

Brief Synopsis of Federal Regulations for Investigators Who Hold an IND

I. Introduction

The following information is intended to provide sponsor-investigators with information to guide them through the FDA requirements for sponsor-investigators who hold an IND. The federal regulations for INDs are found under [21 CFR 312](#). For more information, review the FDA's Center for Drug Evaluation and Research (CDER) web site www.fda.gov/cder.

Below is a synopsis of requirements specific to sponsor-investigators who hold INDs. This document is intended to be a guide, but does not include the complete text of the regulations. Hyperlinks are included throughout this document so that you may read the corresponding regulations. Sponsor-investigators must review and be familiar with the federal regulations before undertaking these responsibilities.

Sponsor-investigators are also required to follow all federal regulations and Washington University policies and guidance for human subjects research. Federal regulations are found in [45 CFR 46](#), [21 CFR 50](#) and [21 CFR 56](#). Washington University policies and guidance for human subjects research are available on the Human Research Protection Office's (HRPO) website at <http://hrpohome.wustl.edu/>.

II. What is a Sponsor-Investigator?

When an Investigator holds an IND for the product being tested in a particular research study, he/she must also assume the role of the Sponsor, and is called a "Sponsor-Investigator." The FDA defines a Sponsor-Investigator as "an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor" [[21 CFR 312.3](#)].

III. What must the Sponsor-Investigator report to the FDA?

Sponsor-investigators have extensive reporting requirements under FDA regulations.

1. New protocol [21 CFR 312.30a](#)

Once the IND has been approved by the FDA, the sponsor-investigator must submit a new protocol for any study not contained in the IND application. The protocol can be submitted before or after IRB approval. The study may not begin until the protocol has been reviewed by the FDA and approved by the IRB.

2. Changes in the protocol [21 CFR 312.30b](#)

The following protocol changes must be submitted to the FDA.

- For *Phase 1 studies*, any change that significantly affects the safety of subjects.
- For *Phase 2 and 3 studies*, any change that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study.
- For all studies, a protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided the FDA is

Brief Synopsis of Federal Regulations for Investigators Who Hold an IND

subsequently notified by protocol amendment and the reviewing IRB is notified, as well.

- See examples found in [21 CFR 312.30 \(b\)](#)
 - increase in drug dosage or duration of exposure
 - significant increase in the number of subjects under study
 - addition of a new test/procedure intended to improve monitoring for, reduce risk of a side effect
 - dropping of a test intended to monitor safety

3. **New investigator** [21 CFR 312.30c](#)

The addition of a new investigator must be reported to the FDA within 30 days of the investigator being added. The IND may not be shipped to the new investigator until the FDA has been notified. *Investigator* means 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 an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. "Subinvestigator" includes any other individual member of that team.

4. **Information amendments** [21 CFR 312.31](#)

Any essential information that is not included in a protocol amendment, IND safety report, or annual report must be submitted to the FDA. Examples of essential information include new toxicology, chemistry, or other technical information or a report regarding the discontinuation of a clinical investigation. Information amendments should be submitted as necessary, but not more than every 30 days.

5. **IND safety/adverse events reports** [21 CFR 312.32](#)

The sponsor-investigator shall notify FDA and all participating investigators in a written IND safety report of a) any adverse experience associated with the use of the drug that is both serious and unexpected; or b) any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity. Guides to adverse event and safety reporting are indicated below:

- ***Unexpected fatal or life-threatening*** experiences that are associated with the investigational drug must be reported to the FDA *by fax or telephone as soon as possible*, but no later than 7 days after the sponsor-investigator initially receives the information.
- ***Serious and unexpected adverse events*** associated with the use of the drug that are not fatal or life-threatening ***and any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity*** must be submitted to the FDA as soon as possible, but no later than 15 days after the sponsor-investigator initially receives the information.

For multiple site studies, the sponsor-investigator must have written procedures in place to receive, process, and report to the FDA serious adverse events which occur at participating sites. In general, participating investigators should report serious adverse

Brief Synopsis of Federal Regulations for Investigators Who Hold an IND

events to the sponsor-investigator within 24 hours of having knowledge of the event.

The sponsor-investigator shall promptly investigate all safety information received. If the results of a sponsor-investigator's investigation show that an adverse drug experience not initially determined to be reportable per the above guidelines is reportable, the sponsor-investigator shall report such experience in a written safety report as soon as possible, but in no event later than 15 calendar days after the determination is made. Results of a sponsor-investigator's investigation of other safety information shall be submitted, as appropriate, in an information amendment or annual report.

6. **Annual reports** [21 CFR 312.33](#)

The sponsor-investigator must submit an annual progress report to the FDA. This report is due within 60 days of the anniversary date that the IND went into effect. This requirement is also referenced in [\[21 CFR 312.64\]](#). The expected contents of the progress report are included in [21 CFR 312.33](#).

7. **Withdrawal of an IND** [21 CFR 312.38](#)

Sponsor-investigators must inform the FDA of the desire to withdraw an IND. If an IND is withdrawn because of safety reasons, the sponsor should promptly inform the FDA, all participating investigators and all reviewing IRBs.

8. **Discontinuation of an investigation** [21 CFR 312.31\(a\)2](#) , [21 CFR 312.56\(b\)](#), [21 CFR 213.56\(d\)](#)

A sponsor that discovers that an investigator is not complying with the signed agreement (Form FDA-1572), the general investigational plan or the requirements of 21 CFR 312 or other applicable parts shall promptly secure compliance or discontinue shipments of the investigational drug and end the investigator's participation in the investigation. All drug should be returned to the sponsor or disposed of and the FDA should be notified.

If the sponsor-investigator determines that an investigational drug presents an unreasonable and significant risk to subjects, she/he must discontinue the investigation within 5 working days after determining that the investigation should be discontinued. The FDA, all IRBs and all investigators who have at any time participated in the investigation should be notified. A report of the discontinuation of the investigation should be submitted to the FDA within 5 working days of the discontinuance.

9. **Financial disclosure reports** [21 CFR 312.57b](#) and [Financial Disclosure FDA Guidance](#)

Any changes to financial disclosure information must be promptly reported to the FDA during the investigation and for 1 year following completion of the study.

IV. What records must a sponsor-investigator maintain?

The sponsor-investigator is responsible for maintaining the following records during and for 2 years after the date a marketing application is approved for the drug for the indication for which it is being investigated. If no application is to be filed or if the application is not

Brief Synopsis of Federal Regulations for Investigators Who Hold an IND

approved for such an indication, the sponsor-investigator is responsible for maintaining the following records until 2 years after the investigation is discontinued and FDA is notified (IRB or other requirements may differ) [\[21 CFR 312.62\]](#). The sponsor-investigator must make these available to FDA inspectors at their request. For multi-site studies, the sponsor-investigator must ensure that all participating investigators maintain the following records.

1. **Drug accountability** [21 CFR 312.57a](#)

The sponsor-investigator must maintain records showing receipt, shipment, or other disposition of the investigational drug.

2. **Financial interest** [21 CFR 312.57b](#)

A sponsor shall maintain complete and accurate records showing any financial interest as defined in [54.4\(a\)\(3\)](#) paid to clinical investigators by the sponsor of the covered study. A sponsor shall also maintain complete and accurate records concerning all other financial interests of investigators subject to [21 CFR 54](#). The sponsor-investigator is responsible for ensuring all participating investigators provide the sponsor-investigator with sufficient accurate financial information to allow the sponsor-investigator to submit complete and accurate certification or disclosure statements. The sponsor-investigator shall 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 [\[21 CFR 312.64\]](#).

3. **Case Histories** [21 CFR 312.62b](#)

The sponsor-investigator must maintain accurate case histories that record all observations and other data pertinent to the investigation on each subject who received the investigational drug and each subject who was employed as a control in the investigation. [\[21 CFR 312.62\]](#). Case histories include the case report forms and supporting data such as signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

V. What are the sponsor-investigator's responsibilities as a sponsor?

The sponsor-investigator carries all responsibilities toward co-investigators that are normally assigned to the sponsor.

1. **General responsibilities of sponsors** [21 CFR 312.50](#)

The sponsor-investigator is responsible for

- selecting qualified investigators and providing them with the information they need to conduct an investigation properly.
- ensuring proper monitoring of the investigation.
- ensuring that the investigation is conducted in accordance with the general investigational plan and protocols contained in the IND.
- maintaining an effective IND with respect to the investigations.

Brief Synopsis of Federal Regulations for Investigators Who Hold an IND

- ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug.
2. **Selection and monitoring of investigators** [21 CFR 312.53 – 312.56](#)
The sponsor-investigator is responsible for
 - selecting qualified investigators and monitors.
 - ensuring that the study drug is shipped only to participating investigators.
 - informing co-investigators of new observations with regard to the investigational drug and progress of the study.
 - reviewing on-going investigations, including assuring compliance of all investigators with the protocol, reviewing and evaluating safety and efficacy data of the investigational drug, and discontinuing studies that are deemed to pose an unreasonable and significant risk to subjects.
 3. **Recordkeeping and record retention** [21 CFR 312.57](#)
The sponsor-investigator is responsible for maintaining study records, as described above in [Part IV](#) of this document.
 4. **Inspection of sponsor’s records and reports** [21 CFR 312.58](#)
The sponsor-investigator must allow FDA employees access to all records and reports at their request. Drug Enforcement Administration and Department of Justice employees must be given access to records and reports involving controlled substances at their request.
 5. **Disposition of unused supply of investigational drug** [21 CFR 312.59](#)
If the investigation is terminated, suspended, discontinued, or completed, the sponsor-investigator is responsible for assuring that all participating investigators return any unused supplies of the investigational drug to the sponsor-investigator, or otherwise provide for disposition of the unused supplies of the drug under [21 CFR 312.59](#) [[21 CFR 312.62](#)]. The sponsor-investigator must maintain records of the disposition of the drug as described in [Part IV](#) of this document.

VI. What are the sponsor-investigator’s responsibilities *as an investigator*?

As an investigator, the sponsor-investigator has all the responsibilities of investigators in any clinical trial.

1. **General responsibilities of investigators** [21 CFR 312.60](#)
The sponsor-investigator is responsible for
 - ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations.
 - protecting the rights, safety, and welfare of subjects under the investigator’s care
 - ensuring the control of drugs under investigation.
2. **Control of the investigational drug** [21 CFR 312.61](#)

Brief Synopsis of Federal Regulations for Investigators Who Hold an IND

The sponsor-investigator must administer the investigational drug only to subjects under his/her direct supervision, or under the supervision of a sub-investigator responsible to the investigator. The sponsor-investigator must also ensure that the investigational drug is not given to any person not authorized to receive it.

3. **Investigator recordkeeping and record retention** [21 CFR 312.62](#)

The sponsor-investigator is responsible for maintaining adequate records of the disposition of the drug, including dates, quantity, and use by subjects. This is further described in [Part IV](#) of this document.

4. **Investigator reports** [21 CFR 312.64](#)

The sponsor-investigator must provide reports to the FDA as described above in [Part III](#) of this document.

5. **Assurance of IRB review** [21 CFR 312.66](#)

The sponsor-investigator is responsible for

- assuring that a qualified IRB will be responsible for initial and continuing review and approval of the investigation.
- assuring that he/she will report to the IRB all changes and unanticipated problems involving risk to human subjects or others.
- assuring that he/she will not make any changes in the investigation without prior IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

6. **Inspection of sponsor-investigator's records and reports** [21 CFR 312.68](#)

The sponsor-investigator must allow FDA employees access to all records and reports at their request. A sponsor-investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to [21 CFR 312.62](#) [[21 CFR 312.68](#)]. The sponsor-investigator is not required to divulge participant names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.

7. **Handling of controlled substances** [21 CFR 312.69](#)

The sponsor-investigator must take adequate precautions to ensure the safe and secure handling of controlled substances. The sponsor-investigator shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

VII. Additional FDA Regulatory References

For additional information, refer to the following links:

- Electronic Records and Electronic Signature [21 CFR 11](#)
- Financial Disclosures by Clinical Investigators [21 CFR 54](#)

Brief Synopsis of Federal Regulations for Investigators Who Hold an IND

- Current Good Manufacturing Practice In Manufacturing, Processing, Packing or Holding of Drugs; General [21 CFR 210](#)
- Current Good Manufacturing Practice for Finished Pharmaceuticals [21 CFR 211](#)
- Drugs for Human Use [21 CFR 314](#)
- Bioavailability and Bioequivalence Requirements [21 CFR 320](#)
- Over-The-Counter (OTC) Human Drugs Which are Generally Recognized as Safe and Effective and Not Misbranded [21 CFR 330](#)
- Biologics Licensing [21 CFR 601](#)

V111. Additional references:

- [FDA Guidance](#): Investigator Responsibilities-Protecting the Rights, Safety, and Welfare of Study Subjects
- [FDA Form 1572](#) – Statement of Investigator
- [FDA Form 3454](#) – Certification: Financial Interests and Arrangements of Clinical Investigators
- [FDA Form 3455](#) – Disclosure: Financial Interests and Arrangements of Clinical Investigators
- [Clinical Research Forms Library](#)
- [FDA guidance](#)-Adverse Event Reporting to the IRB
- [OHRP guidance](#)-Guidance on Reporting Unanticipated Problems to the IRB