application any serious adverse event, whether or not considered related to the investigational drug; including serious adverse reactions which are listed currently in the protocol or investigator's brochure. This report must include an assessment of whether there is a reasonable possibility that the drug caused the event.

   Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported to the Sponsor in accordance with the protocol unless there is evidence suggesting that a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the Investigator must immediately report the suspected adverse reaction to the Sponsor.

   The Investigator must record non-serious adverse events and report them to the Sponsor according to the timetable for reporting specified in the protocol.

   d. **Final Report** [21 CFR 312.64]
   The Investigator shall provide the Sponsor with a final report shortly following

completion of the study site's participation in the clinical study.

4. **Investigator record-keeping and record retention requirements [**21 CFR 312.62]

    a. **Disposition of the investigational drug***:* The Investigator is required to maintain accurate records of the disposition of the investigational drug, including the date(s) and quantity (quantities) of the drug dispensed to research subjects and the date(s) and quantity (quantities) of the drug returned unused by research subjects.

b. Upon completion, termination, suspension, or discontinuance of the clinical study, the Investigator shall **return all unused supplies of the investigational drug to the Sponsor** of the IND application or otherwise provide for the disposition of the unused supplies of the drug in accordance with the directive(s) of the Sponsor.

c. **Case Histories [**21 CFR 312.62]
The Investigator is required to prepare and maintain (i.e., for each research subject administered the investigational drug or employed as a control in the evaluation of the drug) adequate and accurate case histories that record all observations and other data pertinent to the evaluation of the investigational drug.

Case histories include the case report forms and supporting data; the latter including, but not limited to, signed and dated consent forms and source medical record information including physician progress notes, hospital chart(s), and nurses' notes.

d. **Record Retention**

The Investigator shall retain the required records for a period of 2 years following the date that the FDA approves a marketing application for the drug for the clinical indication for which it is being investigated; or, if no application for marketing is to be filed or if the marketing application is not approved for the clinical indication being studied until 2 years after the FDA has been notified that the investigation of the drug for the clinical indication is discontinued. See *VCU policy on record retention*.

5. **Inspection of Investigator's records and reports** [21 CFR 312.68]

The Investigator shall, upon request from any properly authorized officer or employee of the Food and Drug Administration and at reasonable times, permit such officer or employee to access, copy, and verify any required records and reports.

Investigators are not required to divulge research subject names unless the records of particular individuals require a more detailed study of the case histories, or unless there is reason to believe that the records do not represent actual case studies or do not represent the actual results obtained.

Key References

Code of Federal Regulations for Drugs

- www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312

FDA Website for Investigator-Initiated Investigational New Drug (IND) Applications

- www.fda.gov/drugs/investigational-new-drug-ind-application/investigator-initiated-investigational-new-drug-ind-applications

ICH E6 Good Clinical Practice Guidelines for Industry

- www.fda.gov/media/93884/download
- https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/regulations-good-clinical-practice-and-clinical-trials

VCU Faculty Held IND and IDE Procedure Handbook

- https://research.vcu.edu/media/office-of-research-and-innovation/clinical/procedure_handbook.pdf

VCU Policy:

- Reporting Sponsor-Investigator IND or IDE- https://policy.vcu.edu/universitywide-policies/policies/reporting-sponsor-investigator-ind-or-ide.html
- Research Data Ownership, Retention, Access, and Security- https://policy.vcu.edu/universitywide-policies/policies/research-data-ownership-retention-access-and-security.html
    - GS111 for Clinical Research- http://www.lva.virginia.gov/agencies/records/sched_state/GS-111.pdf

VCUHS Policies Related to Clinical Research including:

- VCUHS Policy Investigational Drugs - research.vcu.edu/secure/compliance_program/vcuhs/investigational_drugs.pdf

- VCUHS Policy Conduct of Clinical Research in Patient Care Areas - research.vcu.edu/secure/compliance_program/vcuhs/vcuhs_research_patient_care_areas.pdf

For specific questions at VCU/VCUHS contact the FDA Program Manager:
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