

SPONSOR-INVESTIGATOR IDE TRAINING MODULE 2:

*Sponsor-Investigator Responsibilities for Significant Risk
Device Studies
Records, Reports, & IDE Modifications*

IND/IDE Support Program

June 2020



OVERVIEW

- Regulatory Responsibilities of a Sponsor for Significant Risk Device Studies
- Regulatory Responsibilities of an Investigator for Significant Risk Device Studies
- Maintenance of Records
- Reports: Content and Suggested Format
- IDE Modifications

REGULATORY RESPONSIBILITIES OF A SPONSOR FOR SIGNIFICANT RISK DEVICE STUDIES

RESPONSIBILITIES OF SPONSOR FOR SIGNIFICANT RISK DEVICE STUDIES

- Obtain FDA and IRB Approval
- Selecting Investigators and Monitors
- Device Control
- Investigator Agreements
- Informing Investigators
- Monitoring
- Sponsor Records and Reports
- Labeling
- Promotion of Investigational Devices

21 CFR 812

OBTAIN FDA AND IRB APPROVAL

- A sponsor cannot begin an investigation or any part of an investigation until the IRB and the FDA have both approved the protocol.
- The Sponsor would submit an IDE application to the FDA, and submit the study for review by the CHOP IRB via the eIRB system.

21 CFR 812.42

SELECTING INVESTIGATORS & MONITORS

- A sponsor is responsible for selecting investigators qualified by training and experience to investigate the device.
- A sponsor is responsible for selecting monitors qualified by training and experience to monitor the study.

21 CFR 812.43

DEVICE CONTROL

- A sponsor may only ship investigational devices to qualified investigators that are participating in the study.



21 CFR 812.43

INVESTIGATOR AGREEMENTS

- A sponsor is responsible for obtaining a signed agreement from each participating investigator that includes:
 - Investigator's curriculum vitae
 - Statement of the investigator's relevant experience
 - Explanation of the circumstances that led to termination of a study if the investigator was involved in an investigation or other research that was terminated,
 - The investigator's commitment statement

Please see supplement for template and additional information

INFORMING INVESTIGATORS

- A sponsor is responsible for supplying all investigators participating in the study with copies of the protocol and relevant study materials, as well as a report of prior investigations of the device.



21 CFR 812.45

MONITORING

- A sponsor is responsible for ensuring and securing compliance from investigators.
- A sponsor who discovers that an investigator is not complying with the signed agreement, the protocol, the IDE requirements, any other applicable FDA regulations, or any conditions of approval stipulated by the reviewing IRB or FDA must:
 - promptly either secure compliance, or
 - discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation.
 - A sponsor must also require that the investigator dispose of or return the device, unless this action would jeopardize the rights, safety, or welfare of a subject.

21 CFR 812.46

MONITORING (CONT'D)

- A sponsor is responsible for evaluating any unanticipated adverse device effects (UADE).
- If a sponsor determines that a UADE presents an unreasonable risk to subjects, they must terminate either the study or the part(s) of the investigations that present that risk as soon as possible.
- This termination should occur no later than 5 working days after the sponsor makes this determination, and no later than 15 working days after the sponsor first received notice of the UADE.
- The study cannot be resumed without IRB and FDA approval.

SPONSOR RECORDS

- The sponsor is responsible for maintaining accurate and complete records relating to the investigation.
- These records include:
 - all correspondence including required reports,
 - records of shipment of the device
 - records of disposition of the device
 - signed investigator agreements (including financial disclosure information)
 - records concerning complaints and adverse device effects
 - any other records that FDA requires to be maintained (either due to FDA regulations or if there is a specific requirement for a particular study)

SPONSOR REPORTS

- The sponsor must submit the following reports in a timely manner to FDA, the IRBs, and/or the investigators:
 - Unanticipated Adverse Device Effects
 - Withdrawal of IRB Approval
 - Withdrawal of FDA Approval
 - Current List of Investigators
 - Progress Reports
 - Recalls and Device Disposition
 - Final Report
 - Informed consent
 - Significant Risk Device Determination
 - Any Other Reports



21 CFR 812.150

LABELING

- An investigational device or its immediate package is required to have a label with the following information:
 - The name and place of business of the manufacturer, packer, or distributor;
 - The quantity of contents, if appropriate; and
 - The statement, "CAUTION Investigational device. Limited by Federal (or United States) law to investigational use."
- The label must also describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.
- The labeling of an investigational device must not contain any false or misleading statements, or imply that the device is safe or effective for the purposes that the study is investigating.

21 CFR 812.5

LABELING (CONT.)

- The sponsor should provide detailed information on device labeling in the investigational protocol. This information may vary depending on the device and the nature of the study.
- Product labeling should be sufficient to ensure stability of the test article for the duration of the study (storage requirements, calibration procedures), bear sufficient directions for proper administration, and detail procedures to follow in the event of patient injury.

21 CFR 812.5

PROMOTION OF INVESTIGATIONAL DEVICES

- A sponsor, investigator, or any person acting for or on behalf of a sponsor or investigator **cannot**:
 - Promote or test market an investigational device, until after FDA has approved the device for commercial distribution.
 - Commercialize an investigational device by charging the subjects or investigators a higher price than that necessary to recover costs of manufacture, research, development, and handling.
 - Unduly prolong an investigation. If data developed by the investigation indicate a premarket approval (PMA) cannot be justified, the sponsor must promptly terminate the study.
 - Represent that an investigational device is safe or effective.

21 CFR 812.7

PROMOTION OF INVESTIGATIONAL DEVICES (CONT.)

- However, a sponsor may advertise the study to recruit potential subjects using IRB approved materials. Appropriate advertising methods include newspaper, radio, TV, bulletin boards, posters, and flyers.
- FDA considers direct advertising for study subjects to be the start of the informed consent and subject selection process.

21 CFR 812.7

REGULATORY RESPONSIBILITIES OF INVESTIGATORS FOR SIGNIFICANT RISK DEVICE STUDIES

RESPONSIBILITIES OF INVESTIGATORS FOR SIGNIFICANT RISK DEVICE STUDIES

- General Responsibilities
- Informed Consent
- Supervision of Device Use
- Financial Disclosure
- Device Disposal
- Investigator Reports



21 CFR 812

GENERAL RESPONSIBILITIES

- The investigator is responsible for protecting the rights, safety, and welfare of subjects.
- An investigator must conduct the investigation in accordance with the signed agreement with the sponsor, the study protocol, IDE regulations, other applicable FDA regulations, and any conditions of approval imposed by the IRB and FDA.
- While awaiting approval of an IDE application, an investigator may determine whether or not potential subjects would be interested in participating in an investigation, but may not obtain informed consent or allow any subjects to participate prior to IRB and FDA approval.

21 CFR 812.100-110

INFORMED CONSENT

- An investigator is responsible for obtaining informed consent.



21 CFR 812

SUPERVISION OF THE DEVICE

- An investigator can use the investigational device only with subjects under his/her supervision and cannot provide an investigational device to any person not authorized to receive it.

21 CFR 812.110

FINANCIAL DISCLOSURE

- The investigator should provide financial information to the sponsor, including but not limited to the financial disclosure.
- The investigator must update the information if any relevant changes occur during the course of the investigation and for one year following completion of the study.

**21 CFR 812.110;
21CFR 54**

DEVICE DISPOSAL

- Once the study or the investigator's participation in the study is completed or terminated, an investigator is responsible for returning any remaining supply of the device to the sponsor or dispose of the device as the sponsor directs.

21 CFR 812.110

INVESTIGATOR RECORDS

- The investigator is responsible for maintaining accurate and complete records of the investigation.
- These records include:
 - all correspondence including required reports,
 - records of receipt, use, or disposition of the investigational device,
 - records of each subject's case history and exposure to the device,
 - the protocol and documentation (date and reason) for each deviation from the protocol,
 - any other records that FDA requires to be maintained (either due to FDA regulations or if there is a specific requirement for a particular study)

INVESTIGATOR RECORDS (CONT'D)

Record Type	What is required for this?
Receipt, use, or disposition of the investigational device	<ul style="list-style-type: none">• Type and quantity of device• Date of receipt• Batch number or code• Name of person that received, used, or disposed of each device• Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of
Records of each subject's case history and exposure to the device	<ul style="list-style-type: none">• Signed and dated consent forms• Condition of each subject upon entering the study• Medical history• Record of the exposure to the investigational device, including the date and time of each use and any other therapy• Observations of adverse device effects• Medical records• Results of all diagnostic tests• Case report forms• Any other supporting data

MAINTENANCE OF RECORDS

MAINTENANCE OF RECORDS

- Sponsors and investigators must maintain the required records for a period of two years after:
 - the date the investigation is completed or terminated, or
 - the date the records are no longer required to support a PMA or PDP, whichever date is later.
- An investigator or sponsor may withdraw from the responsibility to maintain records for the time required by transferring custody to another person who will accept responsibility for them.
 - If an investigator or sponsor transfers custody of the records to another person, FDA must be notified within 10 working days after the transfer occurs.

21 CFR 812.140

MAINTENANCE OF RECORDS (CONT.)

- Sponsors, IRBs, and investigators are required to allow authorized FDA employees reasonable access at reasonable times to inspect and copy all records of an investigation. Upon notice, FDA may inspect and copy records that identify subjects.
- FDA has the authority to inspect facilities at which investigational devices are being held, manufactured, packed, installed, used, or implanted.

21 CFR 812.145

REPORTS TO THE FDA

SPONSOR REPORTS

Type of Report	What goes in it?	To whom and when do I need to submit the report?
UADE	The results of an evaluation of an unanticipated adverse device effect	To FDA and all reviewing IRBs and investigators; within 10 working days after the sponsor first receives notice of the adverse effect.
Withdrawal of Approval	Notification that approval was withdrawn	If IRB approval withdrawn, sponsor must notify FDA, all reviewing IRBs and participating investigators within 5 working days. If FDA approval withdrawn, sponsor must notify all reviewing IRBs and participating investigators within 5 working days.
Current List of Investigators	List of the names and addresses of all current investigators	To FDA; every 6 months
Recalls and Device Disposition	Any request that an investigator return, repair, or dispose of any unit of an investigational device, and the reason for the request.	To FDA all reviewing IRB's must be notified within 30 working days after the request was made.
Failure to Obtain Informed Consent	A copy of any report by an investigator of the use of a device without first obtaining informed consent	To FDA within 5 working days after receipt of the notice of such use.

SPONSOR REPORTS (CONT'D)

Type of Report	What goes in it?	To whom and when do I need to submit the report?
Significant Risk (SR) Determination	A report of the IRB determination the device was an SR device (not NSR)	If an IRB determines a device is an SR device and not an NSR as previously determined, the sponsor notifies FDA within 5 working days after the sponsor learns of the IRB's decision.
Progress Report	Progress report of study conduct in past year (since last annual report)	To the IRB a continuing review must be submitted at regular intervals but at least yearly. To the FDA at least yearly, if not more frequently (if FDA directs) for SR studies.
Final Report	Final report of study conduct	To the IRB, as part of protocol close out. To the FDA, when the Sponsor has completed the study.
Other reports	Requested information about the investigation.	Upon IRB or FDA request.

INVESTIGATOR REPORTS

INVESTIGATOR REPORTS

Type of Report	What goes in it?	To whom and when do I need to submit the report?
UADE	The occurrence of an unanticipated adverse device effect	To the Sponsor and IRB; within 10 working days after the investigator first receives notice of the adverse effect.
Withdrawal of IRB Approval	Notification that IRB approval was withdrawn	To the Sponsor within 5 working days.
Deviations from Investigational Plan	Notification of deviation	To the Sponsor and IRB; if an emergency* within 5 working days; if not an emergency, sponsor approval should be obtained prior to deviation.
Failure to Obtain Informed Consent	A copy of any report by an investigator of the use of a device without first obtaining informed consent	To the Sponsor and IRB; within 5 working days after occurrence.

*defined as: deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency

INVESTIGATOR REPORTS (CONT'D)

Type of Report	What goes in it?	To whom and when do I need to submit the report?
Progress Report	Progress report of study conduct in past year (since last annual report)	To the IRB at regular intervals but at least yearly. To the FDA at least yearly.
Final Report	Final report of study conduct	To the Sponsor and IRB, within 3 months after study termination or completion.
Other reports	Requested information about the investigation.	Upon IRB or FDA request.

FDA REGULATIONS REGARDING IRB'S

- Institutions must have written procedures for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject

21 CFR 56.108(a)(3) and (4) 45

IDE MODIFICATIONS

CHANGES IN INVESTIGATIONAL PLAN THAT REQUIRE PRIOR APPROVAL

- A sponsor should obtain FDA approval (and IRB approval if appropriate) prior to a change in the investigational plan.
 - There are exceptions to this requirement, please see reference below* for full list.
- The IDE supplement submitted to the FDA should be labeled with the IDE number on the cover sheet and submitted in duplicate with a valid eCopy. The outside wrapper of the submission should identify the contents as an "IDE Supplement."

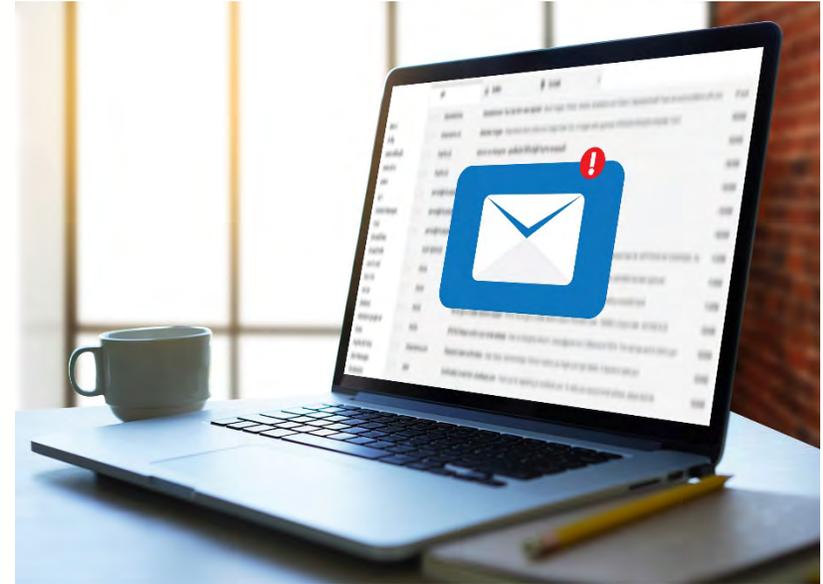
CHANGES THAT DO NOT REQUIRE PRIOR FDA APPROVAL

- The sponsor of an IDE may modify the device and/or clinical protocol without approval of a new IDE application or IDE supplement if the modifications meet certain criteria (please see reference below* for full information).
- The notice must be provided to FDA within 5 working days of the change being made.
 - **Emergency Use**
 - **Certain Developmental Changes**
 - **Certain Changes to the Clinical Protocol**
- These changes may still require IRB Approval.

**21 CFR 812.35; 21 CFR 56*

EMERGENCY USE

- FDA approval is not required prior to a deviation from the investigational plan that is made to protect the life or physical well-being of a subject in an emergency.
- However, this deviation must be reported to FDA within 5-working days after the sponsor learns of it.



21 CFR 812.150(a)(4)

CERTAIN DEVELOPMENTAL CHANGES

- An FDA approved IDE supplement is not required for developmental changes in the device (including manufacturing changes) that:
 - do not constitute a significant change in design or basic principles of operation of the device, and
 - are made in response to information gathered during the course of an investigation.
- This determination is made by the sponsor and must be based on credible information.
- The sponsor must submit a notice of the change to the IDE no later than 5-working days after making the change.
- Changes to devices are deemed to occur on the date the device or manufacturing change, is distributed to the investigator(s). These notices must be identified as a "notice of IDE change."

NOTICE OF DEVELOPMENTAL CHANGES

- For a developmental or manufacturing change to the device, the notice to the FDA must include:
 - a summary of the relevant information on which the change was based
 - a description of the change to the device or manufacturing process (cross-referenced to the appropriate sections of the original device description or manufacturing process)
- FDA will only notify the sponsor if questions arise or additional information is needed.

CERTAIN CHANGES TO THE CLINICAL PROTOCOL

- An FDA approved IDE supplement is not required for changes to clinical protocols that do not affect:
 - The validity of the data or information in the approved protocol
 - The risk/benefit ratio for subjects
 - The scientific soundness of the investigational plan
 - The rights, safety, or welfare of the human subjects involved in the investigation.
- This determination is made by the sponsor
- The sponsor must submit the change to the FDA no later than 5 working days after making the change.

NOTICE OF PROTOCOL CHANGE

- For a protocol change, the notice must include:
 - a description of the change (cross-referenced to the appropriate sections of the original protocol);
 - an assessment supporting the conclusion that the change does not have a significant impact on the study design or planned statistical analysis; and
 - a summary of the credible information that supports the sponsor's determination that the change does not affect the rights, safety, or welfare of the subjects.
- FDA will only notify the sponsor if questions arise or additional information is needed.

CHANGES TO BE SUBMITTED IN THE PROGRESS REPORT

- Changes may be reported in the annual progress report for the IDE if the changes do not affect:
 - the validity of the data or information resulting from the completion of the approved protocol or the relationship of likely patient risk to benefit relied upon to approve the protocol
 - the scientific soundness of the investigational plan
 - the rights, safety, or welfare of the human subjects involved in the investigation
- Minor changes in the following areas would apply:
 - purpose of the study
 - risk analysis
 - monitoring procedures
 - labeling
 - informed consent materials
 - IRB information

IDE SUPPLEMENTS FOR NEW FACILITIES

- FDA will review initial IDE applications where there isn't IRB approval for each site.
- FDA may approve the investigational sites without IRB approval.
- The sponsor is required to submit the IRB approval to the FDA in an IDE supplement.
- If the site is already approved and the supplement is just the certification of IRB approval, FDA usually does not provide a written response to the certification since the site has previously been approved by FDA.

IDE SUPPLEMENTS NEW FACILITIES (CONT'D)

- If the sponsor has determined the number of investigational sites for the study but not yet identified all the sites at the time the IDE is submitted, FDA may grant a waiver to the sponsor.
- The waiver would allow the sponsor to enroll the sites, obtain IRB approvals, and then submit all the certifications of IRB approval to FDA at one time (or at 6 month intervals if it takes that long to enroll the sites) instead of requesting each site as it is identified.

IDE SUPPLEMENTS FOR NEW FACILITIES (CONT'D)

- Once the IDE is approved, the sponsor may submit an IDE supplement to request approval of additional clinical study sites. FDA will respond in writing to the supplement approving or denying the request. The sponsor is required to submit:
 - Identification of the investigational site
 - certification of IRB approval
 - information updating the initial IDE application (if the investigation is changed)
 - a description of any modifications required by the IRB as conditions of approval.
- IRB approval for a new site doesn't need to be included, but should be submitted to the FDA once obtained.

IDE SUPPLEMENTS FOR NEW FACILITIES (CONTD)

- The sponsor may not begin any part of the investigation at an institution until:
 - IRB approval is obtained
 - FDA receives certification of IRB approval
 - FDA approves the supplemental application

ADDRESS FOR IDE CORRESPONDENCE

- Please visit <https://www.fda.gov/about-fda/center-devices-and-radiological-health/cdrh-offices> for the address.
- The IDE correspondence should be submitted in triplicate (2 paper copies and 1 eCopy) and reference the IDE number.
- eCopy can be a CD, DVD, or flash drive.
- Include a statement that the eCopy is an exact duplicate of a paper copy.
- The outside wrapper of each submission should identify the contents, for example, "Original IDE Application," " IDE Supplement," "IDE Report"

RESOURCES

- 21 CFR 812
- 21 CFR 50, 56
- 45 CFR 46
- FDA Presentations
(<http://www.fda.gov/Training/CDRHLearn/>)
- FDA Medical Devices Website
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/default.htm>