

1. IND Sponsor and Investigator Responsibilities

1.1 Welcome



Notes:

Welcome to the ReGARDD Training Modules for IND sponsor-investigator responsibilities. ReGARDD is an academic collaboration that offers Regulatory Guidance for Academic Research of Drugs and Devices and is supported in part by the Clinical and Translational Science Awards Program from the National Center for Advancing Translational Sciences.

This training consists of ten modules. The first nine modules will cover IND sponsor responsibilities and the final module will cover the responsibilities that must be fulfilled by investigators who conduct a clinical investigation run under an IND. Investigators fulfilling a dual

Training Modules on IND Sponsor and Investigator Responsibilities (No Quiz)

role as sponsor and investigator, in other words sponsor-investigators, must fulfill the responsibilities of both sponsors and investigators.

1.2 Main Menu



Notes:

This is your main navigation screen. Please select a module from the Main Menu list. After you have completed a module, you will return to this screen to complete each section of the course. Once all modules have been completed, the menu item "Course Completion" will become available.

2. Introduction to IND Sponsor and Investigator Responsibilities

2.1 Introduction to IND Sponsor and Investigator Responsibilities



Notes:

2.2 Learning Objectives

Introduction to IND Sponsor and Investigator Responsibilities



- ✓ Role of an IND Sponsor-Investigator
- ✓ Two Sets of Responsibilities for Sponsors and Investigators
- ✓ IND Acknowledgement Letter and IND Effective Date
- ✓ Maintaining an Effective IND

Notes:

After completing this training module, the learner will understand the following:

- The role of an IND sponsor-investigator;
- That there are two sets of responsibilities (one for sponsors and one for investigators), and that sponsor-investigators are required to comply with both sets of responsibilities;
- The importance of an IND acknowledgment letter and how to determine the IND effective date; and
- That the sponsor is responsible for maintaining the IND once it becomes effective.

2.3 Who Is an IND Sponsor-Investigator?

Introduction to IND Sponsor and Investigator Responsibilities

Who Is an IND Sponsor-Investigator?

An **IND** is a request to FDA for authorization to administer an investigational drug (or biologic) to humans.

| <u>IND Sponsor</u> | <u>IND Investigator</u> | <u>IND Sponsor-Investigator</u> |
|---|--|--|
| Initiates the clinical investigation | Conducts the clinical investigation | Initiates and conducts a clinical investigation |

Notes:

An IND is a request to the FDA for authorization to administer an investigational drug (or biologic) to humans. An investigational drug is one that is not lawfully marketed in the United States as a drug or if lawfully marketed, used in an off-label manner. In this context, the term “drug” also includes biological products.

The sponsor of an IND is the individual, company, academic institution, or other organization that takes responsibility for and initiates the clinical investigation. The sponsor submits the IND to the FDA, but the sponsor does not actually conduct the investigation - unless the sponsor is a sponsor-investigator.

The investigator is the individual who conducts the clinical investigation and under whose immediate direction a drug is

administered to a subject. In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. Other individual members of the team are known as subinvestigators.

If the same individual both initiates and conducts the investigation, that person is known as the sponsor-investigator. A sponsor-investigator takes responsibility for the investigation, and the drug is administered under his or her direction.

2.4 Responsibilities of IND Sponsors and Investigators



Introduction to IND Sponsor and Investigator Responsibilities

Responsibilities of IND Sponsors and Investigators

Sponsors and investigators each have specific sets of responsibilities.

- IND regulations found in [21 CFR 312](#) describe the responsibilities of sponsors and investigators.
- Sponsor-investigators must fulfill the responsibilities of both the sponsor and the investigator.
- Failure to comply with these responsibilities could result in termination of the IND.

Notes:

Sponsors and investigators each have specific responsibilities that must be fulfilled when conducting a clinical trial under an IND. These responsibilities are described in the IND regulations, which are found

Training Modules on IND Sponsor and Investigator Responsibilities (No Quiz)

in Title 21 Part 312 of the Code of Federal Regulations. Click on the provided link to view the IND regulations.

A sponsor-investigator must fulfill the responsibilities of both the sponsor and the investigator.

It is important for sponsor-investigators to comply with their responsibilities in order to protect the rights, safety, and welfare of subjects and also to protect the integrity of the clinical trial.

Additionally, failure to comply with the sponsor and investigator responsibilities could result in termination of the IND.

This series of training modules will walk through the IND sponsor and investigator responsibilities.

2.5 When Do Sponsor Responsibilities Begin?

Introduction to IND Sponsor and Investigator Responsibilities

When Do Sponsor Responsibilities Begin?

Sponsor responsibilities begin once the IND becomes effective.

Dear Dr. Smith:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA). Please note the following identifying data:

| | |
|-----------------------------|-------------------|
| IND NUMBER ASSIGNED: | 123456 |
| SPONSOR: | John Smith, MD |
| PRODUCT NAME(S): | Drug XYZ |
| DATE OF SUBMISSION: | September 5, 2016 |
| DATE OF RECEIPT: | September 6, 2016 |

IND Acknowledgement Letter

- Assigned FDA review division
- IND number
- Division contact
- Official FDA date of receipt

Notes:

Sponsor responsibilities begin once the IND becomes effective. It is interesting to note that INDs are not approved by FDA but instead become effective following FDA's review and determination that the investigation is safe to proceed.

After submitting an IND, FDA will send an IND acknowledgement letter to the sponsor. The IND acknowledgement letter contains important information including the assigned FDA review division, IND number, division contact, and the official FDA date of receipt.

2.6 When Do Sponsor Responsibilities Begin?

Introduction to IND Sponsor and Investigator Responsibilities

When Do Sponsor Responsibilities Begin?

The official FDA date of receipt starts a 30-day clock for FDA to review the IND.

IND Effective Date

- 30 days after FDA receives the IND, unless FDA notifies the sponsor that the IND has been placed on clinical hold
- Or on earlier notification by FDA that the study is safe to proceed

Notes:

The official FDA date of receipt starts a 30-day clock for FDA to conduct a multidisciplinary review of the IND. By the end of the 30-day review period, if the FDA determines that it is safe to proceed with the clinical trial, the FDA may or may not contact the sponsor about its determination. If the sponsor has not heard anything from FDA by day 30, it is recommended that the sponsor reach out to his or her FDA division contact to confirm that no communications have been lost and the study is safe to proceed.

The IND becomes effective (or goes into effect) 30 days after the FDA receives the IND, unless the sponsor is notified by FDA that a clinical hold has been placed on the IND. This date is known as the IND effective date.

Occasionally, FDA will notify a sponsor prior to the end of the 30-day review period that the study is safe to proceed. If this occurs, then the date of this notification from the FDA is the IND effective date.

The sponsor may not initiate enrollment in the clinical investigation until the IND is effective and the Institutional Review Board, or IRB, has reviewed and approved the investigation.

2.7 Maintaining an Effective IND

Introduction to IND Sponsor and Investigator Responsibilities

Maintaining an Effective IND



The sponsor is responsible for maintaining the IND by submitting protocol amendments, information amendments, safety reports, and annual reports to FDA, as applicable.

Notes:

Once the IND is effective, the sponsor is responsible for maintaining the IND by submitting protocol amendments, information amendments, safety reports, and annual reports to the FDA, as applicable. In general, the sponsor needs to ensure that the information in the IND is accurate and up-to-date.

These IND reporting requirements will be described in more detail in the following training modules, along with the other IND sponsor and investigator responsibilities.

2.8 Additional Information



Introduction to IND Sponsor and Investigator Responsibilities

Additional Information

For more information on IND sponsor and investigator responsibilities, please see FDA's Guidance entitled ["Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators."](#)

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Notes:

For more information on IND sponsor and investigator responsibilities, please see FDA's Guidance entitled "Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators" by clicking on the provided link.

3. Overview of IND Maintenance and Tracking


3.1 Overview of IND Maintenance and Tracking



Notes:

3.2 Learning Objectives

Overview of IND Maintenance and Tracking



- ✓ Modify an Effective IND through Submission of Amendments
- ✓ Types of Amendments
- ✓ Submission Process
- ✓ Implementing Changes
- ✓ IND Serial Numbering System

Notes:

After completing this training module, the learner will understand the following:

- How to modify an effective IND through the submission of IND amendments;
- The types of IND amendments and the kind of information that should be submitted in each category;
- The submission process for IND amendments;
- The timelines associated with implementing changes; and
- The IND serial numbering system that is used to track IND amendments.

3.3 Maintaining an Effective IND Through Submission of Amendments

Overview of IND Maintenance and Tracking



Maintaining an Effective IND Through Submission of Amendments

The sponsor is responsible for maintaining the IND.



New or updated information should be submitted to the IND.

All submissions sent to the IND are tracked by the FDA as amendments.

Notes:


Once the IND is effective, the sponsor is responsible for maintaining the IND.

To maintain an effective IND, the sponsor must ensure that the information in the IND is accurate and up-to-date. As applicable, the sponsor should submit new or updated information to the IND.

After submission of the initial IND, all subsequent submissions sent to the IND are tracked by the FDA as amendments. The sponsor should amend the IND as often as is necessary but should keep in mind that information can be bundled. To the extent feasible, FDA prefers amendments not be submitted more than every 30 days.

3.4 Types of Amendments

Overview of IND Maintenance and Tracking



Types of Amendments

Sponsors are responsible for keeping FDA apprised of all essential information in the IND.

- Protocol Amendment**
New protocol, change in protocol, and new investigator
- Information Amendment**
Chemistry/microbiology, pharmacology/toxicology, clinical/safety, statistics, and clinical pharmacology
- Safety Report**
Information about any serious and unexpected adverse event(s) associated with the use of the drug
- Annual Report**
Brief report of the progress of the investigation

Notes:

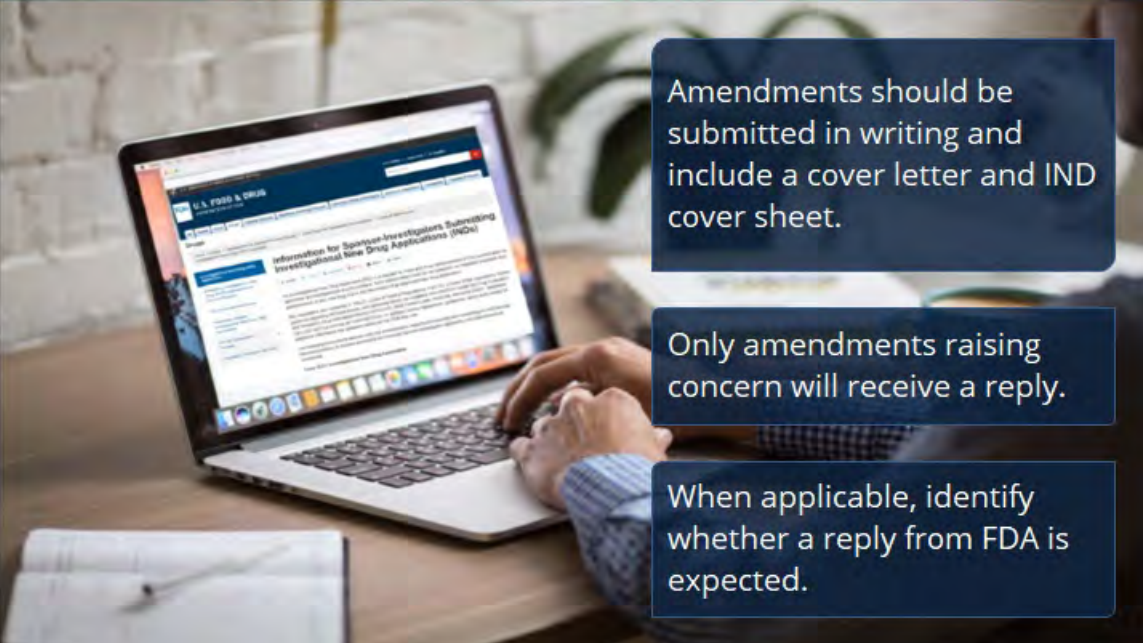
Importantly, sponsors are responsible for keeping FDA apprised of all essential information in the IND. Listed here are the various types of IND amendments that can be used to update information in the IND. While the following training modules will go into detail about the reporting requirements and information contained within each of these IND amendments, we have summarized the types of information that would be submitted in each category on this slide.

Keep in mind that any information that could affect the safe use of the investigational product, the rights, safety, or welfare of study subjects, or the integrity of the clinical trial should be submitted to the IND, even if it does not fall within the scope of the IND amendments listed here.

3.5 Submission of Amendments

Overview of IND Maintenance and Tracking

Submission of Amendments



Amendments should be submitted in writing and include a cover letter and IND cover sheet.

Only amendments raising concern will receive a reply.

When applicable, identify whether a reply from FDA is expected.

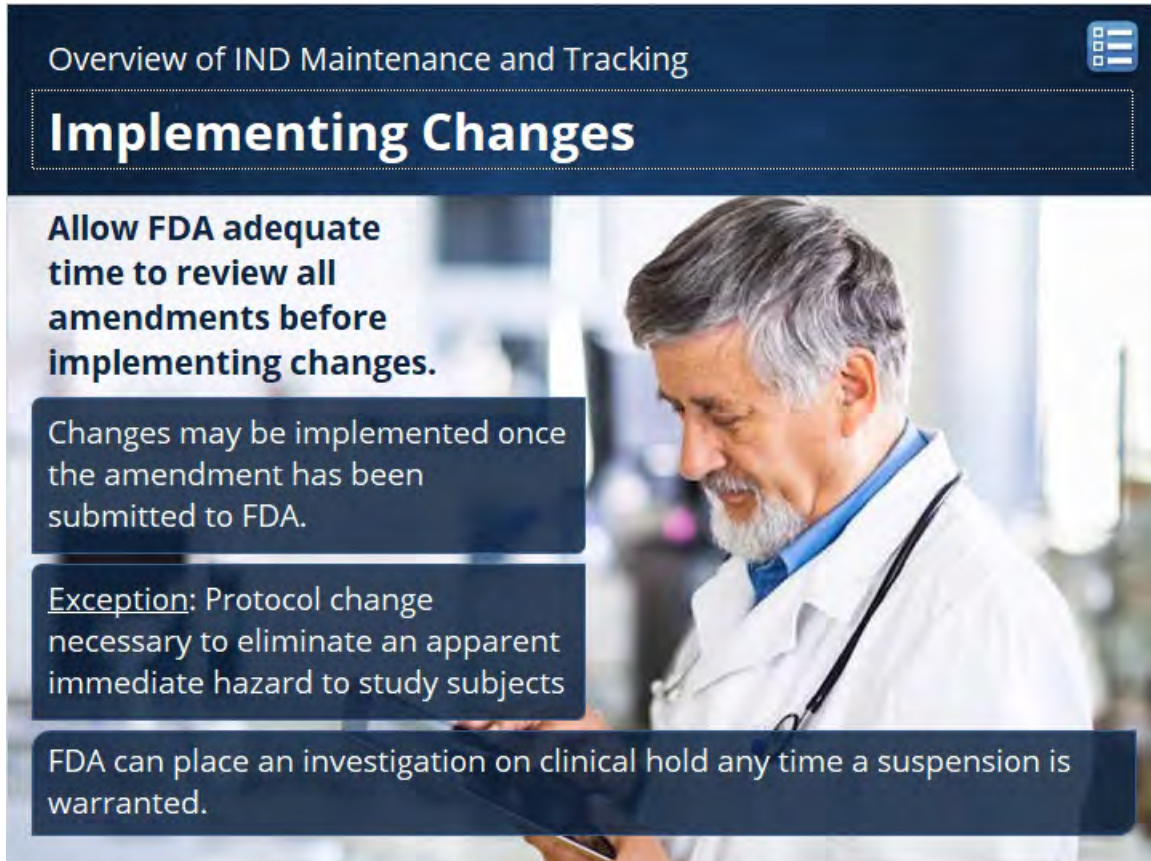
Notes:

When an amendment needs to be submitted to the IND, the request should be submitted in writing and should include a cover letter and IND cover sheet meeting regulations in Title 21 of the Code of Federal Regulations Part 312.23(a). Form FDA 1571 is the cover sheet used most commonly by sponsors, and it can be used for all types of IND submissions. For individual patient expanded access INDs submitted by physicians, Form FDA 3926 may be used to satisfy the cover sheet requirement. The sponsor should clearly identify the reason for the submission in both the cover letter and IND cover sheet.

While all IND amendments are reviewed by the FDA review division upon receipt, the FDA will usually only reply if there are concerns around the proposed changes or newly submitted information.

When applicable, it is important to identify in the IND amendment whether a reply from FDA is expected. For example, if a sponsor would like the FDA to review new information and respond by a certain proposed date, this request should be included in the cover letter.

3.6 Implementing Changes



Overview of IND Maintenance and Tracking

Implementing Changes

Allow FDA adequate time to review all amendments before implementing changes.

Changes may be implemented once the amendment has been submitted to FDA.

Exception: Protocol change necessary to eliminate an apparent immediate hazard to study subjects

FDA can place an investigation on clinical hold any time a suspension is warranted.

Notes:

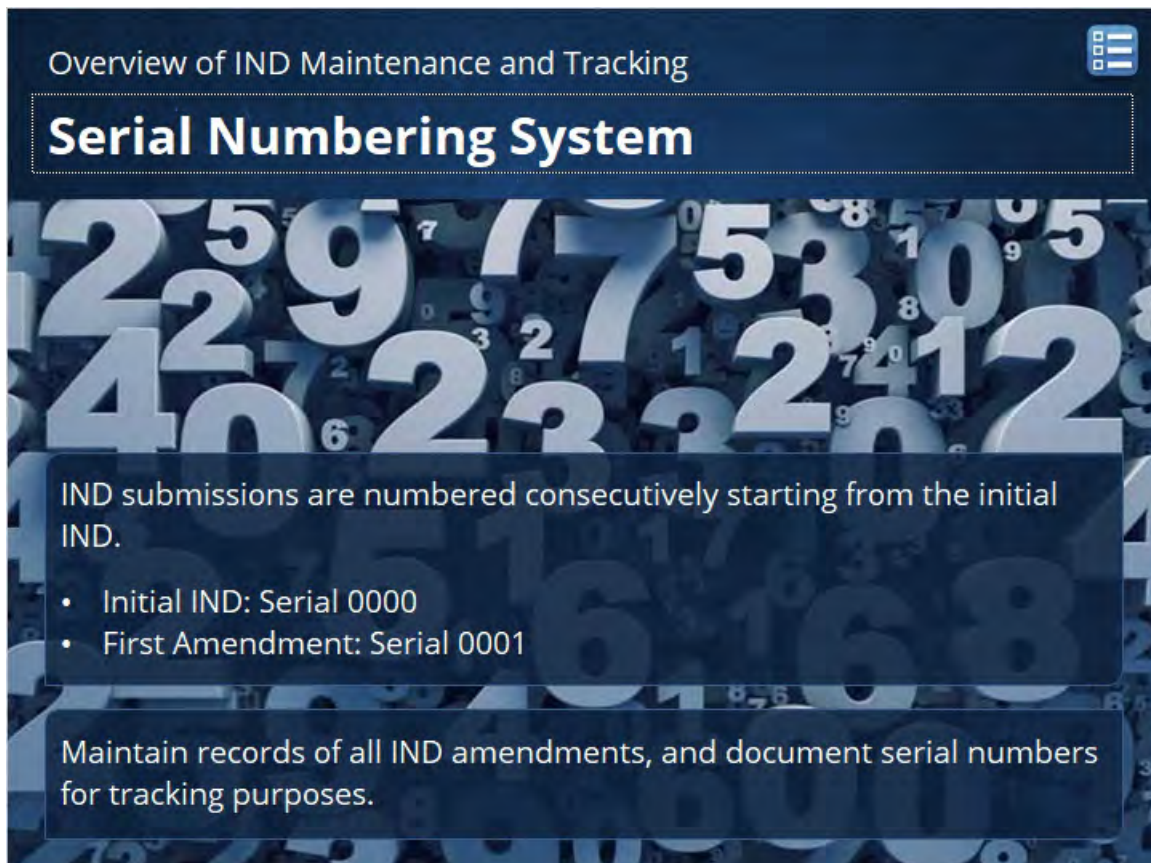
It is recommended that FDA be given adequate time to review all IND amendments before implementing changes.

Unlike the initial IND submission, there is no 30 day review for IND amendments. IND changes may be implemented once the amendment has been submitted to FDA. Sponsors are reminded that any new protocols or changes to ongoing protocols must also be reviewed and approved by an Institutional Review Board, or IRB, prior to

implementation. The only exception to this timeline is for a protocol change that must be implemented to eliminate an apparent immediate hazard to study subjects. In this case, the sponsor may implement the change immediately provided that the FDA and reviewing IRBs are subsequently notified of the change.

While the FDA allows IND changes to be implemented following the submission of an amendment, the FDA does reserve the right to suspend an ongoing study by placing the investigation on clinical hold at any time a suspension is warranted. Thus, sponsors are advised to allow FDA adequate time to review IND changes prior to implementation to avoid a potential clinical hold.

3.7 Serial Numbering System



Overview of IND Maintenance and Tracking

Serial Numbering System

IND submissions are numbered consecutively starting from the initial IND.

- Initial IND: Serial 0000
- First Amendment: Serial 0001

Maintain records of all IND amendments, and document serial numbers for tracking purposes.

Notes:

Finally, the FDA utilizes an IND serial numbering system to track all submissions to the IND.

All IND submissions are numbered consecutively starting from the initial IND.

- The initial IND submission is designated as serial number 0000.
- The first amendment to the IND will be designated as serial number 0001.

All amendments, regardless of the amendment type, should be numbered consecutively in the order in which they are submitted.

It is important to maintain accurate records of all IND amendments and to document serial numbers for tracking purposes. The serial number should be referenced when communicating with the FDA about an IND submission. If a sponsor is uncertain or has questions about the serial number associated with an IND amendment, the FDA review division should be consulted for guidance.

3.8 Additional Information

Overview of IND Maintenance and Tracking



Additional Information



For more information on IND amendments and application reporting, please visit [FDA's website](#).

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Notes:

For more information on IND amendments and application reporting, please visit FDA's website by clicking on the provided link.

4. IND Annual Reports

4.1 IND Annual Reports




IND Annual Reports

Notes:

4.2 Learning Objectives

IND Annual Reports



- ✓ When an IND Annual Report Is Due
- ✓ Content Required for an Annual Report
- ✓ Annual Report with Multiple Protocols

Notes:

After completing this training module, the learner will understand the following:

- When an IND annual report is due;
- The content required for an annual report; and
- How to structure an annual report with multiple protocols that are run under one IND.

4.3 Annual Report Due Date

IND Annual Reports

Annual Report Due Date

Annual reports are required to be submitted within 60 days of the one year anniversary of the IND effective date.

IND Effective Date:

- 30 days after FDA receives the IND, unless placed on clinical hold
- Or on earlier notification by FDA that the study is safe to proceed

Example:

- Effective date: January 20, 2017
- Report due: March 21, 2018

Notes:

Annual reports are required to be submitted within 60 days of the one year anniversary of the IND effective date.

The IND effective date is 30 days after the FDA receives the IND application, unless the sponsor is notified by the FDA that a clinical hold has been placed on the IND. Or if the FDA notifies the sponsor prior to the end of the 30 day review period that the study is safe to proceed, then the date of this notification from the FDA is the IND effective date.

For example, if an IND went into effect on January 20, 2017, the first annual report would be due by March 21, 2018.

4.4 Content for an Annual Report



Notes:

The next several slides will describe the content required for an IND annual report.

We recommend following the template for annual reports available on our website and including all sections outlined. If any sections are not applicable, we recommend stating “Not Applicable” in the report rather than deleting those sections.

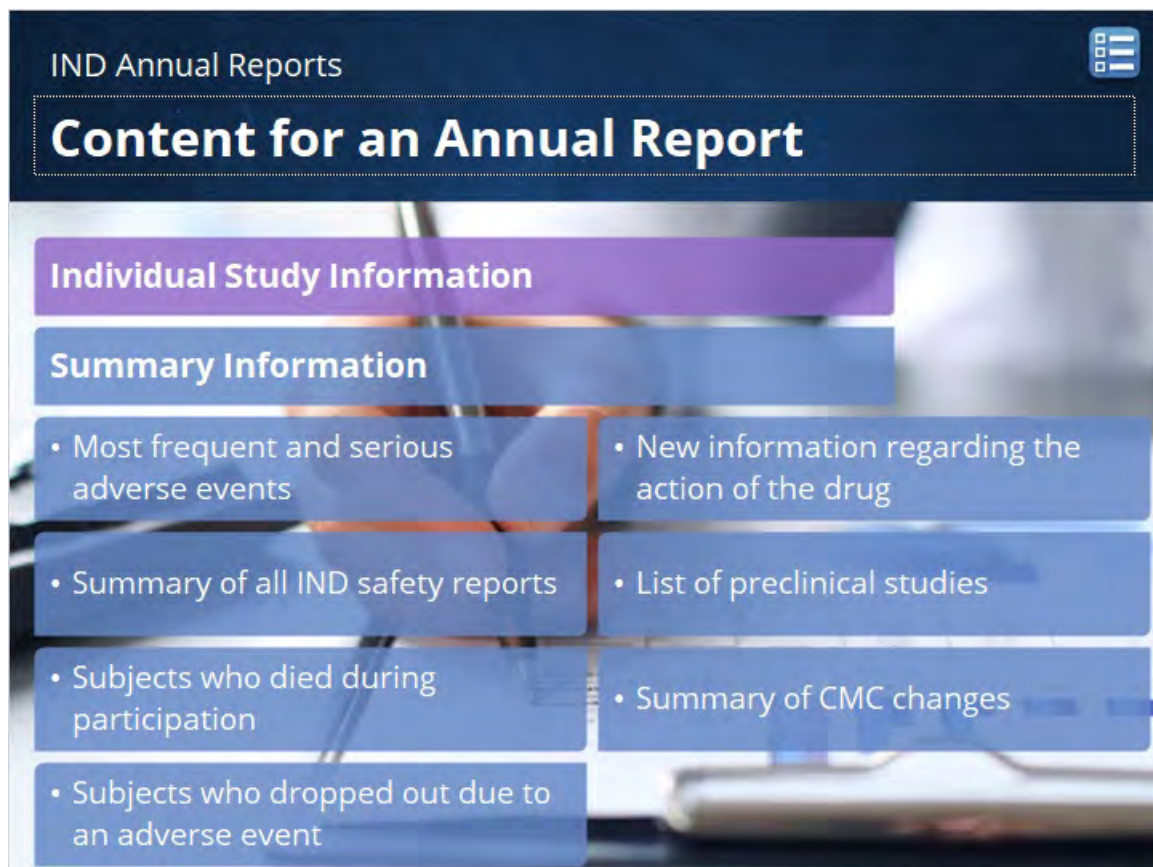
Begin the annual report with individual study information. This section is required to contain the following information for each study:

- First, provide basic information, which includes the study title with any appropriate identifiers such as a protocol number, the purpose of the study, a brief statement identifying the patient population, and a

statement as to whether the study has been completed.

- Next provide enrollment data, which includes the total number of subjects initially planned for inclusion in the study; the number of subjects entered into the study to date tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number of subjects who dropped out of the study for any reason.
- Lastly, if the study has been completed, or if interim results are known, a brief description of any available study results should be included.
-

4.5 Content for an Annual Report



Notes:

The next section of the annual report contains summary information.

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This section should include updates on all clinical and nonclinical investigations from the previous year. Provide information in the following format:

- A narrative or table showing the most frequent and serious adverse events by body system;
- A summary of all 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 any adverse event, whether or not thought to be drug related; and
- A brief description of any information pertinent to understanding the action of the drug, including, for example, information about dose response, information from controlled trials, and information about bioavailability.
- Also include a list of any preclinical studies (including animal studies) that were completed or in progress during the past year and a summary of the major preclinical findings.
- If any significant manufacturing or microbiological changes have been made during the past year, provide a summary of these changes.

For information on safety reports, please see the IND safety reporting training module.

4.6 Content for an Annual Report



Notes:

Next provide a description of the general investigational plan for the coming year to replace what was submitted the previous year.

4.7 Content for an Annual Report



Notes:

If the investigator's brochure has been revised, include a description of the revisions and provide a copy of the new brochure in the annual report. Note that sponsor-investigators are not required to submit an investigator's brochure. If this section is not applicable, state "Not Applicable" in the report.

4.8 Content for an Annual Report



Notes:

The annual report should also include a description of any protocol modifications made during the previous year that were not previously submitted to the IND in a protocol amendment.

For information on amending a protocol, please see the IND protocol amendments training module.

4.9 Content for an Annual Report



Notes:

The annual report should also provide a brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country.

The update on foreign marketing developments is generally only applicable to commercial sponsors. If this section is not applicable, state "Not Applicable" in the report.

4.10 Content for an Annual Report



Notes:

In the last section of the annual report, the sponsor can log any outstanding business with the FDA for which the sponsor requests or expects a reply, comment, or meeting.

4.11 Annual Reports for Multiple Protocols Under One IND

IND Annual Reports

Annual Reports for Multiple Protocols Under One IND

Information must be provided for each active protocol.

Duplicate the same sections below for each protocol:

- Individual Study Information
- Summary Information
- Update to General Investigational Plan
- Update to Investigator's Brochure
- Significant Protocol Updates
- Update on Foreign Marketing Developments
- Log of Outstanding Business

The slide features a dark blue background with a list of seven sections, each in a colored bar. A small icon of three vertical bars is in the top right corner.

Notes:

Please note that multiple protocols can be run under one IND if they are investigating the same product and a similar indication. For information on adding new protocols to an IND, please see the IND protocol amendments training module.

If an IND has multiple protocols, information must be provided for each active protocol in the IND annual report. To do this, repeat the sections outlined in this training module for each protocol being run under the IND.

4.12 Additional Information

IND Annual Reports

Additional Information



For more information on IND Annual Reports, please visit the [FDA's website](#).

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Notes:

For more information on IND annual reports, please visit FDA's website by clicking on the provided link.

5. IND Protocol Amendments

5.1 IND Protocol Amendments

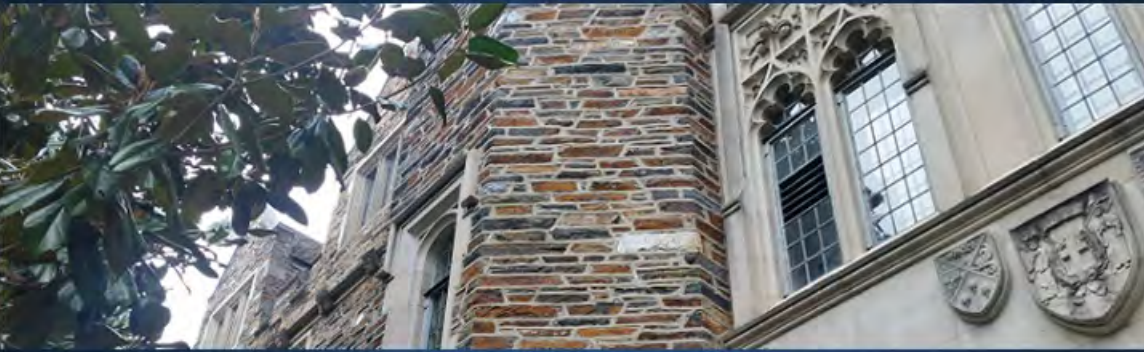


IND Protocol Amendments

Notes:

5.2 Learning Objectives

IND Protocol Amendments



- ✓ Definition of a Protocol Amendment
- ✓ Types of Protocol Amendments
- ✓ Implementing Protocol Amendments
- ✓ Content and Format of Protocol Amendments

Notes:

After completing this training module, the learner will understand the following:

- The definition of a protocol amendment;
- The types of protocol amendments;
- When a sponsor-investigator can implement changes identified in a protocol amendment; and
- The content and format of a protocol amendment.

5.3 What Is a Protocol Amendment?

IND Protocol Amendments

What Is a Protocol Amendment?

A protocol amendment is an IND submission that contains new or updated information concerning the clinical study protocol(s).



Amend the IND to ensure that the clinical investigation is conducted in accordance with the protocol(s).

Notes:

A protocol amendment is an IND submission that contains new or updated information concerning the clinical study protocol(s).

Once an IND is in effect, the sponsor is required to amend the IND to ensure that the clinical investigation is conducted in accordance with the protocol(s) being run under the IND.

5.4 Types of Protocol Amendments



Notes:

There are three types of protocol amendments commonly submitted by academic sponsor-investigators:

- Adding a new protocol to an IND is a new protocol amendment;
- Changing a previously submitted protocol is a change in protocol amendment; and
- Adding a new investigator to carry out a previously submitted protocol is a new investigator amendment.

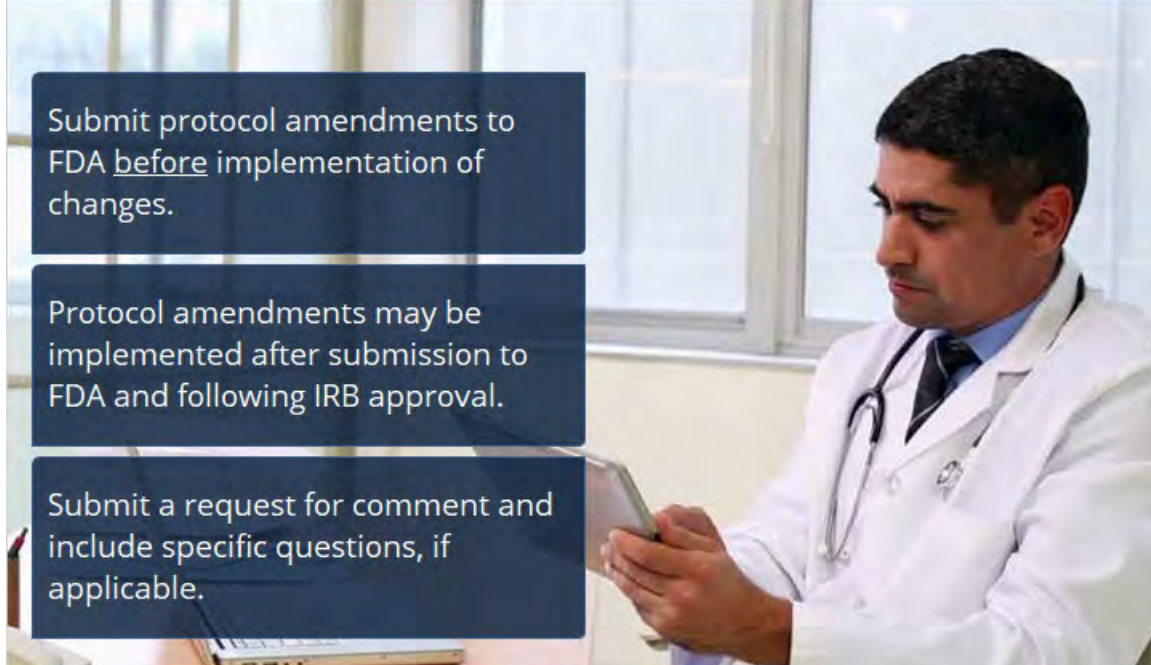
Protocol amendments may be grouped and submitted at 30-day intervals. When several submissions of new protocols or protocol changes are anticipated during a short period, the sponsor is encouraged to include these in a single submission.

•

5.5 Implementing Protocol Amendments

IND Protocol Amendments

Implementing Protocol Amendments



Submit protocol amendments to FDA before implementation of changes.

Protocol amendments may be implemented after submission to FDA and following IRB approval.

Submit a request for comment and include specific questions, if applicable.

Notes:

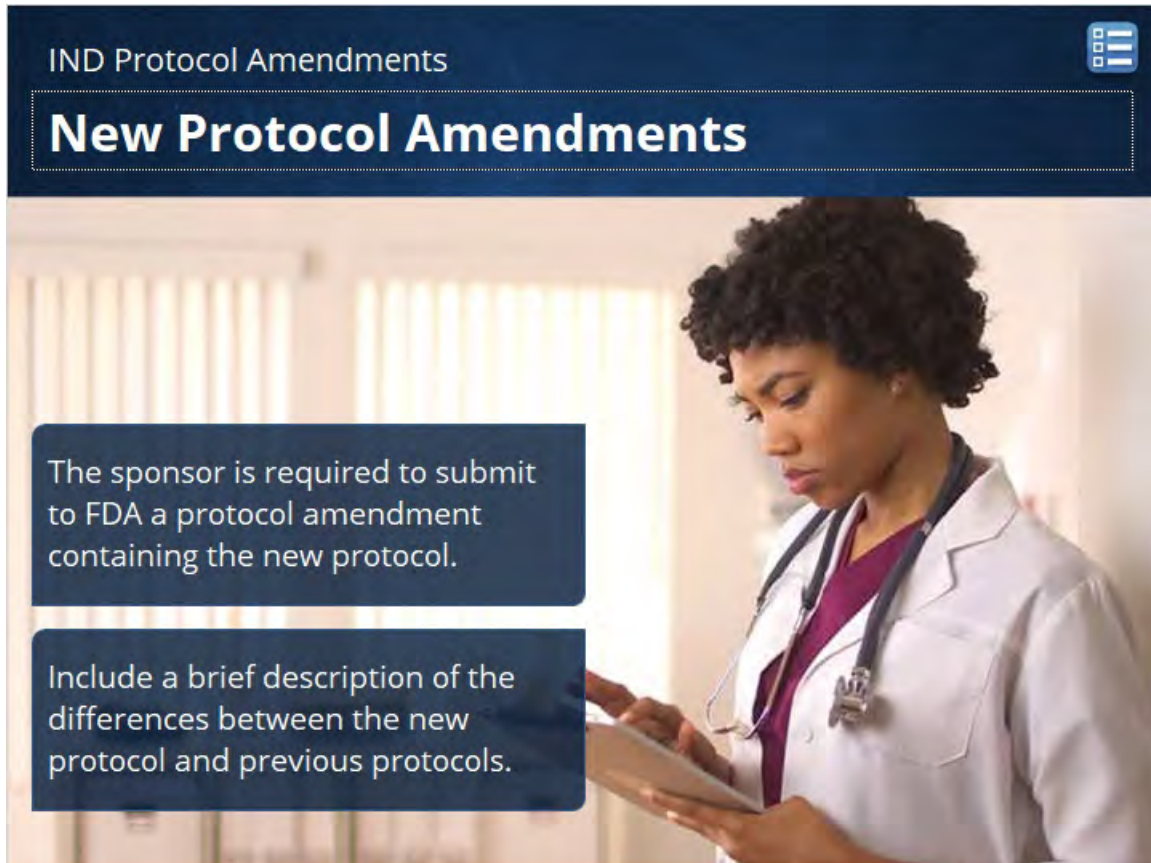
Sponsors are expected to submit protocol amendments for new protocols or changes to existing protocols to the FDA before implementation of the respective changes.

Protocol amendments may be implemented after submission to FDA and following review and approval by an Institutional Review Board, or IRB. The sponsor may comply with these two requirements in either order.

Protocol amendments are reviewed by FDA upon receipt. However, FDA will usually reply only if there are concerns around the submitted information. If the sponsor desires FDA to comment on a protocol

amendment, a request for comment and specific questions should be included in the cover letter of the submission.

5.6 New Protocol Amendments



IND Protocol Amendments

New Protocol Amendments

The sponsor is required to submit to FDA a protocol amendment containing the new protocol.

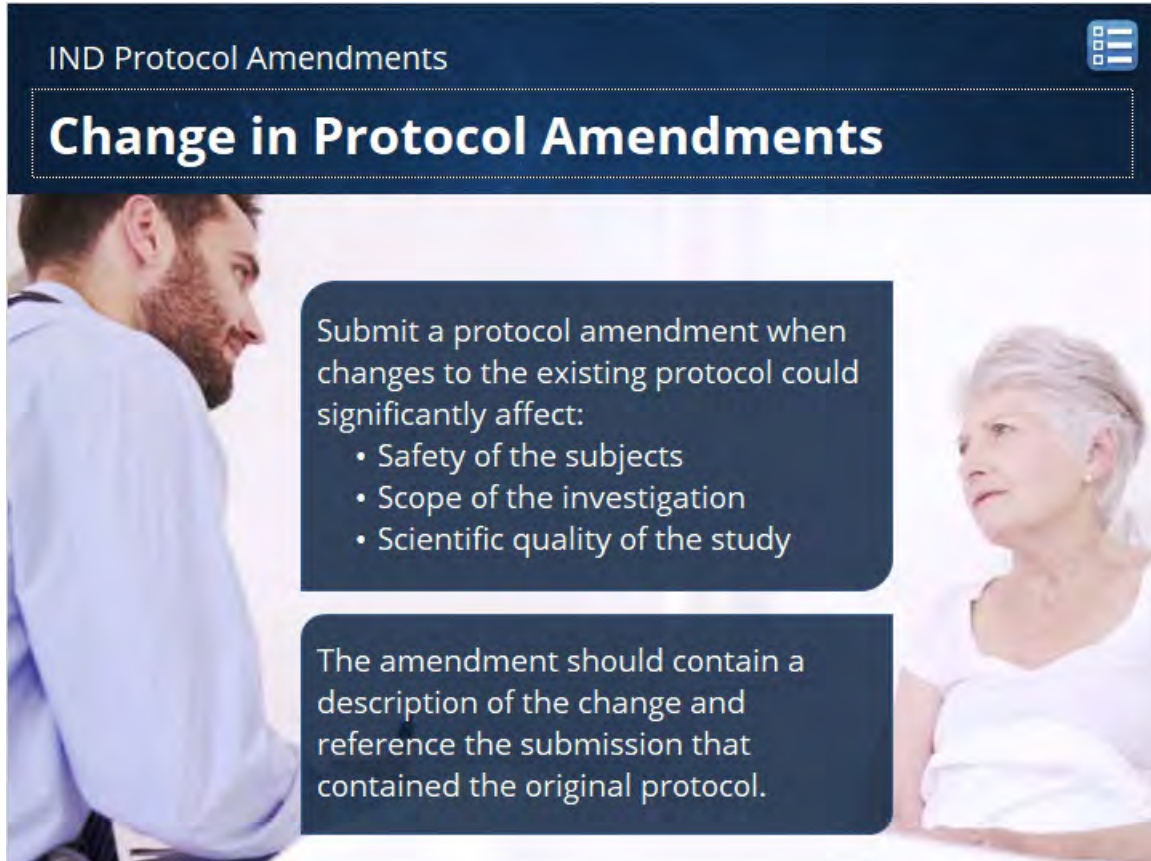
Include a brief description of the differences between the new protocol and previous protocols.

Notes:

An IND may contain multiple protocols if each protocol covers the same drug and a similar indication. If a sponsor intends to conduct a study that is not covered by a protocol already contained in the IND, the sponsor is required to submit to FDA a protocol amendment containing the new protocol.

Additionally, the amendment should include a brief description of clinically significant differences between the new protocol and previous protocols.

5.7 Change in Protocol Amendments



IND Protocol Amendments

Change in Protocol Amendments

Submit a protocol amendment when changes to the existing protocol could significantly affect:

- Safety of the subjects
- Scope of the investigation
- Scientific quality of the study

The amendment should contain a description of the change and reference the submission that contained the original protocol.

Notes:

The IND sponsor is expected to submit a protocol amendment when changes to the existing protocol could significantly affect the safety of subjects, the scope of the investigation, or the scientific quality of the study. For example, any increase in drug dosage beyond that described in the current protocol could significantly affect the safety of subjects, and thus should be submitted as a protocol amendment.

The amendment should contain a brief description of the change and should reference, by date and serial number, the submission that contained the original protocol.

5.8 Change in Protocol Amendments

IND Protocol Amendments

Change in Protocol Amendments




A protocol change intended to eliminate an apparent immediate hazard to human subjects may be implemented immediately, provided that FDA is subsequently notified by a change in protocol amendment and the reviewing IRB is also notified.

Notes:

Please note that a protocol change intended to eliminate an apparent immediate hazard to human subjects may be implemented immediately, provided that FDA is subsequently notified by a change in protocol amendment and the reviewing IRB is also notified.

5.9 New Investigator Protocol Amendments

IND Protocol Amendments



New Investigator Protocol Amendments

Submit a protocol amendment when a new investigator is added to carry out a protocol.

The amendment should include:

- Investigator's name, address, and qualifications;
- Name of each subinvestigator;
- Name and address of research facilities; and
- Name and address of the IRB

FDA should be notified within 30 days of the investigator being added to the study.

Notes:

The IND sponsor is required to submit a new investigator protocol amendment when a new investigator is added to carry out a previously submitted protocol.

The amendment should include the investigator's name, address, and qualifications to conduct the investigation. Additionally, include the name of each subinvestigator working under the supervision of the investigator, the name and address of research facilities to be used, and the name and address of the reviewing IRB.

FDA should be notified within 30 days of the investigator being added to the study.

5.10 Additional Information

IND Protocol Amendments

Additional Information



For more information on IND amendments and application reporting, please visit [FDA's website](#).

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Notes:

For more information on IND protocol amendments, please visit FDA's website by clicking on the provided link.

6. IND Safety Reporting

6.1 IND Safety Reporting




IND Safety Reporting

Notes:

6.2 Learning Objectives

IND Safety Reporting



- ✓ IND Safety Reporting Requirements
- ✓ Criteria for Reporting Adverse Events in an IND Safety Report
- ✓ IND Safety Reporting Timelines
- ✓ How to Prepare and Submit IND Safety Reports

Notes:

After completing this training module, the learner will understand the following:

- The IND safety reporting requirements;
- The criteria for reporting adverse events in an IND safety report;
- The IND safety reporting timelines; and
- How to prepare and submit IND safety reports.

6.3 Safety Reporting Requirements

IND Safety Reporting

Safety Reporting Requirements

Submit IND safety reports for the following:

- Serious and unexpected adverse events associated with the use of the study drug
- Any clinically important increase in the rate of occurrence of a serious adverse event associated with the study drug
- Findings from other studies that suggest a significant risk in humans
- Findings from animal or in vitro testing that suggest a significant risk in humans

Notes:

An IND sponsor is required to submit written IND safety reports to notify FDA and participating investigators of the following:

- Any serious and unexpected adverse event that is associated with the use of the study drug;
- Any clinically important increase in the rate of occurrence of a serious adverse event associated with the study drug over that listed in the protocol or investigator's brochure;
- Any findings from other studies that suggest a significant risk to humans exposed to the drug; and
- Any findings from animal or in vitro testing with the drug that suggest a significant risk in humans.

IND sponsors are responsible for promptly reviewing all available

information relevant to the safety of the drug to determine if the information meets the criteria for a written IND safety report. Other relevant information that does not meet the criteria for a written IND safety report should be submitted as an information amendment or included in the annual report.

To clarify which types of adverse events must be submitted in an IND safety report, we're next going to walk through the definitions of adverse events that are serious, unexpected, and associated with the use of the study drug.

6.4 What Is a Serious Adverse Event?



IND Safety Reporting

What Is a Serious Adverse Event?

- An adverse event occurring at any dose that results in any of the following outcomes:
 - Death
 - A life-threatening situation
 - Inpatient hospitalization or prolongation of existing hospitalization
 - A persistent or significant disability/incapacity
 - A congenital anomaly/birth defect
- Other important medical events that require medical or surgical intervention to prevent one of the outcomes listed above

Notes:

A “serious” adverse event is an adverse event occurring at any dose that, in the view of either the investigator or sponsor, results in any of

the following outcomes:

- Death;
- A life-threatening situation;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability or incapacity; or
- A congenital anomaly or birth defect.

Additionally, other important medical events may be considered serious when, based upon appropriate medical judgment, they jeopardize the subject and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic reactions requiring intensive treatment or the development of drug dependency or drug abuse.

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6.5 What Is an Unexpected Adverse Event?

IND Safety Reporting

What Is an Unexpected Adverse Event?



- Any adverse event not listed in the investigator's brochure (IB) or package insert or not listed at the specificity or severity that has been observed
- If an IB is not required or available, any adverse event not consistent with the risk information described in the current IND

Notes:

An “unexpected” adverse event is any adverse event that is not listed in the investigator’s brochure, or IB, or package insert or is not listed at the specificity or severity that has been observed.

If an IB is not required or available, an “unexpected” adverse event is any adverse event that is not consistent with the risk information described in the current IND.

For example, if the IB referred only to elevated hepatic enzymes or hepatitis, then hepatic *necrosis* would be unexpected (by virtue of greater severity).

Note that “unexpected” also refers to adverse events that are

mentioned in the investigator's brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

When new adverse event information is received, it is the sponsor's responsibility to determine whether the event is "unexpected" for IND safety reporting purposes.

6.6 What Is an Adverse Event Associated with the Use of the Drug?

IND Safety Reporting

What Is an Adverse Event Associated with the Use of the Drug?

- Any adverse event in which there is a reasonable possibility that the drug caused the event
- Reasonable possibility
 - Evidence suggests a causal relationship between the drug and the event.
- Evaluate available evidence and make a judgement about the likelihood that the drug caused the adverse event.

Notes:

An adverse event associated with the use of the drug is any adverse event in which there is a reasonable possibility that the drug caused the event. For the purposes of IND safety reporting, "reasonable

possibility” means there is evidence to suggest a causal relationship between the drug and the adverse event. The sponsor must evaluate the available evidence and make a judgement about the likelihood that the drug caused the adverse event.

6.7 Review of Safety Information

IND Safety Reporting

Review of Safety Information

An IND safety report should be submitted for any adverse event that is serious, unexpected, and associated with the use of the drug.

The sponsor is responsible for promptly reviewing all available adverse event information to determine if it meets the criteria for a written IND safety report.

Notes:

An IND safety report should be submitted for any adverse event that is serious, unexpected, and associated with the use of the drug as described on the previous slides.

The sponsor is responsible for promptly reviewing all available adverse event information to determine if it meets the criteria for a written IND safety report.

6.8 Safety Reporting Timelines

| IND Safety Reporting | |
|---|---|
| Safety Reporting Timelines | |
| Type of Event | FDA Timeline |
| Unexpected fatal or life-threatening adverse events | 7 calendar days |
| Unexpected serious adverse events (not fatal or life-threatening) | 15 calendar days |
| New findings that suggest significant risk to human subjects | 15 calendar days |
| Follow-up safety reports | As relevant information is available (15 calendar days) |

Notes:

If it is determined that an adverse event meets the criteria for a written IND safety report as described on the previous slides, the sponsor must submit the report to FDA within specific timelines based on the information being reported.

IND safety reports are categorized as 7-day reports, 15-day reports, and follow-up reports.

Safety reports for unexpected fatal or life-threatening adverse events must be reported as soon as possible, but no later than 7 calendar days after the sponsor's initial receipt of the information.

Unexpected serious adverse events that are not fatal or life-

threatening must be reported within 15 calendar days after the sponsor receives the information.

New findings that suggest significant risk to human subjects must also be reported within 15 calendar days.

Any relevant additional information obtained by the sponsor that pertains to a previously submitted IND safety report must be submitted as a follow-up safety report as soon as the information is available but no later than 15 calendar days after the sponsor receives the information. For example, if information on concomitant medications is obtained after the initial safety report is submitted, and such information is relevant to evaluating the adverse event, a sponsor must submit a follow-up safety report.

6.9 How to Prepare IND Safety Reports

IND Safety Reporting

How to Prepare IND Safety Reports

Submit via [Form FDA 3500A \(MedWatch\)](#) or in a narrative format.



Include a brief narrative describing the adverse event and any other relevant information.

Identify all safety reports previously submitted to the IND concerning similar adverse events.

Submit IND safety reports to all of the sponsor's INDs under which the drug is being administered.

Notes:


Safety reports are most often submitted to the IND by completing Form FDA 3500A (also known as the MedWatch form for mandatory reporting). To view Form 3500A, please click on the provided link. Alternatively, safety reports may be submitted in a narrative format.

The IND safety report should include a brief narrative describing the adverse event and any other relevant information.

Each IND safety report must also identify all safety reports previously submitted to the IND concerning similar adverse events and analyze the significance of the adverse event in light of previous, similar reports.

If the sponsor holds multiple INDs for the drug, the safety report should be submitted to all of the sponsor's INDs under which the drug is being administered.

6.10 Additional Information



IND Safety Reporting

Additional Information

For more information on IND safety reporting requirements, please see FDA's Guidance entitled "[Safety Reporting Requirements for INDs and BA/BE Studies.](#)"

For instructions on completing Form FDA 3500A, please see FDA's [General Instructions for Form FDA 3500A MedWatch \(for Mandatory Reporting\)](#).

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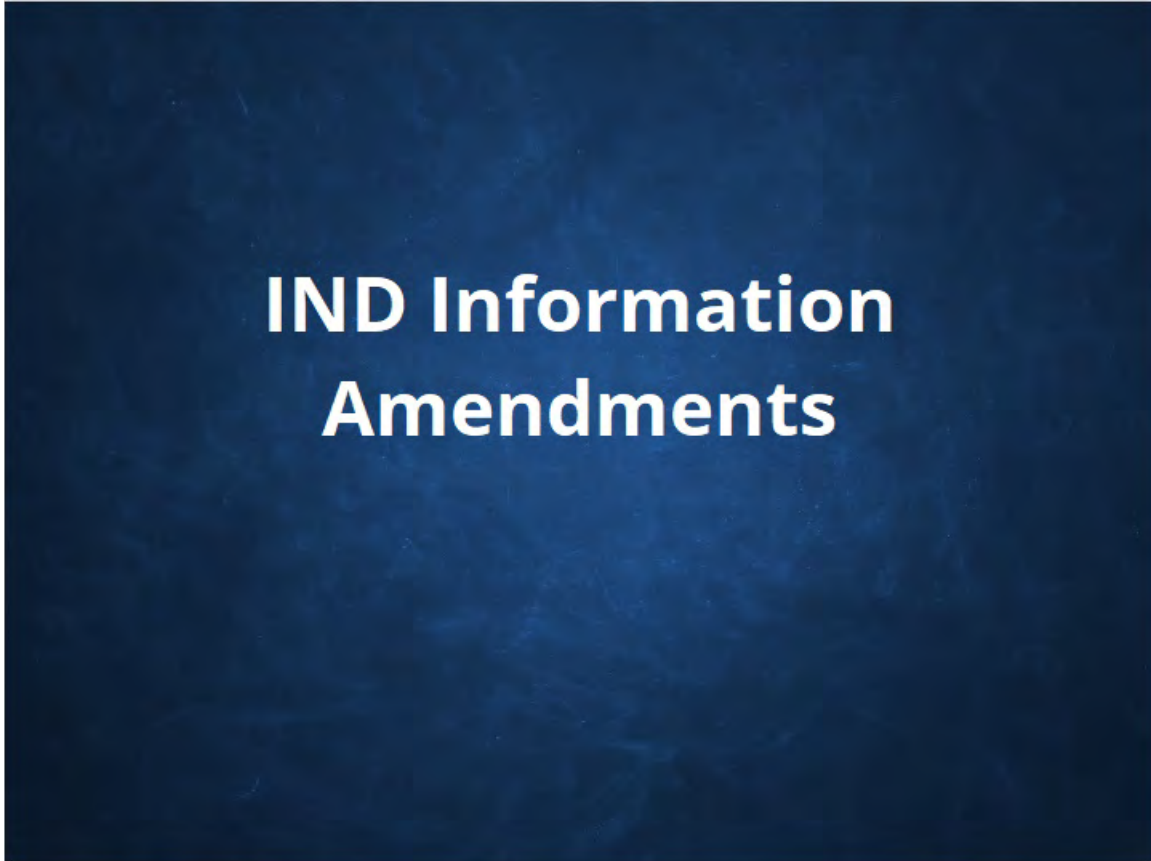
Notes:

For more information on IND safety reporting requirements, please see FDA's Guidance entitled "Safety Reporting Requirements for INDs and BA/BE Studies" by clicking on the provided link.

For instructions on completing the Form FDA 3500A, please see FDA's General Instructions for Form FDA 3500A MedWatch (for Mandatory reporting).

7. IND Information Amendments


7.1 IND Information Amendments



Notes:

7.2 Learning Objectives

IND Information Amendments



- ✓ Definition of an Information Amendment
- ✓ Types of Information Amendments
- ✓ Frequency of Information Amendments
- ✓ Content and Format of an Information Amendment

Notes:

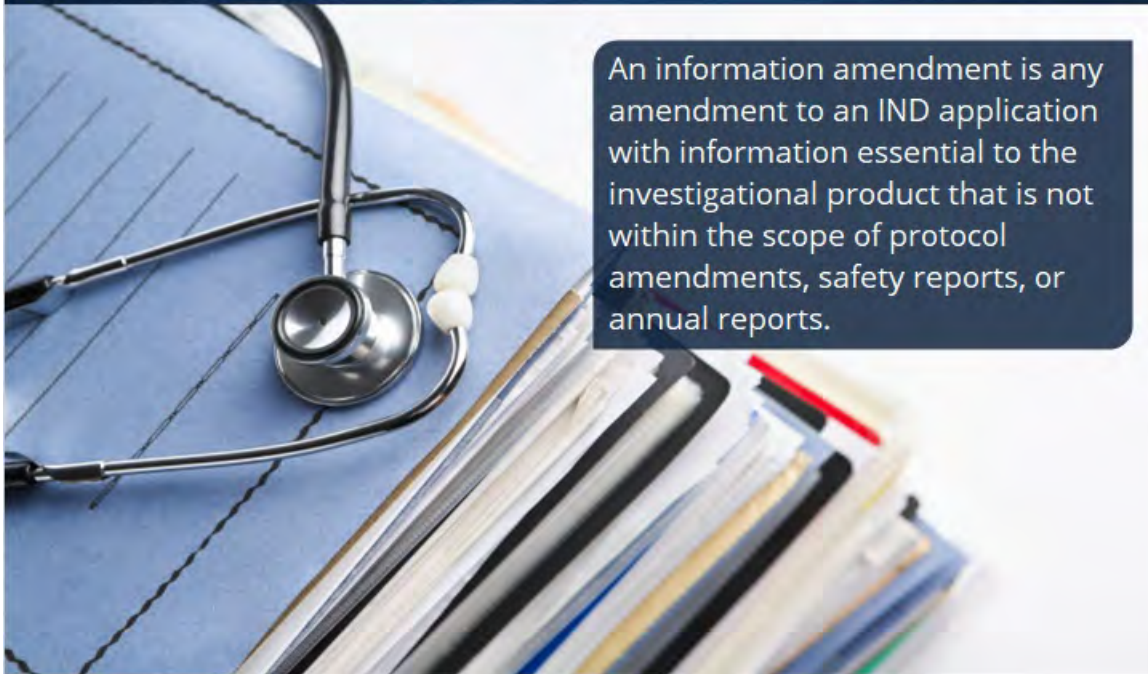
After completing this training module, the learner will understand the following:

- The definition of an information amendment;
- The types of information amendments;
- The frequency at which to submit information amendments; and
- The content and format of an information amendment.

7.3 What Is an Information Amendment?

IND Information Amendments

What Is an Information Amendment?

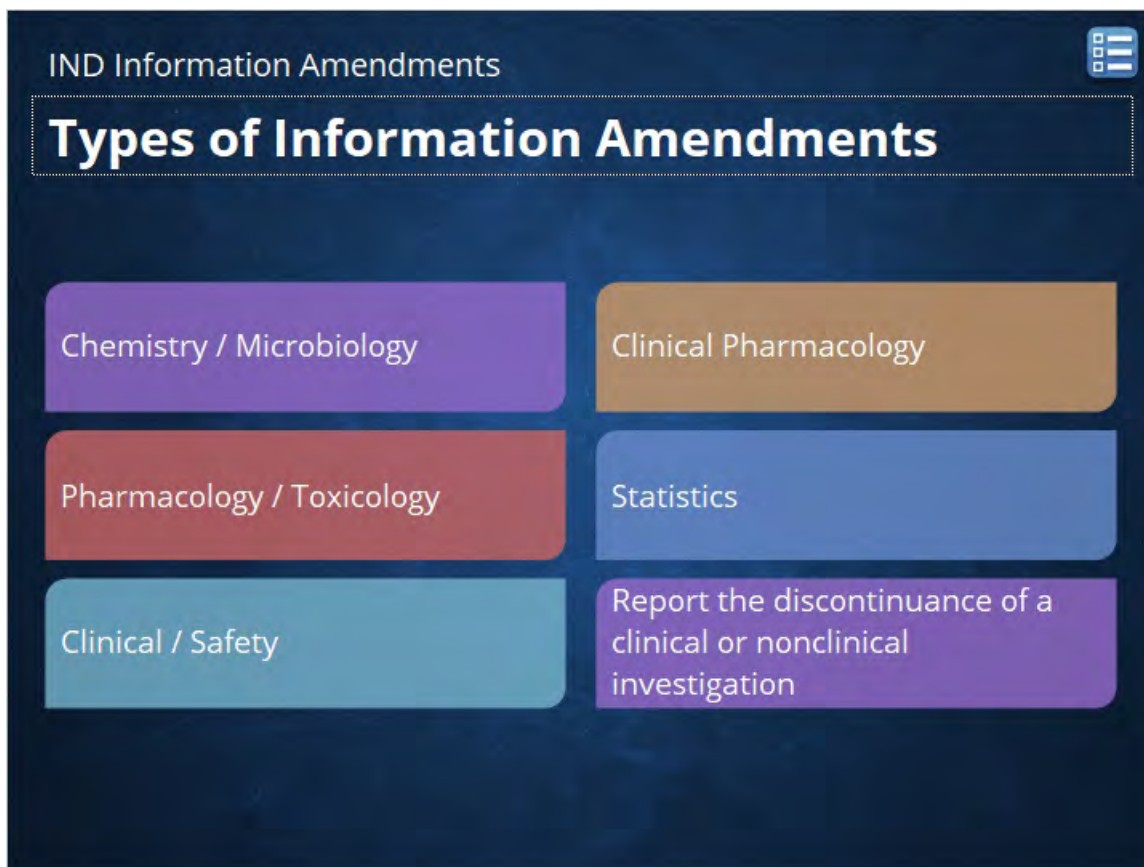


An information amendment is any amendment to an IND application with information essential to the investigational product that is not within the scope of protocol amendments, safety reports, or annual reports.

Notes:

An information amendment is any amendment to an IND application with information essential to the investigational product that is not within the scope of protocol amendments, safety reports, or annual reports.

7.4 Types of Information Amendments



Notes:

Information amendments are categorized based on the type of information included within the submission. FDA recognizes the following categories of information amendments: Chemistry/Microbiology, Pharmacology/Toxicology, Clinical/Safety, Clinical Pharmacology, and Statistics.

An information amendment can also be submitted to report the discontinuance of a clinical or nonclinical investigation.

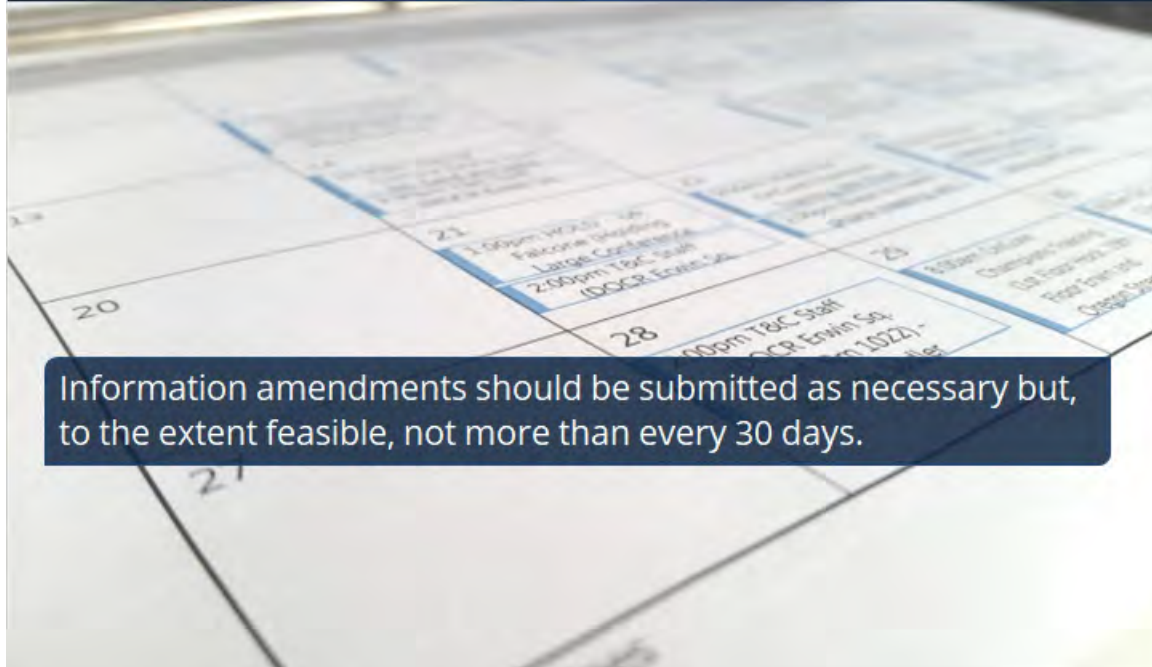
Information amendments often include new chemistry, toxicology, or other technical information relevant to the clinical studies being conducted under the IND. For example, if there is a change to product manufacturing once the IND is in effect, updated information about the manufacturing process should be provided in a Chemistry/Microbiology

information amendment.

7.5 Frequency of Information Amendments

IND Information Amendments

Frequency of Information Amendments




Information amendments should be submitted as necessary but, to the extent feasible, not more than every 30 days.

Notes:

Information amendments should be submitted as necessary but, to the extent feasible, not more than every 30 days.

7.6 Content and Format Requirements

IND Information Amendments



Content and Format Requirements

Any information amendment submitted under an IND application is required to bear prominent identification of its contents.

- *"Information Amendment: Pharmacology-Toxicology"*

Information amendments should contain the following:

- A statement of the nature and purpose of the amendment
- An organized submission of the data in a format appropriate for scientific review
- A request for FDA's comment and specific questions if the sponsor desires FDA feedback

Notes:

Per regulation, any information amendment submitted under an IND application is required to bear prominent identification of its contents in the cover letter. An example of the format for identifying your information amendment is provided here.

In addition, all information amendments should contain the following:

- A statement of the nature and purpose of the amendment;
- An organized submission of the data in a format appropriate for scientific review; and
- Lastly, a request for FDA's comment and specific questions should be included in the cover letter of the submission if the sponsor desires FDA feedback.

If the amendment includes a significant amount of information, a table of contents should also be provided.

7.7 Additional Information

IND Information Amendments

Additional Information

For more information on IND information amendments, please visit [FDA's website](#).

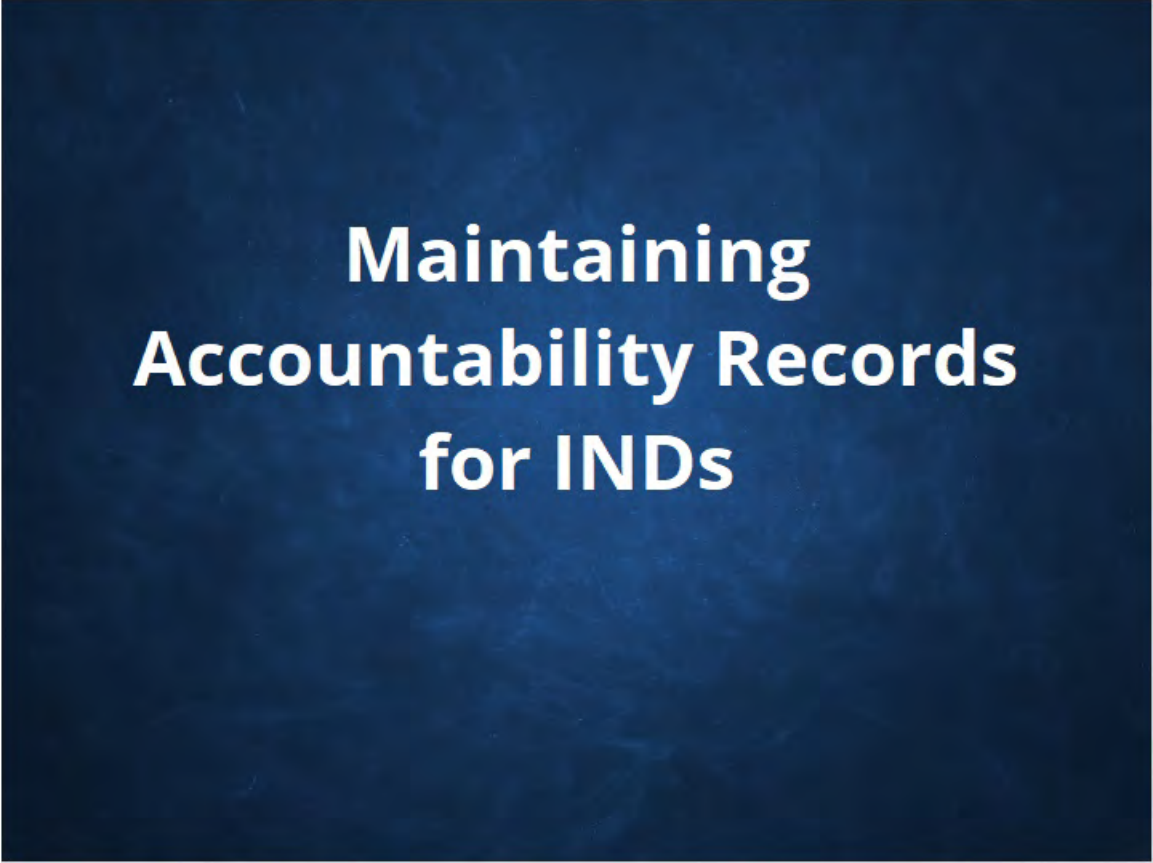
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Notes:

For more information on IND information amendments, please visit FDA's website by clicking on the provided link.

8. Maintaining Accountability Records for INDs

8.1 Maintaining Accountability Records for INDs



Maintaining Accountability Records for INDs

Notes:

8.2 Learning Objectives

Maintaining Accountability Records for INDs



- ✓ Records That Need to Be Maintained and Accounted for by the IND Sponsor
- ✓ Requirements for Any Unused Supply of the Investigational Drug
- ✓ Requirements for Controlled Drug Substances
- ✓ Length of Time Records Need to Be Retained


Notes:

After completing this training module, the learner will understand the following:

- The records that need to be maintained and accounted for by the IND sponsor;
- The requirements for any unused supply of the investigational drug;
- The requirements for controlled drug substances; and
- The length of time that records need to be retained.

8.3 Records That Must Be Maintained

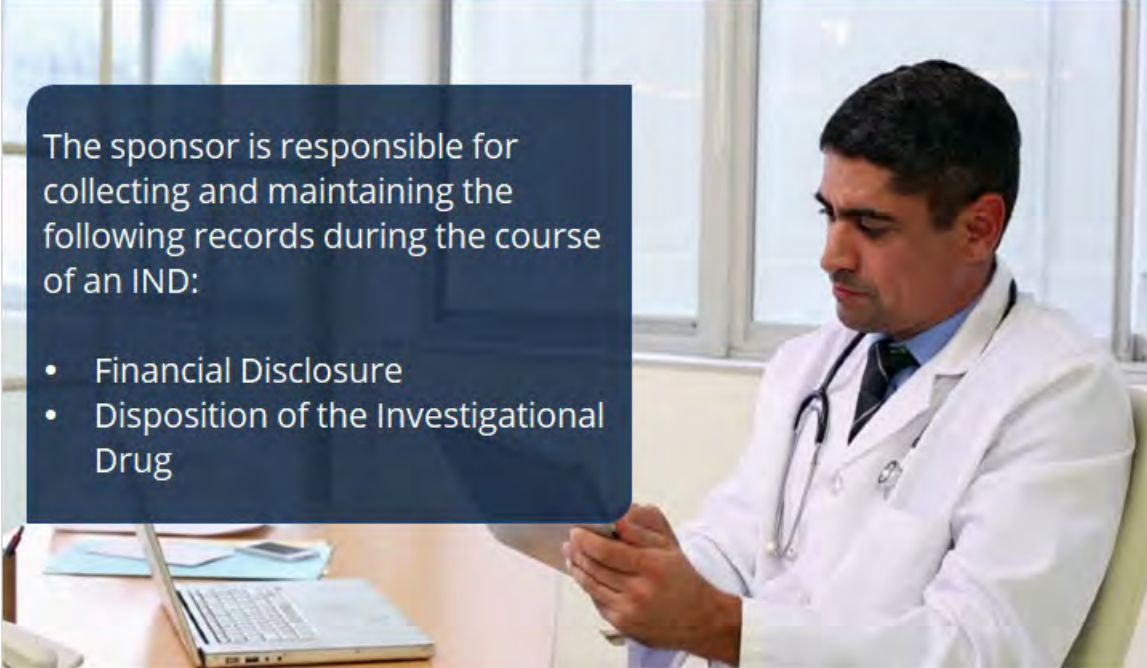
Maintaining Accountability Records for INDs



Records That Must Be Maintained

The sponsor is responsible for collecting and maintaining the following records during the course of an IND:

- Financial Disclosure
- Disposition of the Investigational Drug



Notes:

The sponsor is responsible for collecting and maintaining the following records during an IND:

- Financial disclosure and
- Disposition of the investigational drug

8.4 Recordkeeping: Financial Disclosure

Maintaining Accountability Records for INDs



Recordkeeping: Financial Disclosure

Maintain complete and accurate records concerning investigator financial interests:

- Any financial arrangement where the value of the compensation could be influenced by the outcome of the study
- Any significant payments of other sorts
- Any proprietary interest in the tested product
- Any significant equity interest in any sponsor

Notes:

The sponsor must maintain complete and accurate records of financial interests for all investigators directly involved in the conduct of a clinical study that may support a marketing application. Financial interests that should be captured and maintained by the sponsor include the following:

- Any financial arrangement where the value of the compensation to the investigator could be influenced by the outcome of the study;
- Any significant payments of other sorts from any sponsor, such as a grant to fund ongoing research or compensation in the form of equipment;
- Any proprietary interest in the tested product held by an investigator; and
- Any significant equity interest in any sponsor held by an investigator.

Financial disclosure forms are only required to be submitted to the FDA in a marketing application and are often not applicable to sponsor-investigator initiated studies. Please see the training module on financial disclosure to learn more.

8.5 Recordkeeping: Disposition of the Investigational Drug

Maintaining Accountability Records for INDs

Recordkeeping: Disposition of the Investigational Drug

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

These records are required to include, the name of the investigator to whom the drug is shipped, and the date, quantity, batch or code mark of each shipment.

Notes:

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

These records are 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.

8.6 Disposition of Unused Investigational Drugs

Maintaining Accountability Records for INDs



Disposition of Unused Investigational Drugs



Assure the return of all unused supplies of the drug.

May authorize alternative disposition of unused supplies.

Notes:

The sponsor must assure the return of all unused supplies of the investigational drug from each individual investigator whose participation in the investigation is discontinued or terminated.

The sponsor may authorize alternative disposition of unused supplies of the investigational drug provided this alternative disposition does not expose humans to risks from the drug.

8.7 Handling Controlled Substances



Maintaining Accountability Records for INDs

Handling Controlled Substances

If the drug is listed in any schedule of the Controlled Substance Act:

- Records must be made available to the Drug Enforcement Administration if requested
- Take adequate precautions:
 - Store in a securely locked enclosure
 - Store in a location with limited access

Notes:

If an investigational drug is a substance listed in any schedule of the Controlled Substances Act, records concerning shipment, delivery, receipt, and disposition of the drug must be made available to the Drug Enforcement Administration of the U.S. Department of Justice for inspection and copying if requested.

In addition, the sponsor must assure that adequate precautions are taken to control access to the drug. This includes storing the drug in a securely locked enclosure and in a location with limited access to prevent theft.

8.8 Retaining Records

Maintaining Accountability Records for INDs

Retaining Records

Retain required records for:

- 2 years after a marketing application is approved for the drug
- Or 2 years after shipment and delivery of the drug is discontinued

The sponsor must allow FDA to have access to and copy and verify any records and reports relating to a clinical investigation.

Notes:

A sponsor must retain the required records and reports under an IND for:

- At least 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 notified.

FDA can at any time and without cause inspect the sponsor records to determine compliance with applicable IND regulations. The sponsor must allow FDA to have access to and copy and verify any records and reports relating to a clinical investigation conducted under an IND. Upon written request, the sponsor must submit requested records or reports, or copies of these documents, to FDA. If the sponsor becomes

aware that an investigator is failing to maintain or make available records or reports, the sponsor should discontinue shipments of the drug to that investigator.

8.9 Additional Information

Maintaining Accountability Records for INDs

Additional Information

For more information on maintaining accountability records, please see federal regulations found in 21 CFR 312.

- [312.57](#) - Recordkeeping and record retention
- [312.58](#) - Inspection of sponsor's records and reports
- [312.59](#) - Disposition of unused supply of investigational drug


[Return to the Main Menu](#)

Notes:

For more information on maintaining accountability records, please see federal regulations found in 21 CFR 312 by clicking on the provided links.

9. IND Monitoring and Multi Center Trials

9.1 IND Monitoring and Multi-Center Trials



IND Monitoring and Multi-Center Trials

Notes:

9.2 Learning Objectives

IND Monitoring and Multi-Center Trials



- ✓ Purpose of Monitoring a Clinical Investigation
- ✓ Sponsor Is Responsible for Monitoring the Investigation
- ✓ Risk-Based Approach for Monitoring
- ✓ Sponsor Requirements for Conducting a Multi-Center Trial

Notes:

After completing this training module, the learner will understand the following:

- The purpose of monitoring a clinical investigation;
- That the sponsor is responsible for monitoring the investigation;
- That FDA recommends a risk-based approach for monitoring; and
- Sponsor requirements for conducting a multi-center trial.

9.3 Monitoring



IND Monitoring and Multi-Center Trials

Monitoring

Monitoring is a quality control tool for determining whether study activities are being carried out as planned so that deficiencies can be identified and corrected.

Effective monitoring is critical for the protection of human subjects and the conduct of high quality investigations.

Calories
Heart rate
Blood sugar
Blood pressure

Notes:

All clinical investigations conducted under an IND should be monitored, including multi-center trials, single-center trials, and those conducted by sponsor-investigators.

Monitoring is a quality control tool for determining whether study activities are being carried out as planned so that deficiencies can be identified and corrected.

Effective monitoring is critical for the protection of human subjects and the conduct of high quality investigations.

9.4 Sponsor Responsibility for Monitoring

IND Monitoring and Multi-Center Trials

Sponsor Responsibility for Monitoring



The sponsor is responsible for monitoring the progress of all clinical investigations being conducted under the IND.

The sponsor should select individuals qualified by training and experience to monitor the progress of the investigation.

Notes:

The sponsor is responsible for monitoring the progress of all clinical investigations being conducted under the IND. However, the regulations do not specify how the sponsor is to conduct such monitoring.

If the sponsor chooses not to personally monitor the investigation, he or she should select individuals qualified by training and experience to monitor the progress of the investigation.

9.5 Risk-Based Approach to Monitoring

IND Monitoring and Multi-Center Trials

Risk-Based Approach to Monitoring

Develop a monitoring plan that is tailored to the specific data integrity and human subject protection risks of the investigation.

Prospectively identify critical data and processes that if inaccurate, not performed, or performed incorrectly, would threaten the protection of human subjects or the integrity of the study results.



Notes:

Since the regulations are not specific about how sponsors are to conduct monitoring, FDA recommends a risk-based approach that focuses on preventing or mitigating important and likely risks to data quality and to processes critical to ensure human subject protection. Thus the sponsor should develop a monitoring plan that is tailored to the specific data integrity and human subject protection risks of the investigation.

While developing a monitoring plan, sponsors should prospectively identify critical data and processes that if inaccurate, not performed, or performed incorrectly, would threaten the protection of human subjects or the integrity of the study results. Examples of critical data and processes that could be included in a monitoring plan include verification that informed consent was properly obtained and that administration of the investigational product was completed in

accordance with the protocol.

9.6 Monitoring Methods



Notes:

Monitoring can take place either at the site of the clinical investigation or at a remote centralized location. The sponsor should prospectively determine which method is appropriate for their study based on a risk assessment.

On-site monitoring is an in-person evaluation of the clinical investigation and is useful for identifying data entry errors and missing data in source records. On-site monitoring can also be used to assess investigator supervision, compliance with the protocol, and control of the investigational drug. On-site monitoring can therefore be particularly helpful early in a study, especially if the protocol is

complex and includes novel procedures with which investigators may be unfamiliar.

Centralized monitoring is a remote evaluation of the clinical investigation and relies on electronic systems for review of records and communication. Centralized monitoring allows for review of data in real time, and it also identifies higher risk sites that the sponsor may wish to target with on-site monitoring. FDA encourages use of centralized monitoring practices, where appropriate.

A combination of on-site and centralized monitoring can also be used. If sponsors intend to rely heavily on centralized monitoring practices, they are encouraged to include one or more on-site monitoring visits as part of the monitoring plan.

9.7 Monitoring Activities

IND Monitoring and Multi-Center Trials

Monitoring Activities



- Communication with the investigator and study site staff
- Review of the study site's processes, procedures, and records
- Verification of the accuracy of data submitted to the sponsor

Notes:

Once the monitoring plan is developed, the sponsor is responsible for ensuring that monitoring activities are conducted according to the plan. Monitoring activities include:

- Communication with the investigator and study site staff;
- Review of the study site's processes, procedures, and records; and
- Verification of the accuracy of data submitted to the sponsor.

If the monitor identifies any non-compliance, these findings should be evaluated to determine whether additional actions, such as training of the clinical investigator or site staff, are necessary to ensure human subject protection and data quality. If non-compliance is discovered at any site, the sponsor should promptly secure compliance or discontinue the study at that site.

9.8 Additional Information

IND Monitoring and Multi-Center Trials

Additional Information



For more information on monitoring, please see FDA's Guidance entitled ["Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring."](#)

Notes:

For more information on monitoring, please see FDA's Guidance entitled "Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring" by clicking on the provided link.

9.9 Requirements of IND Sponsors of Multi-Center Trials

The infographic is titled "IND Monitoring and Multi-Center Trials" and "Requirements of IND Sponsors of Multi-Center Trials". It lists five requirements for IND sponsors of multi-center trials, each in a colored box:

- Select qualified investigators and provide them with information to conduct the study.
- Collect financial disclosure information, if appropriate.
- Obtain the investigator's qualifications and a signed investigator statement.
- Obtain IRB approval letters from each site.
- Only ship the investigational product to participating investigators.

Notes:

A multi-center trial is a clinical investigation that is conducted at more than one site. Under the IND regulations, sponsors of multi-center trials are required to:

- Select qualified investigators and provide them with information required to conduct the study properly;
- Collect financial disclosure information, if appropriate;
- Obtain the investigator's qualifications and a signed investigator

statement;

- Obtain Institutional Review Board, or IRB, approval letters from each site; and
- Only ship the investigational product to participating investigators.

The sponsor may wish to obtain investigator's qualifications by requesting a CV from participating investigators. Additionally, Form FDA 1572 may be used to meet the requirement for a signed investigator statement.

9.10 Requirements of IND Sponsors of Multi-Center Trials

The infographic is titled "IND Monitoring and Multi-Center Trials" and "Requirements of IND Sponsors of Multi-Center Trials". It lists five requirements for IND sponsors of multi-center trials, each in a colored box:

- Review and evaluate safety and effectiveness data provided by investigators.
- Send IND safety reports to the IND and to each site.
- Keep each investigator informed of new observations on the drug.
- Maintain current, complete, and accurate records.
- Monitor the investigation to ensure compliance.

Notes:

IND sponsors of multi-center trials are responsible for oversight of all

investigations and ensuring that all investigators are updated with information necessary to safely conduct the clinical investigation. The sponsor should promptly review and evaluate safety and effectiveness data provided by investigators. If the sponsor identifies any reportable safety events, the sponsor should report this information to the IND and to each site in an IND safety report. Each investigator must also submit IND safety reports to their IRB.

The sponsor should keep each participating investigator informed of new observations on the drug, particularly with respect to adverse events and safe use. Such information may be distributed to investigators by means of periodically revised investigator's brochures or other appropriate means.

It is also the sponsor's responsibility to maintain current, complete, and accurate records that pertain to each site. This includes up-to-date information on investigator qualifications and financial disclosure information, when applicable.

Lastly, the sponsor is responsible for continued oversight of all investigators to ensure that the study is conducted correctly and that all sites are following the protocol. The sponsor should monitor the investigation to ensure compliance.

9.11 Additional Information

IND Monitoring and Multi-Center Trials

Additional Information



For more information on multi-center trials, please see federal regulations found in [21 CFR 312 Subpart D-Responsibilities of Sponsors and Investigators](#).

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Notes:

For more information on sponsor responsibilities when conducting multi-center trials, please see federal regulations found in 21 CFR 312 Subpart D-Responsibilities of Sponsors and Investigators by clicking on the provided link.

10. Financial Disclosure

10.1 Financial Disclosure



Financial Disclosure

Notes:

10.2 Learning Objectives

Financial Disclosure



- ✓ Purpose of Financial Disclosure
- ✓ Definitions Pertaining to Financial Disclosure
- ✓ When Financial Disclosure Is Required
- ✓ Interests That Must Be Disclosed
- ✓ Responsible Parties

Notes:

After completing this training module, the learner will understand the following:

- The purpose of financial disclosure;
- The definitions pertaining to financial disclosure;
- When financial disclosure is required;
- The interests that must be disclosed; and
- The responsible parties for financial disclosure.

10.3 Purpose of Financial Disclosure

Financial Disclosure

Purpose of Financial Disclosure

Intended to eliminate bias and preserve the integrity of the data submitted in a marketing application

Information is used in the Agency's assessment of the reliability of the data.

Notes:


Financial disclosure is intended to eliminate bias and preserve the integrity of the data submitted in a marketing application for a drug, biologic or device.

The FDA may consider clinical studies inadequate, and the data inadequate, if appropriate steps have not been taken to minimize the risk of financial bias.

Financial disclosure information is submitted in a marketing application and is used in the Agency's assessment of the reliability of the data.

10.4 Financial Disclosure Definitions Per 21 CFR 54

Financial Disclosure



Financial Disclosure Definitions Per 21 CFR 54

Clinical Investigator – Individual directly involved with treatment or evaluation of research subjects, including spouse and each dependent child

Covered Clinical Study – Any study relied upon to establish that the product is effective, or where a single investigator makes a significant contribution to the demonstration of safety, for a marketing application

Sponsor - Any party supporting a particular study at the time it was carried out

Applicant - The party who submits a marketing application to FDA for approval and is responsible for submitting financial disclosure statements

Notes:

The definitions pertaining to financial disclosure are found in Title 21 of the Code of Federal Regulations Part 54.

For the purpose of financial disclosure:

- A clinical investigator is an individual directly involved with treatment or evaluation of research subjects. The term clinical investigator also includes the spouse and each dependent child of the investigator, but it does not include those who provide ancillary or intermittent care that do not make direct and significant contributions to the data.
- A covered clinical study is any study relied upon to establish that the product is effective, or where a single investigator makes a significant

contribution to the demonstration of safety, for a marketing application.

- The sponsor of a covered clinical study is any party supporting a particular study at the time it was carried out. For example, if one party designed and conducted the covered clinical study, a second party provided funding, and a third party provided the test product, there would be three sponsors of the covered clinical study.
- An applicant is the party who submits a marketing application to FDA for approval and is responsible for submitting financial disclosure statements.

Please note that the financial disclosure definitions of clinical investigator and sponsor are broader than those found in the IND and IDE regulations.

10.5 When Is Financial Disclosure Required?

Financial Disclosure

When Is Financial Disclosure Required?

Applicants who submit a marketing application are required to submit information concerning the compensation to, and financial interests and arrangements of, any clinical investigator conducting a covered clinical study.

- Any study relied upon to establish effectiveness
- Any study in which a single investigator makes a significant contribution to the demonstration of safety

Notes:

Applicants who submit a marketing application are required to submit information concerning the compensation to, and financial interests and arrangements of, any clinical investigator conducting a covered clinical study.


As a reminder, a covered clinical study is any study submitted in a marketing application that is relied upon to establish effectiveness of the product or any study in which a single investigator makes a significant contribution to the demonstration of safety.

Covered clinical studies, in general, do not include phase 1 tolerance studies or pharmacokinetic studies, most clinical pharmacology studies, large open safety studies conducted at multiple sites, and expanded access protocols. Non-commercial studies that are conducted for the

purpose of publication and will not be submitted as part of a marketing application are also generally not considered covered clinical studies.

Please note that the definition of covered clinical studies does not distinguish between foreign and domestic clinical sites.

10.6 Financial Disclosure Responsibilities

A graphic titled "Financial Disclosure Responsibilities" with a dark blue header. The background is a blurred image of a financial document. The graphic contains three main sections: 1. "Sponsor's responsibility to collect financial disclosure information" in a dark blue box. 2. "Each clinical investigator must provide sufficient and accurate financial information to the sponsor." followed by a bullet point: "• Commit to promptly update this information if any relevant changes occur during the course of the study and for one year following the completion of the study." in a dark blue box. 3. "Applicant's responsibility to report financial information to the FDA" in a dark blue box. A small icon of three vertical bars is in the top right corner of the header.

Financial Disclosure

Financial Disclosure Responsibilities

Sponsor's responsibility to collect financial disclosure information

Each clinical investigator must provide sufficient and accurate financial information to the sponsor.

- Commit to promptly update this information if any relevant changes occur during the course of the study and for one year following the completion of the study.

Applicant's responsibility to report financial information to the FDA

Notes:

It is the sponsor's responsibility to collect financial disclosure information from investigators for covered clinical studies that will be used for a marketing application.

Each clinical investigator must provide sufficient and accurate financial information to the sponsor and must commit to promptly update this

information if any relevant changes occur during the course of the study and for one year following the completion of the study.

It is the applicant's responsibility to report financial information to the FDA when a marketing application is submitted. The applicant must submit certification that no clinical investigators of covered clinical studies had financial interests with the sponsor, or the applicant must submit a disclosure statement that describes the nature of the investigator's financial interests and the steps taken to minimize bias.

10.7 Financial Interests That Must Be Disclosed

Financial Disclosure

Financial Interests That Must Be Disclosed

- Any compensation by any sponsor in which the value of compensation is affected by study outcome
- Any proprietary interest in the tested product
- Any equity interest in any sponsor of the covered clinical study whose value cannot be readily determined through reference to public prices
- Any equity interest in any sponsor of the covered clinical study if that sponsor is a publicly held company and the interest exceeds \$50,000
- Significant payments of other sorts that have a cumulative monetary value of \$25,000 or more made to the investigator or the investigator's institution

Notes:

The financial interests and arrangements that must be disclosed by each clinical investigator of a covered clinical study are as follows:

- Any compensation by any sponsor in which the value of

Training Modules on IND Sponsor and Investigator Responsibilities (No Quiz)

compensation is affected by study outcome,

- Any proprietary interest in the tested product,
- Any equity interest in any sponsor of the covered clinical study whose value cannot be readily determined through reference to public prices,
- Any equity interest in any sponsor of the covered clinical study if that sponsor is a publicly held company and the interest exceeds \$50,000, and
- Significant payments of other sorts that have a cumulative monetary value of \$25,000 or more made to the investigator or the investigator's institution.

If a clinical investigator or their spouse or dependent child is a full or part-time employee of a sponsor of the covered clinical study, financial disclosure is not required.

10.8 Additional Information

Financial Disclosure

Additional Information



For more information on financial disclosure, please see FDA's Guidance entitled ["Financial Disclosure by Clinical Investigators."](#)

Return to the Main Menu

Notes:

For more information on financial disclosure, please see FDA's Guidance entitled "Financial Disclosure by Clinical Investigators" by clicking on the provided link.

11. IND Investigator Responsibilities

11.1 IND Investigator Responsibilities



Notes:

11.2 Learning Objectives

IND Investigator Responsibilities



- ✓ Role of an IND Investigator
- ✓ General Responsibilities of an IND Investigator
- ✓ Specific Responsibilities of an IND Investigator

Notes:

After completing this training module, the learner will understand the following:

- The role of an IND investigator;
- The general responsibilities of an IND investigator; and
- The specific responsibilities of an IND investigator to control the investigational drug, maintain records, report to the IND sponsor, and assure IRB review.

11.3 Who Is an IND Investigator?

The infographic features a background image of a doctor in a white coat with a stethoscope. Overlaid on this are three dark blue boxes with white text. At the top, the title 'Who Is an IND Investigator?' is in a large white font. Below it, a paragraph defines an IND. The three boxes then list the roles and responsibilities of the IND Sponsor, IND Investigator, and IND Sponsor-Investigator.

IND Investigator Responsibilities

Who Is an IND Investigator?

An **IND** is a request to FDA for authorization to administer an investigational drug (or biologic) to humans.

| IND Sponsor | IND Investigator | IND Sponsor-Investigator |
|---|--|--|
| Initiates the clinical investigation | Conducts the clinical investigation | Initiates and conducts a clinical investigation |

Notes:

An IND is a request to the FDA for authorization to administer an investigational drug (or biologic) to humans. An investigational drug is one that is not lawfully marketed in the United States as a drug or if lawfully marketed, used in an off-label manner. In this context, the term “drug” also includes biological products.

The sponsor of an IND is the individual, company, academic institution, or other organization that takes responsibility for and initiates the clinical investigation. The sponsor submits the IND to the FDA, but the sponsor does not actually conduct the investigation - unless the sponsor is a sponsor-investigator.

The investigator is the individual who conducts the clinical investigation and under whose immediate direction a drug is

administered to a subject. In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. Other individual members of the team are known as subinvestigators.

If the same individual both initiates and conducts the investigation, that person is known as the sponsor-investigator. A sponsor-investigator takes responsibility for the investigation, and the drug is administered under his or her direction. Sponsor-investigators have additional responsibilities beyond the responsibilities of an investigator that are reviewed in this module.

11.4 General Responsibilities of IND Investigators

IND Investigator Responsibilities

General Responsibilities of IND Investigators

- Ensure that an investigation is conducted according to the signed investigator statement, investigational plan, and applicable regulations.
- Protect the rights, safety, and welfare of subjects.
- Obtain informed consent.

Notes:

Investigators have general responsibilities that must be fulfilled when

conducting a clinical study under an IND. Investigators must ensure that the clinical study is conducted according to the signed investigator statement, the investigational plan, and applicable regulations.

It is also the investigator's responsibility to protect the rights, safety and welfare of subjects and obtain informed consent for each subject. Note that there may be exceptions to the requirement to obtain informed consent in emergency situations.

11.5 Control of the Investigational Drug



IND Investigator Responsibilities

Control of the Investigational Drug

Administer the drug only to subjects under the investigator's personal supervision or under the supervision of a subinvestigator.

Do not supply the investigational drug to any person not authorized to receive it.

Notes:

The investigator must also maintain control of the investigational drug. To fulfill this responsibility, investigators must administer the drug only to subjects under their personal supervision or under the supervision of a subinvestigator.

Furthermore, the investigator should not supply the investigational drug to any person not authorized to receive it.

If the investigational drug is a controlled substance, the investigator must take adequate precautions, including storage of the investigational drug in a securely locked enclosure and in a location with limited access to prevent theft.

11.6 Investigator Record Keeping



Notes:

Investigators are responsible for retaining records associated with the disposition of the drug and subject case histories.

Investigators are required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator should return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug as instructed by the sponsor.

Investigators are also required to prepare and maintain adequate and

accurate case histories that record all observations and other data pertinent to the investigation on each individual enrolled in the investigation. Case histories include the case report forms and supporting data. Examples of supporting data that should be maintained are signed and dated consent forms, progress notes of the physician, the individual's hospital charts, and the nurses' notes. The case history for each individual should document that informed consent was obtained prior to participation in the investigation.

11.7 Investigator Record Retention

IND Investigator Responsibilities

Investigator Record Retention



Retain required records for:

- 2 years after a marketing application is approved for the drug and indication
- Or 2 years after the investigation is discontinued and FDA is notified

Notes:

Investigator records are required to be maintained:

- For two years after a marketing application is approved for the drug and indication for which it is being investigated;
- Or, if no application is to be filed or if the application is not approved, until two years after the investigation is discontinued and FDA is

notified.

Local and protocol-specific regulations regarding record retention may apply as well.

FDA can at any reasonable time and without cause inspect the investigator records to determine compliance with applicable IND regulations. The investigator must allow FDA to have access to and copy and verify any records and reports made by the investigator. The investigator is not required to disclose subject 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.

11.8 Investigator Reports



IND Investigator Responsibilities

Investigator Reports

- Progress reports
- Safety reports
- Final report
- Financial disclosure reports

Notes:

Investigators should prepare and submit to the sponsor the following

complete, accurate, and timely reports.

Progress reports on the conduct of the study should be submitted at regular intervals as determined by the sponsor but at least yearly.

Safety reports must be immediately submitted for any serious adverse event, whether or not considered drug related, and should include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are serious adverse events must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event. In that case, the investigator must immediately report the event to the sponsor. Non-serious adverse events must be reported to the sponsor according to the timetable specified in the protocol.

A final report must be provided shortly after completion of the investigator's participation in the investigation.

The investigator must also provide sufficient financial information as required by the sponsor. The investigator should promptly update this information if any relevant changes occur during the course of the investigation and for one year following the completion of the study. Please see the training module on financial disclosure to learn more.

11.9 Assurance of IRB Review



IND Investigator Responsibilities

Assurance of IRB Review

- Ensure IRB oversight.
- Promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others.
- Do not make any changes in the research without IRB approval.

Notes:

The investigator must ensure that the investigation has proper Institutional Review Board, or IRB, oversight. The IRB will be responsible for the initial and continuing review and approval of the investigation.

The investigator must also promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others.

Lastly, the investigator must not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

11.10 Additional Information

IND Investigator Responsibilities

Additional Information



For more information on investigator responsibilities, please see FDA's Guidance entitled ["Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects."](#)

[Return to the Main Menu](#)

Notes:

For more information on investigator responsibilities, please see FDA's Guidance entitled "Investigator Responsibilities - Protecting the Rights, Safety, and Welfare of Study Subjects" by clicking on the provided link.

12. Course Completion

12.1 Course Completion



Notes:

Congratulations!

You have completed the Training Modules on IND Sponsor and Investigator Responsibilities!

Click the Close Course button to close this course.

Click the Return to Main Menu button to return to the main menu and review any sections of this course.