SPONSOR-INVESTIGATOR TRAINING: MODULE 2

Sponsor Training and Investigator Responsibilities

IND/IDE Support Program

April 23, 2020

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OVERVIEW

- Sponsor Regulatory Obligations
- Investigator Regulatory Obligations
- Overlapping Regulatory Obligations of Sponsors and Investigators
- Summary: Required Reporting Documents

SPONSOR REGULATORY OBLIGATIONS

- Selecting and Informing Site Investigators
- Monitoring: Review of Ongoing Investigations
- Maintain the IND: IND Change Reporting and Progress/Status Reporting
- Drug Safety (IND Safety Reporting)
- IND Protocol(s) and Review
- Pharmacology and Toxicology
- Investigational Product Handling and Accountability

SELECTING AND INFORMING INVESTIGATORS

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SELECTING INVESTIGATORS

- Sponsors are responsible for selecting investigators qualified by training and experience and providing them with the information they need to conduct an investigation properly (21 CFR 312.50)
- Before permitting an investigator to begin participation in an investigation, the sponsor must obtain the following (21 CFR 312.53):
    - (1) A signed investigator statement (Form FDA-1572)
    - (2) Curriculum vitae or other statement of qualifications of the investigator showing the education, training, and experience that qualifies the investigator as an expert in the clinical investigation of the study drug for the use being studied.

INFORMING INVESTIGATORS

- Before the investigation begins, the sponsor should provide all relevant study materials to the investigators and should consider conducting a study protocol-dedicated training session for all key personnel at the site.
- The sponsor must continuously keep each participating investigator informed of updated study documents (protocols, investigator brochures, adverse event profiles, etc) as well as updated safety information.
  - When new information is available to the study team, or when an amendment is approved by the IRB, the information and updated documents should be distributed by email or by an in-person meeting with the study team

Additional references: 21 CFR 312.32; 21 CFR 312.23(a)(5)

MONITORING AND REVIEW OF ONGOING INVESTIGATIONS

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MONITORING: REVIEW OF ONGOING INVESTIGATIONS

- Sponsors are responsible for ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND (21 CFR 312.50).
- **Selecting Monitors**
  - A sponsor must select a monitor qualified by training and experience to monitor the progress of the investigation (21 CFR 312.53(d))
- **Review of Ongoing Investigations**
  - The sponsor must monitor the progress of all clinical investigations being conducted under its IND (21 CFR 312.56(a))
- **The ORC as Study Monitor**
  - The Office of Research Compliance (ORC) conducts regular institutional monitoring of clinical research. The ORC may also provide study monitoring as a service. If interested, pleas reach out to the Office of Research Compliance at ORC@email.chop.edu.

MONITORING: REVIEW OF ONGOING INVESTIGATIONS

- A sponsor who discovers that an investigator is not complying with the general investigational plan, or protocol, or the requirements of this part or other applicable parts must:
  - Promptly either secure compliance, or
  - Discontinue shipments of the investigational new drug to the investigator and end the investigator's participation in the investigation.
  - If the investigator's participation in the investigation is ended, the sponsor must require that the investigator dispose of or return the investigational drug in accordance with the requirements of 312.59 and must notify FDA. (21 CFR 312.56)

MONITORING: REVIEW OF ONGOING INVESTIGATIONS

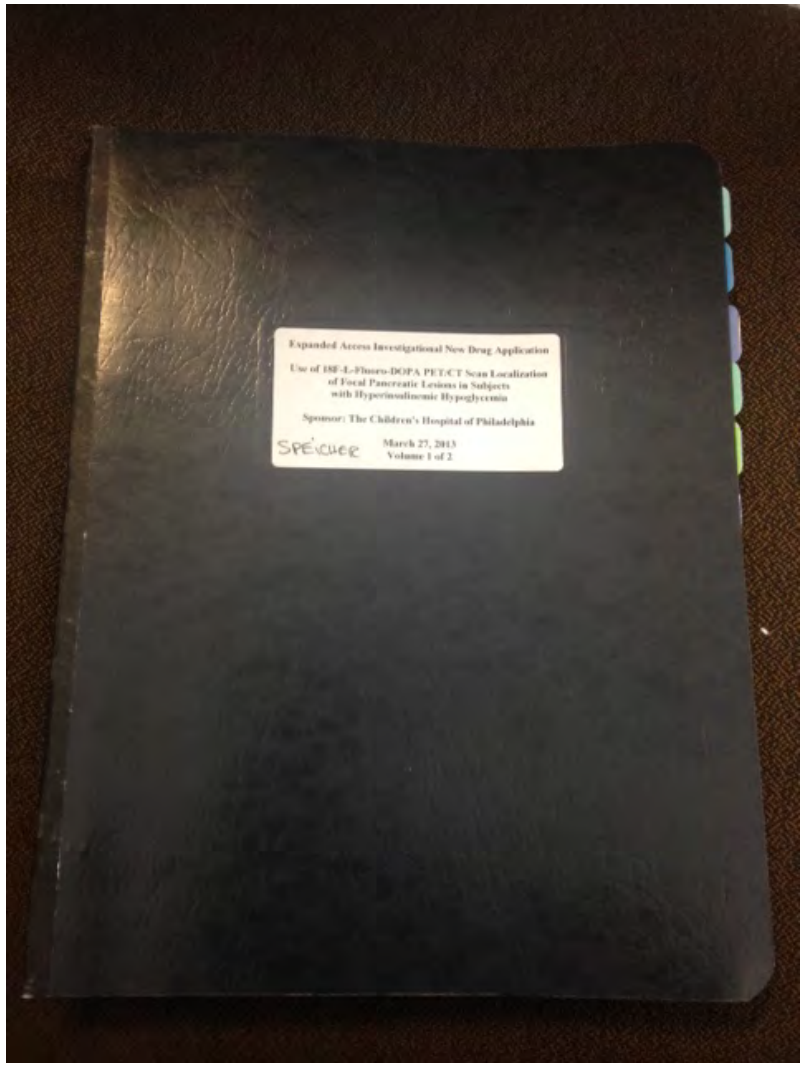
- The sponsor must review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator.
  - The sponsors must make such reports to FDA regarding information relevant to the safety of the drug as are required under 312.32.
  - The sponsor must make annual reports on the progress of the investigation in accordance with 312.33. (21 CFR 312.56)

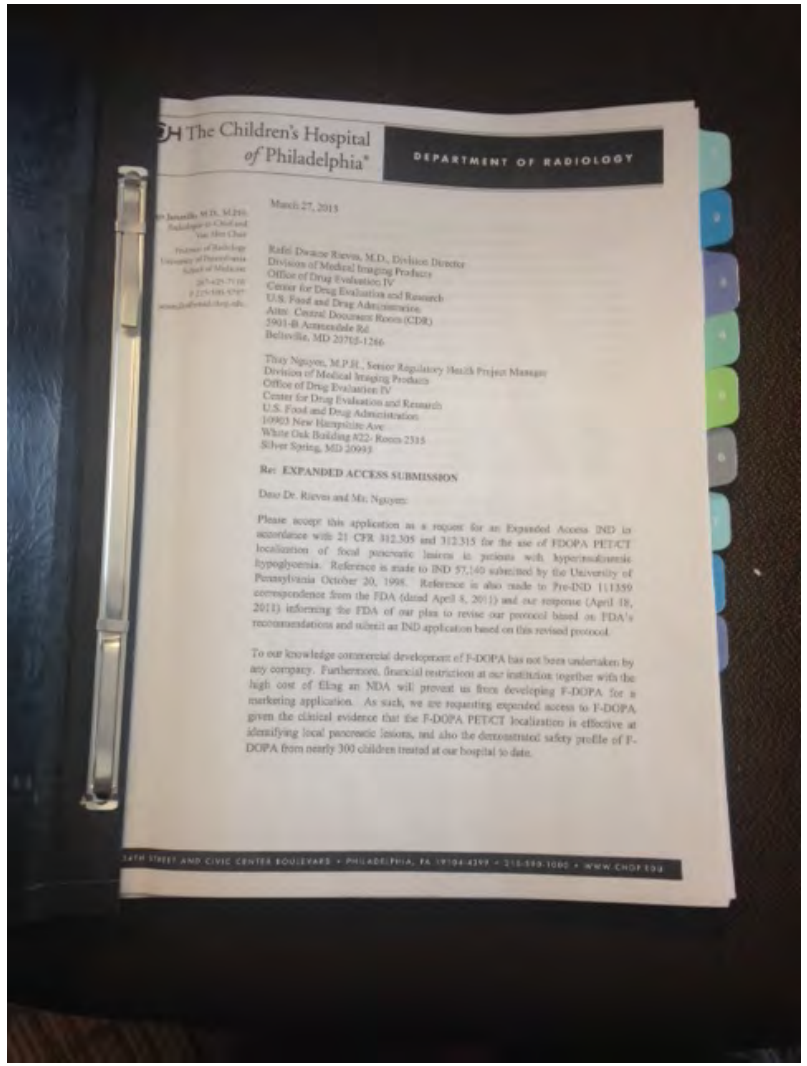
MAINTAIN THE IND

MAINTAIN THE IND: REPORTING

- Anything submitted to the FDA in the initial application must be maintained and reported to the FDA if any changes are made. These can be submitted as protocol amendments or information amendments.
- Protocol and information amendments could result from changes to any of the following sections of the IND application:
  - FDA Form 1572: Investigator Agreement
  - Protocol
  - Investigator's Brochure
  - Chemistry, Manufacturing, and Control Information
  - Pharmacology and Toxicology Information
  - Previous human experience with the investigational drug
  - Additional information

PREPARING AN FDA SUBMISSION





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PREPARING AN FDA SUBMISSION:

- Submissions for drug studies are sent to the Center for Drug Evaluation and Research (CDER)
- Submissions for studies of biologics are sent to the Center for Biologics Evaluation and Research (CBER)
- Contents of submission:
  - Cover letter clearly indicating the type of submission
  - Form FDA 1571 is required with all correspondence
    - Note: with the exception of sINDs which may be opened with a Form FDA 3926
  - Table of contents listing all documents in the submission
  - Clean and tracked changes documents
  - Summary of changes (for updated protocols, Investigator's Brochures, etc.)

You may email with the FDA Regulatory Project Manager. CHOP email to FDA is secure.
Phone conversations with the FDA should always be followed by email to document correspondence.

FDA SUBMISSIONS TO CBER

- CBER (Center for Biologics Evaluation and Research) at the FDA has specific guidance that must be followed:
  - Bind each complete packet and separate sections using tabs
  - Number of copies: 1 original and 2 copies
  - Pagination: Beginning to end, not each section
  - Large submissions: Notify Regulatory Project Manager at the FDA
  - Electronic Media: Include a CD and clearly mark as “Electronic Media”

PROTOCOL AMENDMENTS

PROTOCOL AMENDMENTS

Types of FDA Protocol Amendments	Purpose of Submission	When should it be submitted to the FDA?	Special Considerations?
New Protocol	A Sponsor/Sponsor-Investigator would like to open another protocol under their open IND	Changes must be submitted to the FDA prior to being implemented.	
Change in Protocol	There are changes to a previously submitted protocol that need to be reported to the FDA.	Changes should be submitted to the FDA prior to being implemented.	This includes: -Phase 1 protocol changes that significantly affect subject safety -Phase 2 or 3 protocol changes that significantly affects subject safety, the scope of the investigation, or the scientific quality of the study
New Investigator	A new investigator is added to a previously submitted protocol.	Within 30 days of the investigator being added.	-When there are multiple submissions of this type, they can be reported in 30 day intervals

Note: A protocol change intended to eliminate hazard to subjects may be implemented immediately, and both FDA and IRB are notified.

PROTOCOL AMENDMENTS

- When several submissions of new protocols or protocol changes are anticipated during a short period, the sponsor is encouraged, to the extent feasible, to ***include these all in a single submission***.
- Amendments to the IND that contain new or revised protocols should:
  - Build logically on previous submissions
  - Be supported by additional information, and the rationale for the changes must be clearly explained
- New protocols under an IND may begin provided two conditions are met (in either order):
  1. The sponsor has submitted the protocol to FDA for its review and approval; and
  2. The protocol has been approved by the Institutional Review Board (IRB).

PROTOCOL AMENDMENT: *CONTENT AND FORMAT*

- A protocol amendment must *be clearly identified as such (i.e. "Protocol Amendment: New Protocol", "Protocol Amendment: Change in Protocol", or "Protocol Amendment: New Investigator"*).
- If the sponsor would like the FDA to comment on the submission, this should be requested in the submission, and the specific questions for the FDA should be clearly listed.

- **New protocol**
  - A copy of the new protocol and a brief description of the most clinically significant differences between it and previous protocols.
- **Change in protocol**
  - A brief description of the change and reference (date and number) to the submission that contained the updated protocol.
- **New investigator**
  - The investigator's name, qualifications to conduct the investigation, reference to the previously submitted protocol, and all additional information about the investigator's study as is required under 312.23(a)(6)(iii)(b).

INFORMATION AMENDMENTS

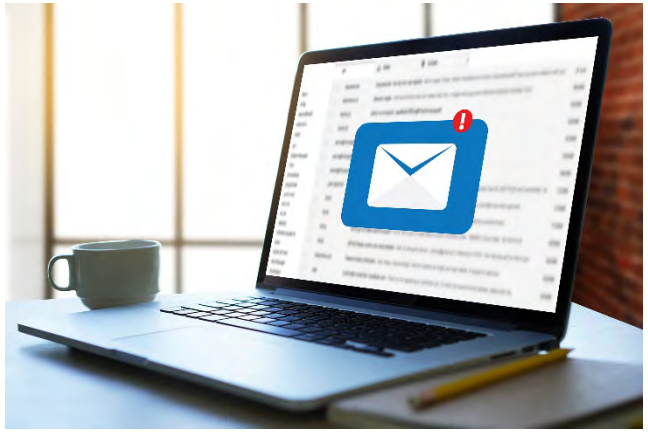
INFORMATION AMENDMENT

- An information amendment is used to report essential information of the IND that is not within the scope of a protocol amendment, IND safety reports, or annual report. Examples of information requiring an information amendment include:
  - New toxicology, chemistry, or other technical information related to safety
  - Changes to the chemistry, manufacturing and controls (CMC) of the study drug
  - A report regarding the discontinuance of a clinical investigation.

- Information amendments to the IND should be submitted as necessary but not more than every 30 days.

For additional information about 'Information Amendments', specifically related to changes to the CMC section or the Pharmacology and Toxicology Section, please see supplement.

IND SAFETY REPORTING



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IND SAFETY REPORTING

- It is the Sponsor's responsibility to review all information relevant to the safety of the study drug, which can be obtained from the manufacturer, from publications, from FDA drug alerts, from foreign or domestic sources, or from other investigations including animal studies.
- The sponsor is required to submit IND safety reports for suspected adverse events/reactions that are observed in the clinical study, at domestic or foreign study sites.
- What needs to be reported?
  - Unexpected fatal or life-threatening suspected adverse reaction reports
  - Unexpected and serious suspected adverse reaction
  - Increased rate of occurrence of serious suspected adverse reactions
  - Findings from other studies, animal, and in-vitro testing that suggest a significant risk in humans exposed to the drug

DEFINITIONS

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related
Suspected Adverse Reaction	When there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event
Life-threatening adverse event or Life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It is not an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

DEFINITIONS (CONTD)

Term	Definition
Serious adverse event* or serious suspected adverse reaction	An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: • Death, a life-threatening adverse event, • inpatient hospitalization or prolongation of existing hospitalization, • a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, • or a congenital anomaly/birth defect. • Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Unexpected adverse event or unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered "unexpected" if: • It is not listed in the study documents (protocol, IB, consent, etc) or is not listed at the specificity or severity that has been observed; • "Unexpected," also refers to adverse events or suspected adverse reactions 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.

Protocol may include differing definitions of serious adverse event (look first at protocol)*

SPONSOR REVIEW OF SAFETY INFORMATION

The sponsor must promptly review all information:

- Relevant to the safety of the drug obtained from investigations
- Received by the sponsor from foreign or domestic sources, including:
  - Information derived from any clinical or epidemiological investigations,
  - Animal or in vitro studies,
  - Reports in the scientific literature,
  - Unpublished scientific papers,
  - Reports from foreign regulatory authorities and
  - Any reports of foreign commercial marketing experience (for drugs not approved in the US).

- Any information that suggests increased risk requires prompt reporting to the FDA and Investigators

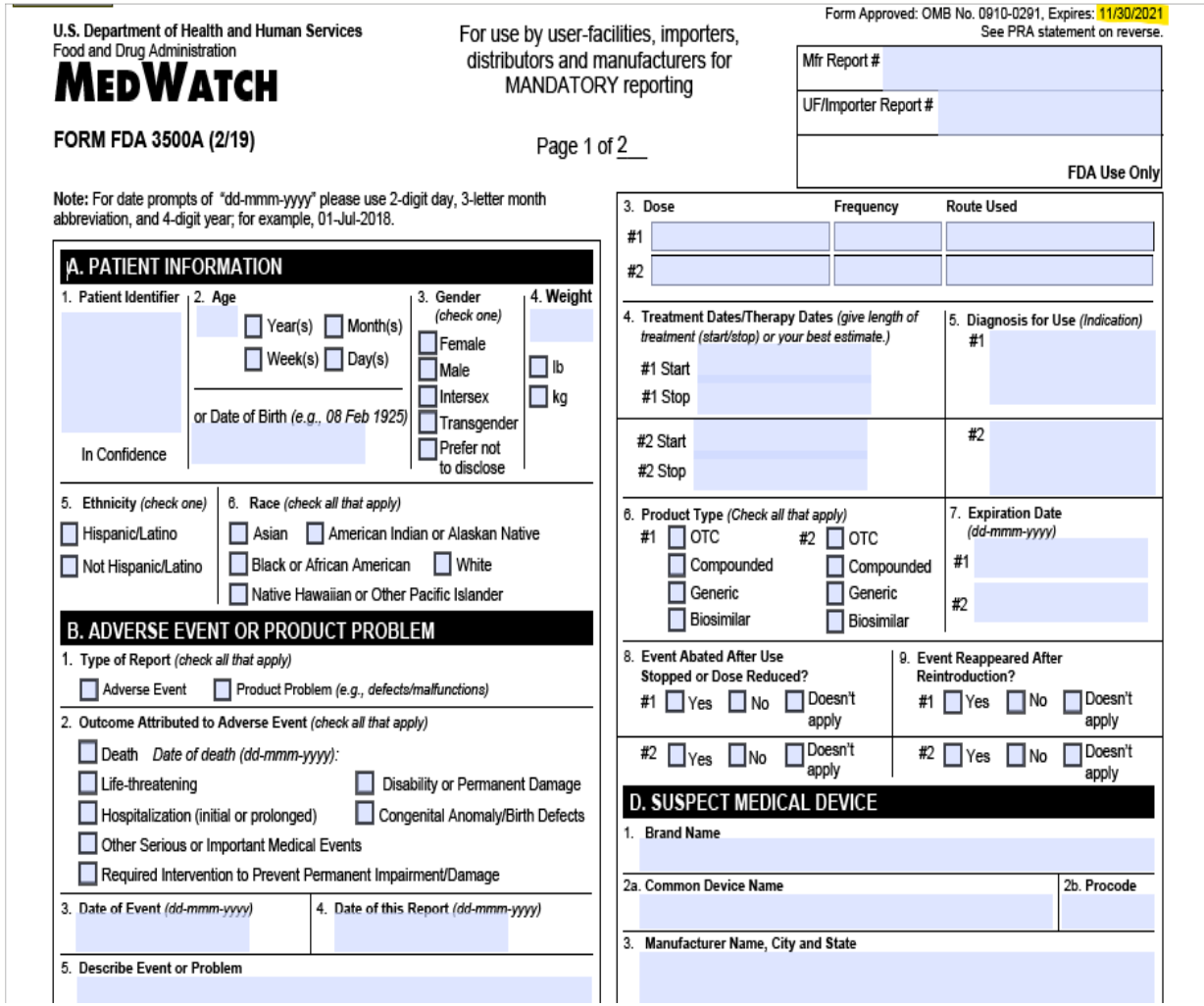
TYPES OF SAFETY REPORTS

Type of Event	Types of Safety Reports	FDA Reporting Timeframe
Unexpected fatal or life threatening adverse event or adverse reaction associated with the study drug	Telephone/Fax	No later than 7 days of receipt of information
Serious and Unexpected adverse events or adverse reactions	Written	No later than 15 days of receipt of information*
New/additional information relevant to the initial report is received (ex: new test results, change in clinical course, additional procedures, etc).	Follow-Up	In a timely manner

*Adverse Events or Adverse Reactions that were initially determined to not be reportable, but later found to be reportable should follow this timeline for reporting.

IND SAFETY REPORTING

- Safety Reports are sent to the FDA using the FDA Form 3500A (MedWatch)
- FDA may require a sponsor to submit IND safety reports in a format or at a frequency different than that required.
- The sponsor may also follow a different reporting format or frequency, which is usually proposed in the initial IND application.
- If the adverse event/adverse reaction does not meet criteria for expedited FDA reporting, it would get reported either as an informational amendment or included the annual report.



U.S. Department of Health and Human Services
Food and Drug Administration
MEDWATCH
FORM FDA 3500A (2/19)

For use by user-facilities, importers, distributors and manufacturers for MANDATORY reporting

Page 1 of 2

Form Approved: OMB No. 0910-0291, Expires: 11/30/2021
See PRA statement on reverse.

Mfr Report #
UF/Importer Report #
FDA Use Only

Note: For date prompts of "dd-mmm-yyyy" please use 2-digit day, 3-letter month abbreviation, and 4-digit year; for example, 01-Jul-2018.

A. PATIENT INFORMATION

1. Patient Identifier — In Confidence
2. Age — Year(s) Month(s) Week(s) Day(s) — or Date of Birth (e.g., 08 Feb 1925)
3. Gender (check one) — Female, Male, Intersex, Transgender, Prefer not to disclose
4. Weight — lb, kg
5. Ethnicity (check one) — Hispanic/Latino, Not Hispanic/Latino
6. Race (check all that apply) — Asian, American Indian or Alaskan Native, Black or African American, White, Native Hawaiian or Other Pacific Islander

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. Type of Report (check all that apply) — Adverse Event, Product Problem (e.g., defects/malfunctions)
2. Outcome Attributed to Adverse Event (check all that apply) — Death (Date of death (dd-mmm-yyyy):), Life-threatening, Disability or Permanent Damage, Hospitalization (initial or prolonged), Congenital Anomaly/Birth Defects, Other Serious or Important Medical Events, Required Intervention to Prevent Permanent Impairment/Damage
3. Date of Event (dd-mmm-yyyy)
4. Date of this Report (dd-mmm-yyyy)
5. Describe Event or Problem

3. Dose / Frequency / Route Used — #1, #2
4. Treatment Dates/Therapy Dates (give length of treatment (start/stop) or your best estimate.) — #1 Start, #1 Stop, #2 Start, #2 Stop
5. Diagnosis for Use (Indication) — #1, #2
6. Product Type (Check all that apply) — #1 OTC, Compounded, Generic, Biosimilar; #2 OTC, Compounded, Generic, Biosimilar
7. Expiration Date (dd-mmm-yyyy) — #1, #2
8. Event Abated After Use Stopped or Dose Reduced? — #1 Yes, No, Doesn't apply; #2 Yes, No, Doesn't apply
9. Event Reappeared After Reintroduction? — #1 Yes, No, Doesn't apply; #2 Yes, No, Doesn't apply

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2a. Common Device Name
2b. Procode
3. Manufacturer Name, City and State

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IND ANNUAL REPORTING

IND ANNUAL REPORT

- All INDs (including sINDs and eINDs) require annual reporting to the FDA.
- Annual Reports must be submitted within 60 days (+/-) of the Anniversary date that the IND went into effect.
- Sections Include:

    1) Summary of the IND and Reporting Period
    2) Summary Information
    3) Protocol Modifications
    4) Outstanding Business with Respect to the IND

Note: Modifications of the experimental design of Phase 1 studies that do not affect critical safety assessments are required to be reported to FDA only in the annual report. (312.23 IND Application)

IND ANNUAL/STATUS REPORTING

- The Annual Report needs to include the following information:
  - Title, protocol number, purpose, patient population, status of the study
  - The total number of subjects initially planned for inclusion in the study; the number 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 who dropped out of the study for any reason.
  - Summary information obtained during the previous year's clinical and nonclinical investigations, including if the study has been completed, or if interim results are known, a brief description of any available study results.

OTHER IND REPORTING FOR SPONSORS

INACTIVATION/REACTIVATION

- If no subjects are enrolled on the study for over two years, or the study is on clinical hold for longer than a year, the FDA may inactivate the IND.
- If the sponsor would like to reactivate the IND, a protocol amendment must be submitted. The FDA will respond within 30 days of receipt.

CHANGE IN SPONSOR

- To transfer ownership of an IND to another party, the holder needs to notify the FDA in writing. The letter should include the following:
  - Name of transferee
  - Address of transferee
  - Name of responsible official of transferee
  - Effective date of transfer
  - Signature of the transferring official
  - Typewritten name and title of the transferring official.
- The new holder should submit a letter of acceptance of the transfer and an update of the information contained in the IND, where appropriate.

WITHDRAWAL AND TERMINATION

- A Sponsor may choose to withdraw (or close out) an IND at any time, via a Close Out Report
  - All investigations end, protocol is also closed with the IRB
- The FDA may decide to terminate an IND
  - This may be due to deficiencies in the IND, how a study was conducted, or if the study has been in inactive status for greater than 5 years

- Templates available: Through the IND/IDE Support Program

INVESTIGATOR REGULATORY OBLIGATIONS

SUMMARY: REGULATORY OBLIGATIONS OF AN INVESTIGATOR

- Personally supervise investigation
- Protocol and regulatory compliance
- Protect rights, safety, welfare of subjects
- Obtain informed consent
- Obtain and maintain subject case histories

PERSONALLY SUPERVISE THE INVESTIGATION

- The investigator will:
  - personally conduct or supervise the study conduct at the site
  - ensure that individuals involved in the study conduct (ie on delegation of authority log) are informed about their obligations with regards to the study.
  - This includes (but is not limited to):
    - Developing procedures as needed
    - Conducting training as needed
    - Holding and documenting routine meetings

PROTOCOL & REGULATORY COMPLIANCE

- The Investigator must:
  - Adhere to the study protocol and ensure that the investigation at their site is conducted accordingly
  - Provide timely progress and final reports to the sponsor
  - Assure they have appropriate IRB approval and oversight
  - Promptly report to the IRB all changes in the research activity
  - Report all unanticipated problems involving risk to human subjects or others
  - Agree not to make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects

PROTECT RIGHTS, SAFETY, AND WELFARE

- An investigator is responsible for protecting the rights, safety, and welfare of study subjects
- This includes reading and understanding the information in the investigator's brochure, including the potential risks and side effects of the drug
- The investigator must also agree to report to the sponsor adverse experiences that occur in the course of the investigation(s)

OBTAIN INFORMED CONSENT

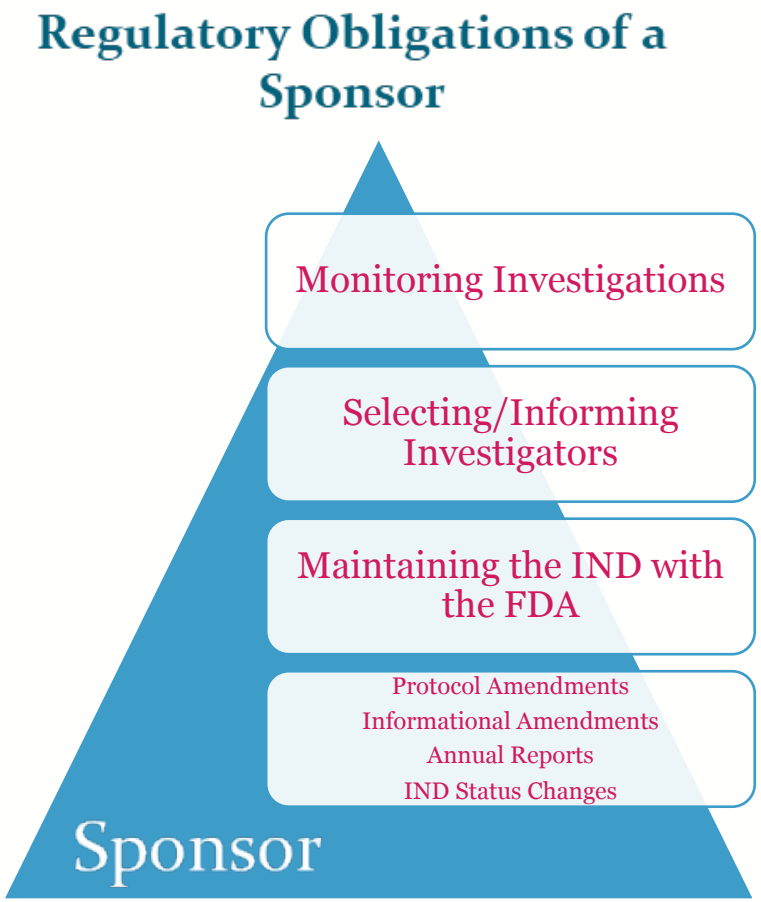
- An investigator is required to obtain the informed consent of each subject who is enrolled to the study in accordance with regulations.
- The investigator is responsible to inform any potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent are met.
- Document the informed consent process (conducted prior to participation in the study)
- Obtain both parental signatures, if required
- Provide a copy of the consent to the subject/family

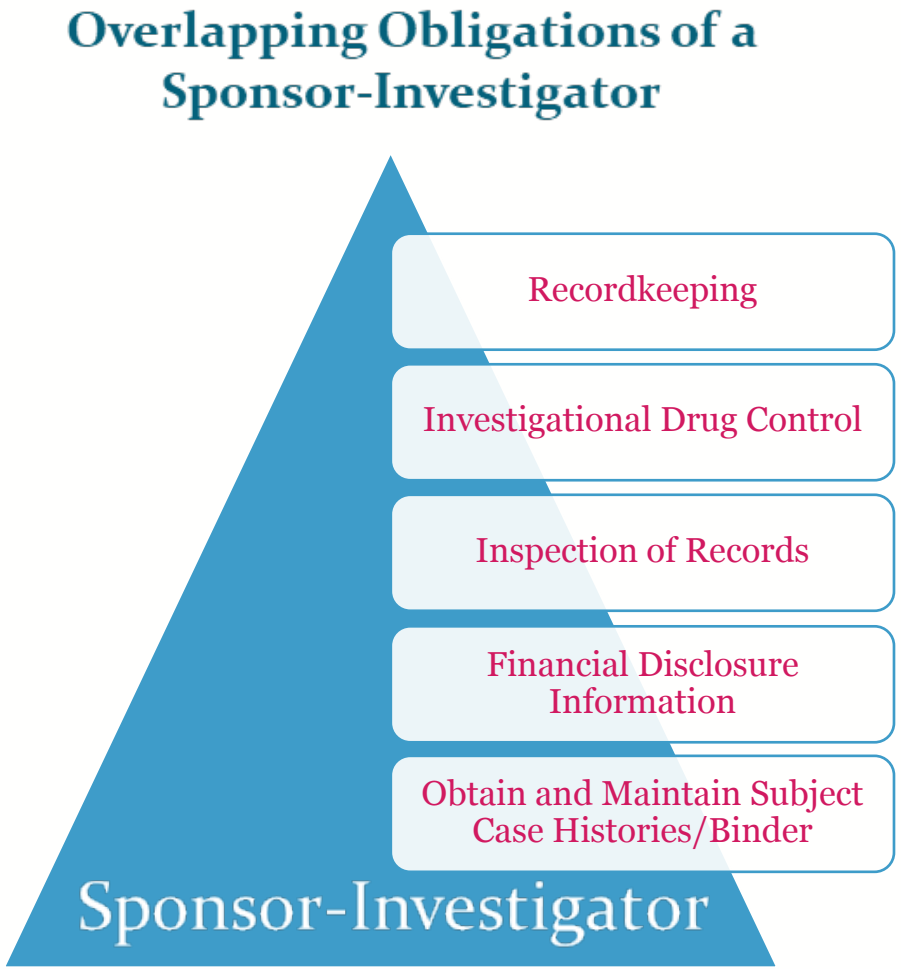
SUBJECT CASE HISTORIES

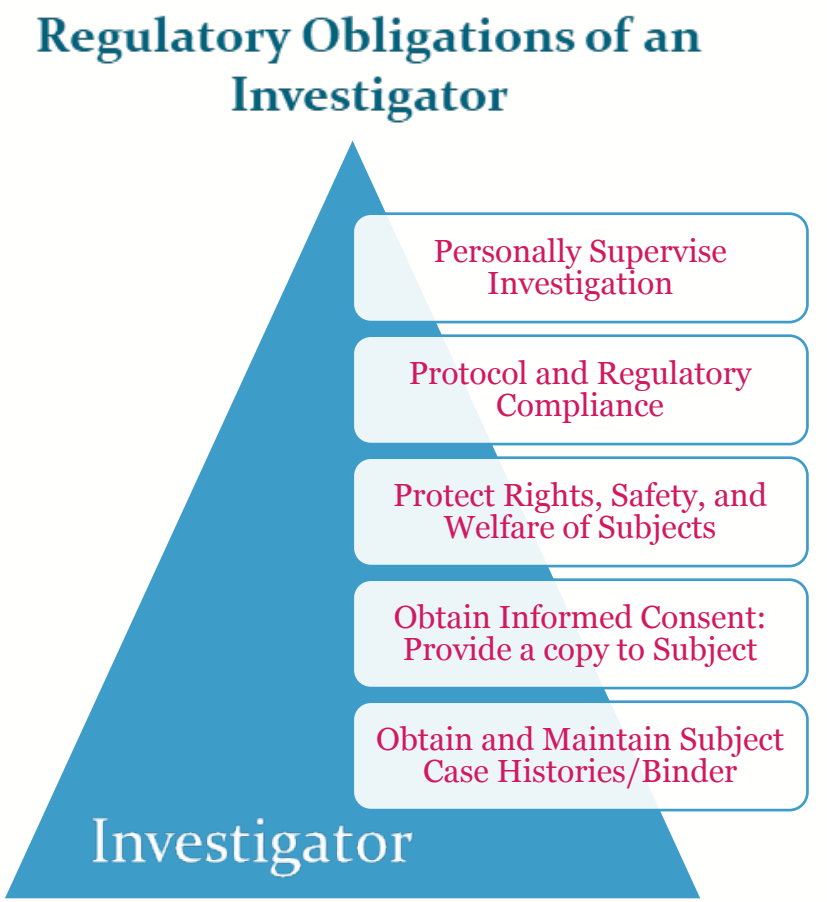
- An Investigator is responsible for maintaining case histories for all study participants.
- This includes (but is not limited to):
  - Signed and dated consent forms, including documentation of informed consent process conducted prior to study participation.
  - Medical records (EPIC charts, progress notes, etc)

OVERLAPPING SPONSOR AND INVESTIGATOR RESPONSIBILITIES

SUMMARY OF OBLIGATIONS







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SUMMARY: *SPONSOR & INVESTIGATOR*

- Recordkeeping
  - Regulatory
  - Investigational Product
  - Data collected under IND
- Investigational Drug Control/ Accountability
- Permit Inspection of records

RECORDKEEPING RESPONSIBILITIES

Recordkeeping Type	Sponsor Responsibility	Investigator Responsibility
Study Drug	Responsible for the receipt, shipment, and disposition of the study drug for all sites.	Responsible for the receipt and disposition of study drug, from when it gets on site to when it leaves the site.
Case Histories	The Sponsor maintains case histories. They keep the de-identified study data that is provided by the investigational sites.	The investigator is required to create and maintain study participant's case histories.
Record Retention	Retain records for all sites for 2 years (after marketing application for drug is approved) or for 2 years after shipment of study drug was discontinued and FDA was notified.	Same as Sponsor; CHOP record retention policy requires records be maintained for at least 10 years after subject turns 18 (for greater than minimal risk studies).
Financial Interest	Responsible to maintain records of financial interest (generally financial disclosure forms) for all investigators at all sites	Responsible to maintain records of financial interest of investigators at the site; also responsible to update sponsor within 1 year of study closure with any updates

INVESTIGATIONAL DRUG CONTROL

Sponsor:

- Ships study drug to investigators participating in the investigation.
- CHOP policy mandates use of the CHOP Investigational Drug Service for INDs
- The sponsor ensures that all unused study drug (from sites) is either returned or destroyed.

Investigator:

- Ensures the study drug is given only to study participants, and is administered under their supervision or by a delegated sub-investigator
- Additional storage protections are required under Sec. 312.69 if the study drug is a controlled substance in order to prevent theft

Title 21 CFR 312.61, 312.69

INSPECTION OF RECORDS: *SPONSOR*

FDA inspection:

- A sponsor must upon request from any properly authorized officer or employee of the Food and Drug Administration, at reasonable times, permit such officer or employee to have access to and copy and verify any records and reports relating to the study.
- Upon written request by FDA, the sponsor must submit the records or reports (or copies of them) to FDA. The sponsor must discontinue shipments of the drug to any investigator who has failed to maintain or make available records or reports of the investigation as required by this part.

CHOP Office of Research Compliance (ORC) inspection:

- ORC has the right to inspect sponsor records upon request

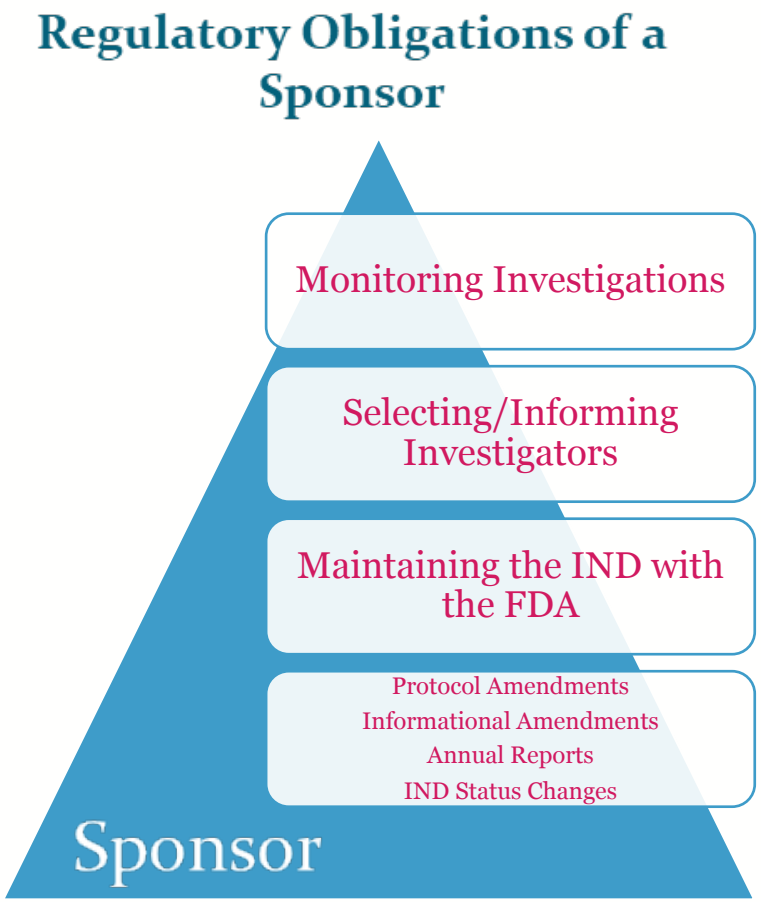
Controlled substances:

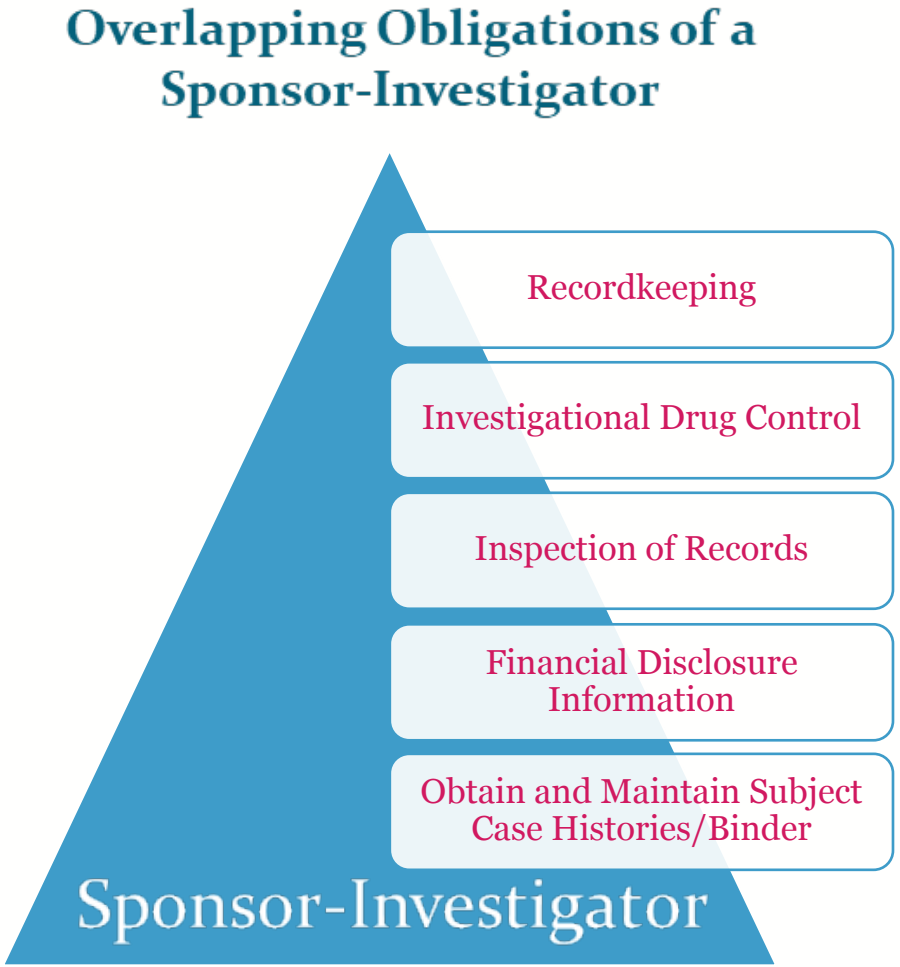
- If an investigational new drug is a substance listed in any schedule of the Controlled Substances Act, study drug records (shipment, delivery, receipt, disposition) must be made available to a DEA inspector.

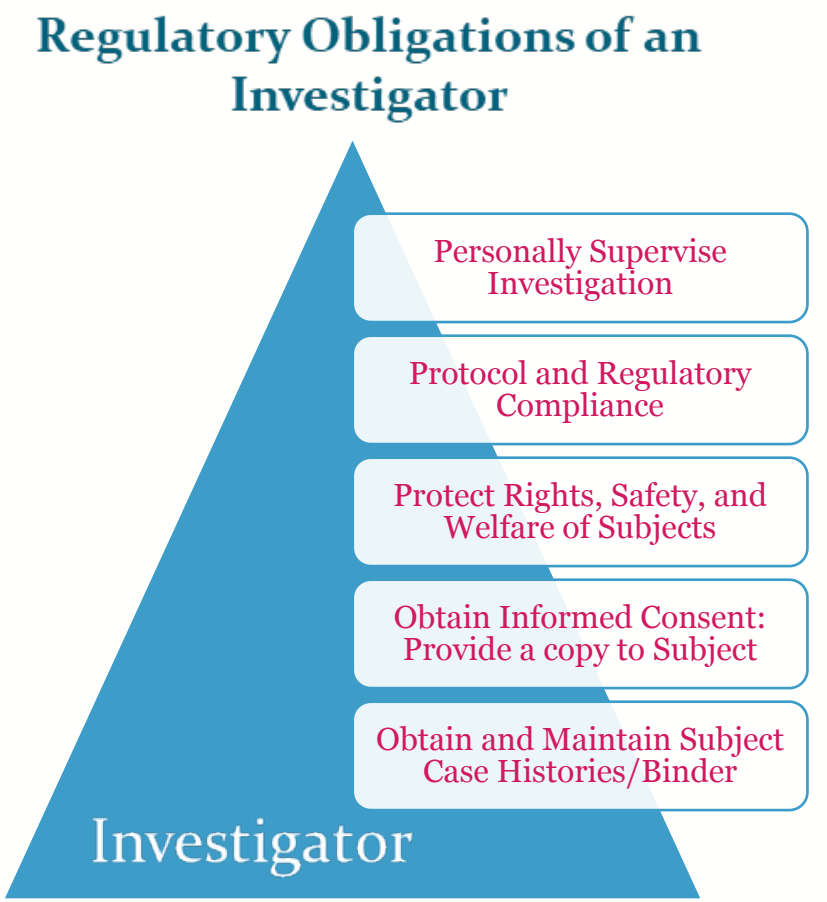
INSPECTION OF RECORDS: *INVESTIGATOR*

- **FDA inspection:**
  - The same as the sponsor, an investigator must upon request from any properly authorized officer or employee of the Food and Drug Administration, at reasonable times, permit such officer or employee to have access to and copy and verify any records and reports relating to the study.
  - The investigator is not required to divulge 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.

SUMMARY OF OBLIGATIONS







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