

# NINDS Standard Operating Procedure

## NINDS SOP 10

SOP Title: CONDUCTING A CLINICAL TRIAL UNDER IND or  
IDE WHEN NINDS IS THE SPONSOR

Version: 1.0

Approval Signature: \_\_\_\_\_  
NINDS Clinical Director

Date of Approval: 11/04/2020  
\_\_\_\_\_

Date of Implementation: 11/09/2020  
\_\_\_\_\_

Previous Versions: \_\_\_\_\_  
N/A

**Table of Contents**

1.	PURPOSE.....	2
2.	POLICY.....	3
3.	ABBREVIATIONS.....	3
4.	ROLES AND RESPONSIBILITIES.....	3
4.1.	NINDS SPONSOR RESPONSIBILITIES.....	4
4.2.	SPONSOR RESPONSIBILITIES DELEGATED TO THE PI.....	6
4.3.	ROLE OF NINDS DSM ENTITIES IN CLINICAL INVESTIGATIONS WITH NINDS- SPONSORED INDs AND IDEs.....	8
5.	PROCEDURES.....	9
5.1.	SUBMISSIONS TO THE FDA.....	9
5.2.	COMMUNICATIONS FROM THE FDA.....	9
5.3.	COMMUNICATIONS BETWEEN SAR, PI, AND NINDS CTU.....	9
5.4.	IND/IDE DETERMINATIONS.....	12
5.5.	FDA MEETINGS.....	12
5.6.	LETTER OF CROSS REFERENCE AUTHORIZATION, SUPPORTING DOCUMENTS FOR AN IND/IDE SUBMISSION.....	12
5.7.	DETERMINING WHETHER A PROTOCOL DEVELOPMENT MEETING IS REQUIRED...	13
5.8.	CURRENT GOOD MANUFACTURING PRACTICES (CGMP) AUDIT.....	13
5.9.	IND/IDE NEW SUBMISSIONS.....	14
5.10.	RECORDKEEPING AND RECORD RETENTION.....	14
5.11.	TRANSFER OF SPONSOR RESPONSIBILITIES TO A CONTRACT RESEARCH ORGANIZATION (CRO) .....	15
5.12.	IND PROTOCOL AMENDMENTS.....	15
5.13.	IDE PROTOCOL AMENDMENTS.....	15
5.14.	IDE SIGNIFICANT RISK DEVICE ADDITIONAL REPORTING.....	16
5.15.	MONITORING OF STUDY CONDUCT.....	16
5.16.	EXPEDITED SAFETY REPORTING.....	17
5.17.	IND/IDE TERMINATION, INACTIVATION, WITHDRAWAL, AND CLOSURE.....	20
5.18.	EXPANDED ACCESS TO INVESTIGATIONAL DRUGS OR DEVICES FOR TREATMENT USE.....	22
6.	LIST OF REFERENCES/APPENDICES.....	23

**1. PURPOSE**

The purpose of this document is to establish National Institute of Neurological Disorders and Stroke (NINDS) policy for, and to provide information and guidance to, NINDS investigators engaged in a U.S. Food and Drug Administration (FDA) regulated clinical investigation involving an IND or IDE. Per the “Revised Policy on Holders of INDs and IDEs at NIH” (October 2, 2017), effective January 15<sup>th</sup>, 2018, INDs and IDEs shall be held by Institutes or Centers rather than by the Principal Investigators. Following this policy, NINDS serves as IND/IDE sponsor for such studies. This document summarizes NINDS processes and practices on how to manage the INDs and IDEs for research within the NINDS intramural research program throughout the life cycle of the clinical investigation.

This document provides a reference for the interaction between the Institute as Sponsor, the Principal Investigator, and the FDA.

## **2. POLICY**

For investigator-initiated clinical research studies at the NINDS requiring an IND or IDE application to the FDA, the Institute (NINDS) shall be listed as the Sponsor. As the Sponsor, NINDS will bear all responsibility for establishing and maintaining an IND/IDE with the FDA. The responsibility of the “Sponsor’s Authorized Representative (SAR)” will be assumed by the Clinical Director of NINDS or his/her designee.

## **3. ABBREVIATIONS**

AE: Adverse Event

ADE: Adverse Device Effect

BA/BE: Bioavailability/Bioequivalence

CFR: Code of Federal Regulations

IRB: Institutional Review Board

CRO: Contract Research Organization

DSM: Data Safety Monitoring

FDA: Food and Drug Administration

HSR: Human Subjects Research

IB: Investigator’s Brochure

IDE: Investigational Device Exemption

IMM: Independent Medical Monitor

IND: Investigational New Drug

ISM: Independent Safety Monitor

LAI: Lead Associate Investigator

NIH: National Institutes of Health

NINDS: National Institute of Neurologic Disorders and Stroke

NINDS CD: NINDS Clinical Director

NINDS CTU: NINDS Clinical Trials Unit

NINDS QA: NINDS Quality Assurance

OHSRP: Office of Human Subjects Research Protections

OHRP: (HHS) Office of Human Research Protections

ORSC: Office of Research Support and Compliance

PDS: Pharmaceutical Development Service

PI: Principal Investigator

SAE: Serious Adverse Event

SAR: Sponsor’s Authorized Representative

SMC: Safety Monitoring Committee

## **4. ROLES AND RESPONSIBILITIES**

At NINDS, the Clinical Trials Unit acts on behalf of the Sponsor’s Authorized Representative for INDs and as the Contact Person for IDEs. At NINDS, the Clinical Director

or designee may serve as the Sponsor's Authorized Representative or Contact Person to the FDA. The Sponsor's Authorized Representative (SAR) is the person who signs the Form FDA 1571 in section 17 for INDs. For IDEs, the Sponsor Name and Contact Person are listed on the Cover Letter. This signature identifies the individual to the FDA who will act on behalf of the sponsor for the IND or IDE. When the SAR signs section 17, he/she acknowledges acceptance of the designated responsibilities of the Sponsor and its authorized representative as detailed in 21 CFR 312.50. When the Sponsor (in the case of NINDS, the Clinical Director) signs the Cover Letter, he/she acknowledges acceptance of the designated responsibilities of the Sponsor and its authorized representative as detailed in 21 CFR 812.

At NINDS, the SAR is supported by the NINDS Clinical Trials Unit (NINDS CTU) for the preparation of FDA submissions, routing of FDA communications between all involved entities including the PI and the monitoring entities, oversight of compliance monitoring (quality assurance), and administration of data and safety monitoring. Within the NINDS CTU, an FDA Regulatory Specialist (FDARS) will be designated as the point of contact for the SAR and the PI.

In the event that the SAR is unavailable for signature on required FDA documents, memorandums, or other relevant documents, the SAR may appoint a designee(s) to act on his/her behalf. The SAR will identify his/her designee(s) to the FDA prior to any designee action.

#### **4.1. NINDS SPONSOR RESPONSIBILITIES**

**The NINDS as Sponsor fulfills the following Sponsor responsibilities to:**

- Serve as point of contact with the FDA.
- Ensure proper quality assurance and compliance of conduct of the investigation in accordance with the general investigational plan and protocol, including:
  - Selection of monitor(s) to oversee the conduct of the protocol; and
  - Establish a Monitoring Plan for the protocol.
- Ensure and monitor the progress of all clinical investigations being conducted under its IND or IDE.
- Ensure the PI performs the delegated duties as listed in section 5.2., below.
  - If NINDS discovers that an investigator is not complying with the signed agreement (Form FDA-1572), the general investigational plan, or the requirements of Subpart D CFR 312.50 or other applicable parts of FDA regulations for an IND, and 21 CFR 812.46 or other applicable parts of the regulations for an IDE, or any condition imposed by the reviewing IRB or FDA, NINDS will promptly:
    - secure compliance, or
    - discontinue shipments of the investigational new drug or device to the investigator (if applicable) and end the investigator's participation in the investigation.

- If the investigator's participation in the investigation is ended, NINDS will require that the investigator dispose of or return the remaining investigational drug or device in accordance with the requirements of Subpart D CFR 312.59 for IND, or 21 CFR 812.46 for an IDE, and shall notify FDA.
- Notify the FDA and all participating investigators if a review identifies potential serious risks, as soon as possible, but no later than 15 calendar days after the determination of possible risk.
  - Upon determination that the investigational drug presents an unreasonable and significant risk to subjects, NINDS, as the Sponsor, shall discontinue those investigations that present the risk.
    - If applicable, notify all off-site Institutional Review Boards, and off-site investigators who have at any time participated in the investigation of the discontinuance.
    - Assure the disposition of all stocks of the drug outstanding for off-site institutions as required by 21 CFR 312.59.
    - The Sponsor shall discontinue the investigation as soon as possible, and in no event later than 5 working days after making the determination that the investigation should be discontinued.
      - The NINDS CTU will prepare a full report of actions for the SAR to submit to the FDA in a timely manner to meet the FDA reporting guidelines; and
      - Upon request, the sponsor will confer with the FDA on the need to discontinue an investigation.
  - Upon determination that an unanticipated adverse device effect presents an unreasonable risk to subjects, the sponsor shall terminate all investigations, or parts of investigations presenting that risk, as soon as possible. Termination shall occur not later than 5 working days after the sponsor makes this determination and not later than 15 working days after the sponsor first received notice of the effect.
    - The sponsor may not resume an investigation terminated for this reason without IRB and FDA approval.
    - The sponsor may not resume a terminated investigation on a significant risk device in any circumstance without IRB and FDA approval.
- 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 a clinical investigation conducted under this part.
  - Upon written request by the FDA, the Sponsor shall submit the records or reports (or copies of them) to the FDA; and
  - Discontinue shipments of the drug to any investigator participating in the clinical investigation who has failed to maintain or make available records or reports of the investigation as required by this part;

- In collaboration with the PI, maintain a central Sponsor's trial master file including, but not limited to, all FDA submissions and communications and Form FDA 1572, (See ICH Good Clinical Practice: Consolidated Guidance E6, Section 8, for a list of Essential Documents to be kept in the sponsor's trial master file; n.b., this is different from a site regulatory binder/file).
  - Financial Disclosure Information is maintained by the NINDS Ethics office with a note to file in the study teams regulatory files.
- In case of multi-site trials, assure the return of all unused supplies of the investigational drug from each individual investigator whose participation in the investigation is discontinued or terminated.
  - Authorize alternative disposition of unused supplies of the investigational drug provided this alternative disposition does not expose humans to risks from the drug.
- Maintain communication with the PI regarding the clinical investigation as described throughout this document.
- Maintain an effective IND/IDE with respect to the investigation.
- Provide a 21 CFR Part 11 compliant clinical trials database.
- Should the Clinical Director act as Principal Investigator in a NINDS sponsored FDA regulated trial under an IND or IDE, he/she will delegate the SAR role to a designee.

#### **4.2. SPONSOR RESPONSIBILITIES DELEGATED TO THE PI**

**At NINDS, the following Sponsor responsibilities will be delegated to the Principal Investigators:**

- Selection of associate investigators qualified by training and experience as appropriate experts to investigate the drug or /device.
- Upon discovery that an associate investigator at the NINDS is not complying with the signed agreement (Form FDA-1572), the general investigational plan, or the requirements of 21 CFR 312 or other applicable parts, shall promptly either secure compliance or end the associate investigator's participation in the investigation.
- If the sponsor ends the clinical investigation, the PI will be responsible for disposing of or returning the investigational drug or device in accordance with the requirements of 21 CFR 312.59 and 812.110(e), respectively, and notify the NINDS CTU.
- Provide on-going monitoring of the study conduct in addition to the protocol monitoring conducted by the external QA monitor identified by the Sponsor (NINDS).
- Provide reports (e.g. Annual/Progress Reports) to the NINDS CTU for submission to FDA.
- Review the Investigator Brochure (IB) at least annually. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information.

- Review all information relevant to the safety of the investigational product (available in published literature, or evolved from this or similar research, including unpublished data), that might affect the risk/benefit analysis for human subjects, or the scientific value of the protocol, and provide to the DSM entity.
- If applicable, distribution of investigational new drugs or devices to investigators participating in the investigation.
- Upon receiving notification from the sponsor that the investigational drug or device presents an unreasonable and significant risk to subjects, the PI will discontinue those investigations that present the risk, as well as:
  - Notify the IRB and all principal investigators who have at any time participated in the investigation of the discontinuance; and
  - Retrieve all stocks of the remaining drug or device as required by 21 CFR 312.59 or 812.46(b)(2), respectively.
- Handling of investigational product, to include:
  - Retain reserve samples of any test article and reference standard identified in, and used in any of the bioequivalence or bioavailability studies described in, 21 CFR 320.38 or 21 CFR 320.63, and release the reserve samples to the FDA upon request, in accordance with, and for the period specified in 21 CFR 320.38; and
  - Have records (i.e., shipment, delivery, receipt, and disposition of the drug) available for inspection and copying (from a properly authorized employee of the Drug Enforcement Administration of the U.S. Department of Justice) if an investigational new drug is a substance listed in any schedule of the Controlled Substances Act (21 U.S.C. 801; 21 CFR part 1308);
- Collect and evaluate the results obtained from the trial. Data collection and management systems using electronic systems must be in compliance with 21 CFR part 11.
- Register and submit results to Clinicaltrials.gov, as per the "NIH Policy on Dissemination of NIH-Funded Clinical Trial Information" of the federal regulations in Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801), as implemented by 42 CFR Part 11 (Final Rule).

***4.2.1 Abbreviated requirements for device protocols with an NSR determination (per 21 CFR 812.2(b)):***

The following categories of investigations are considered to have approved applications for IDE's, unless FDA has notified a sponsor under 812.20(a) that approval of an application is required:

- (1) An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor:
  - (i) Labels the device in accordance with 812.5;
  - (ii) Obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;

- (iii) Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under part 50 and documents it, unless documentation is waived by an IRB under 56.109(c);
- (iv) Complies with the requirements of 812.46 with respect to monitoring investigations;
- (v) Maintains the records required under 812.140(b) (4) and (5) and makes the reports required under 812.150(b) (1) through (3) and (5) through (10);
- (vi) Ensures that participating investigators maintain the records required by 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7); and
- (vii) Complies with the prohibitions in 812.7 against promotion and other practices.

#### **4.3. ROLE OF NINDS DSM ENTITIES IN CLINICAL INVESTIGATIONS WITH NINDS-SPONSORED INDs AND IDEs**

**NINDS as sponsor, designates a study's Data and Safety Monitoring entity (i.e., Principal Investigator, Independent Safety Monitor\*, Safety Monitoring Committee, Data and Safety Monitoring Board) as Sponsor's Safety Monitoring entity, to fulfill the following Sponsor's responsibilities:**

- Review and evaluate the evidence relating to the safety of the drug or device as it is obtained from the investigator(s), upon receiving a suggested determination of relatedness of events and problems (e.g., unanticipated problems (UPs), adverse events (AEs), protocol deviations (PDs), deaths) by the PI.
  - The PI will be responsible for ensuring events and problems are documented on the study AE log.
- In conjunction with the PI, review all information relevant to the safety of the investigational product (as provided by the PI, available in published literature, or evolved from this or similar research, including unpublished data), that might affect the risk/benefit analysis for human subjects, or the scientific value of the protocol.
- **At a minimum, a Safety Monitoring Committee (SMC) level of oversight is required for NINDS IND and IDE clinical trials.**
  - An exception with sufficient justification to withdraw from SMC oversight must be provided and approved in writing by the NIH Clinical Director, with the agreement of the study sponsor.

\*N.B. The term "Independent Safety Monitor" has replaced the previous "Independent Medical Monitor" designation



## **5. PROCEDURES**

### **5.1. SUBMISSIONS TO THE FDA**

- Formal submissions (e.g., determination requests, initial submissions, amendment submissions, meeting requests, response to information requests, annual reports, safety reports):
  - Using NINDS templates, the PI, together with the NINDS CTU, will draft the submission package. The package will be signed by the SAR and submitted to the FDA by the NINDS CTU.
  - The NINDS CTU will provide copies of final correspondence to the PI, and will file in the sponsor's trial master file.
  - Communications must be submitted within specified regulatory timelines.
  - The NINDS CTU/SAR will have final authority on whether a package is submitted as a commercial or research application to the FDA
- Informal submissions (examples: email communication with FDA project manager):
  - Any inquiry from NINDS (from SAR or PI) will be submitted to the FDA by the SAR or designee, after preparation of the inquiry by the PI and NINDS CTU. Responses from the FDA will be relayed promptly to the PI.
  - All communications will be kept in the sponsor's trial master file.

### **5.2. COMMUNICATIONS FROM THE FDA**

- Communications from the FDA to the SAR must be promptly forwarded to the NINDS CTU and PI. The PI is responsible for initiating a response draft and routing it back to the NINDS CTU and CD prior to submission to the FDA.
- During meetings with the FDA (e.g., in-person, telephone conferences), NINDS will be represented by the SAR (or his/her designee, as indicated to FDA), the PI, NINDS CTU regulatory support staff, as well as other staff/collaborators whose expertise is deemed critical to the scope of the meeting.

### **5.3. COMMUNICATIONS BETWEEN SAR, PI, AND NINDS CTU**

- For Initial IND/IDE Application:
  - The NINDS CTU will provide the PI with a submission template for INDs or the required format for IDEs.
  - The PI will complete the required sections.
  - The PI will return the document to the NINDS CTU.
  - The NINDS CTU will review the documents and attachments, add any missing elements, and provide recommendations for revisions, if necessary.
  - The NINDS CTU and PI will communicate regarding timelines for the creation of final documents, internal approvals, and potential setbacks.

- The NINDS CTU will work with the SAR to obtain signature(s) for applicable regulatory documents prior to submitting to the FDA.
- The NINDS CTU will submit all documents to the FDA.
- During the 30-day safety review period the FDA may request additional clinical or scientific information, prior investigations (prior clinical, animal, and laboratory testing of the device), or a prompt response to their review comments. The PI will draft a response to the FDA within the requested timeline. The NINDS CTU will work with the PI to fulfill the request and provide a timely response to the FDA. Once finalized, the NINDS CTU will forward the final response to the SAR for final review, approval, and signature prior to submitting to the FDA.
- In the case of a full or partial hold communication by the FDA, the PI should work closely with the NINDS CTU to resolve the concerns and subsequently formulate a response to hold submission to the FDA. The NINDS CTU will forward final response to the SAR for final review, approval, and signature prior to submitting to FDA.
- The SAR will forward a copy of the FDA IND/IDE acknowledgement letter to the NINDS CTU which includes pertinent information regarding the IND/IDE receipt date, safe to proceed/approval date, and the annual reporting date. The NINDS CTU will maintain a copy of the letter in the sponsor's trial master file and forward this information to the PI.
- The FDA may send clinical or statistical comments (i.e., non-hold comments) after the IND has been deemed safe to proceed and the clinical trial has been initiated. The FDA will send these comments directly to the CTU/SAR who will forward to the PI through the NINDS CTU. The NINDS CTU will work with the PI to fulfill the request and provide a timely response to the FDA. The PI will work closely with the NINDS SAR/CTU to formulate a plan for how these recommendations will be addressed.
- For Annual/Progress Reports:
  - The NINDS CTU will track the anniversary for IND annual reports and IDE progress reports and will submit annual reports within 60 days of the anniversary date.
  - The NINDS CTU will send an email reminder to the PI approximately two months prior to the anniversary date and will provide the PI with the report template.
  - The PI or designee will create the first draft of the report.
    - The PI will populate the AE/ADE log on the NINDS template.
    - The PI will populate the log of protocol deviations.
    - The PI will submit a draft report to the NINDS CTU at least 4 weeks prior to the anniversary date.
  - Upon receipt of the annual/progress report draft from the PI, the NINDS CTU will review the document and attachments. If necessary, the NINDS CTU will provide recommendations for revisions and send the document back to the PI for completion and edits.

- The NINDS CTU/SAR will obtain signature(s) for applicable regulatory documents prior to submitting to the FDA.
- For Clinical Audits/Inspections of IND/IDE Trial:
  - When the SAR is informed of a clinical site inspection by the FDA, an international regulatory authority, or any other applicable entity, communication should be promptly forwarded to the PI and NINDS CTU.
    - The NINDS CTU will notify the applicable NIH oversight bodies including the ORSC and the OHSRP (if applicable).
    - The NINDS CTU will assist the site in preparing for the audit.
- For Notification of Clinical Hold of an IND or IDE for an Approved Trial:
  - In case of a full or partial hold communication by the FDA, the SAR should notify the PI and NINDS CTU immediately.
    - The PI will ensure that no new subjects are recruited to the trial and given the investigational drug or device; patients already in the trial are expected to be taken off therapy involving the investigational drug or device unless treatment continuation is specifically permitted by the FDA in the interest of patient safety.
  - The NINDS CTU, in conjunction with the PI, will work closely to resolve the concerns and subsequently formulate a “response to hold” submission to the FDA.
- For Notification of Approval with Conditions of IDE:
  - An IDE application is approved with conditions if FDA has determined that the sponsor has provided sufficient data to support initiation of subject enrollment in a human clinical study and no subject protection concerns preclude initiation of subject enrollment but additional conditions must be met to address certain outstanding issues.
  - The sponsor may begin subject enrollment upon receipt of IRB approval and in accordance with the limits described in FDA’s decision letter, including the maximum numbers of U.S. subjects and investigational sites, and must submit information addressing the issues identified as conditions of approval in FDA’s letter within 45 days.
- For Notification of Staged Approval of IDE:
  - “Staged approval” or “staged approval with conditions” (which are subsets of approval and approval with conditions decisions), by which FDA may grant IDE approval or approval with conditions for a portion of the intended study cohort, enabling certain outstanding questions to be answered concurrently with enrollment in this cohort. Staged approval permits the clinical investigation to begin in a timely manner while maintaining appropriate subject protections.
- For Notification of Disapproval of IDE:
  - The sponsor may not initiate enrollment in the clinical investigation until the sponsor submits an amendment to the IDE to respond to the deficiencies identified in FDA’s letter and subsequently receives a new letter from FDA granting approval or approval with conditions.

- Time Sensitive Communications with the FDA (e.g. Safety Reports, Significant Amendments):
  - The PI will inform the NINDS CTU of pending time sensitive communications to the FDA, and timelines for the submission will be established. The communication will be prepared and submitted as outlined in 6.1.

#### **5.4. IND/IDE DETERMINATIONS**

The NINDS CTU will assist the PI with the initial determination of the need for an IND exemption of an approved drug in a clinical investigation, as well as for the initial determination of a non-significant risk vs. significant risk status of a medical device. If the PI determines that their protocol meets the IND exemption requirements per 21 CFR 312, the PI should contact the CTU to submit an IND exemption request. If the study utilizes a device and the PI determines the device to be a Significant Risk device study, the PI should contact the CTU to submit an IDE per 21 CFR 812. If the PI determines the device to be a Non-Significant Risk device, the PI should contact the CTU for a risk determination by the Sponsor. In the case of uncertainty or questions regarding whether a prospective trial is subject to the IND/IDE regulations and/or exemption criteria, NINDS CTU will assist the PI in obtaining consultation from the FDA.

#### **5.5. FDA MEETINGS**

The NINDS CTU should be informed of the need for a formal FDA meeting (e.g., a pre-IND meeting per 21 CFR 312.82, pre-IDE meetings per Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program Guidance for Industry and Food and Drug Administration Staff) to receive official FDA consultation on a proposed or ongoing clinical trial. The NINDS CTU will draft a meeting request submission and will assist with meeting preparation.

#### **5.6. LETTER OF CROSS REFERENCE AUTHORIZATION, SUPPORTING DOCUMENTS FOR AN IND/IDE SUBMISSION**

##### ***5.6.1 For IND Submissions***

To satisfy the IND requirements on the Form FDA 1571, section 13, items 7-10, data can either be provided to the FDA directly, or through a cross reference letter authorizing the FDA to utilize information from an existing IND or marketing application. If a substance for investigation is provided by an outside entity already holding an IND, NINDS may request the outside entity to provide supporting data, or to provide a letter of cross-reference authorization. NINDS may also request an Investigator's Brochure, if one exists. For an FDA approved drug, if used as approved (e.g., the same dose, formulation, and route of administration), a package insert may suffice. NINDS delegates the responsibility of obtaining letters of cross-reference authorizations and an Investigator's Brochure to the PI. The NINDS CTU can assist with providing a template letter of cross-reference authorization or can draft and submit these letters at the request of the study team. This

correspondence will be kept on file and will be submitted to the NINDS original IND submission for the FDA's reference.

### **5.6.2 For IDE Submissions**

Information in a master file (MAF) for devices may be incorporated by reference in a sponsor's PMA, 510(k), or IDE, or other submissions to FDA. Their use of information in an MAF can only be authorized by the MAF holder or by a designated agent if so authorized. After FDA has referred to an MAF and the client's application has been approved, authorization cannot be withdrawn.

A MAF holder should provide a letter of authorization directly to the PI with instructions that: (1) the original of the authorization letter be included in the original copy of the client's submission and (2) a copy be placed in each subsequent copy of the client's submission. An authorization letter should not be sent directly to Center for Devices and Radiological Health (CDRH) for inclusion in the MAF or the sponsor's submission.

NINDS delegates the responsibility of obtaining letters of cross-reference authorizations and Manufacturing Information (21 CFR 812.20(b)(3)) to the PI. The NINDS CTU can assist with providing a template letter of cross-reference authorization or with drafting and submitting these letters at the request of the study team. This correspondence will be kept on file and will be submitted to the NINDS original IDE submission for the FDA's reference.

### **5.7. DETERMINING WHETHER A PROTOCOL DEVELOPMENT MEETING IS REQUIRED**

When a PI is planning a clinical protocol that may require an IND (including IND exemptions) or IDE (including NSR devices), the NINDS CTU must be consulted early during the protocol development phase, prior to scientific review. The PI should request a Protocol Development Meeting (PDM) with the NINDS CTU to discuss background information on the trial, potential regulatory issues, the possible need for an IND/IDE, and to agree on timelines.

If it is determined at a later time that an IND or IDE submission is needed and a PDM has not been completed, the PI must request a PDM before NINDS will proceed with the full IND/IDE submission to the FDA.

### **5.8. CURRENT GOOD MANUFACTURING PRACTICES (CGMP) AUDIT**

All drugs manufactured by a noncommercial entity must have a CGMP audit prior to initial IND submission to the FDA. The audit will be conducted by the NIH Office of Research Support and Compliance (ORSC) or a designated contractor at the request of the CTU. The PI is advised to contact and discuss this requirement with the CTU as soon as possible so as to not delay a regulatory submission.

### **5.9. IND/IDE NEW SUBMISSIONS**

The PI must agree to the sponsor-responsibilities delegated by NINDS as outlined in this document, in addition to the obligations as clinical investigator as outlined in 21 CFR 312 (drugs) and 21 CFR 812 (devices).

The PI is responsible for continuing interactions with the NINDS CTU to provide regular updates on the protocol development. The PI is also responsible for continuing communication on timelines for IRB review/approval, pertinent pharmaceutical/device company interactions, tech transfer agreements, and availability of other required IND/IDE documentation. These interactions are critical to ensure a smooth coordination of the IND/IDE application.

Before IRB submission, the PI must provide the NINDS CTU a copy of the near final clinical protocol and informed consent document for review and comment, with the goal to prepare the IND or IDE submission. At this point, the NINDS CTU may provide additional regulatory advice, identify potential regulatory concerns for the IND/IDE submission, and may request additional information for review (e.g., information on the drug/device, manufacturing plans, etc.).

NINDS templates will be used for the preparation of the original IND or IDE application, ensuring all elements of an IND and IDE application are covered. The submission process will be conducted as outlined in section 6.1.

### **5.10. RECORDKEEPING AND RECORD RETENTION**

In addition to the PI responsibilities for recordkeeping and retention, as outlined in 21 CFR 312.63 and 21 CFR 812.110 (i.e., maintaining records of drug disposition, case histories, record retention requirements, and disposing device), the NINDS CTU and the PI will collaboratively maintain the Sponsor's trial master file to fulfill the sponsor's responsibilities of recordkeeping and retention per 21 CFR 312.57. The PI as well as NINDS as sponsor (as represented by the SAR and the NINDS CTU) shall have access to the sponsor's trial master file at any time. NINDS requires the use of an electronic regulatory binder, which should be accessible to the PI, his/her support staff (e.g., protocol navigators), the SAR, as well as the NINDS CTU regulatory support staff.

IND/IDE records will be kept on secure servers and/or in a locked room per federal regulations. Submissions in original format (paper or electronic) will be considered the original records and will be maintained until at least 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated, or after the investigation is discontinued and FDA is notified, or otherwise obligated by NIH policy. For devices, records will be retained for no less than 2 years from the date of release for commercial distribution by the manufacturer per 21 CFR 820.180(b).

The NINDS CTU will ensure the completeness and accuracy of the sponsor's trial master file. If there are multiple studies under one IND or IDE, the NINDS CTU will be the sponsor's entity to maintain the sponsor's trial master file. The PI is responsible for maintaining the regulatory binder (i.e., essential regulatory documents) and IRB approvals.

#### **5.11. TRANSFER OF SPONSOR RESPONSIBILITIES TO A CONTRACT RESEARCH ORGANIZATION (CRO)**

In the case where NINDS has transferred any regulatory obligations of the sponsor to a CRO, the NINDS CTU will interact directly with the CRO for all regulatory support. The PI will maintain communication with the NINDS CTU on all requests for regulatory communication with the CRO. The CRO will prepare regulatory submissions for final review and signatures for submission by the SAR or designee.

The CRO/PI will copy the NINDS CTU on all communications to the PI/CRO pertaining to regulatory correspondence.

#### **5.12. IND PROTOCOL AMENDMENTS**

For clinical protocols under an IND, the PI must inform the NINDS CTU of pending protocol amendments.

Significant changes (including but not limited to: change in a Phase 1 protocol that significantly affects the safety of subjects; or any change in a Phase 2 or 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the trial) to the protocol must be submitted to the FDA before implementation at the clinical site. In contrast to the initial IND submission, if the IND is not on clinical hold, the PI may implement changes to the IND immediately after sending the amendment to the FDA, without waiting 30 days, as long as the amendment has been approved by the IRB (unless the change to the protocol is necessary to eliminate apparent immediate hazards to human subjects).

Non-significant changes to the protocol may be submitted with the annual report or incorporated in the next protocol amendment to the IND. Additional information can be found in 21 CFR 312.30 (b). It is expected that the NINDS CTU will submit all new protocol amendments to the FDA after IRB approval.

#### **5.13. IDE PROTOCOL AMENDMENTS**

For clinical protocols under an IDE, including those with an NSR determination, the PI must inform the NINDS CTU of pending protocol amendments upon IRB review (i.e., prior to IRB approval). However, for studies with an NSR determination, only amendments that change the safety or scientific outcomes of the study need to be submitted for review. The NINDS CTU will use a Checklist for IDE Modifications to determine which type of submission, if any, to the FDA is applicable (see "Changes or Modifications During the Conduct of a Clinical Investigation; Final Guidance for Industry and CDRH Staff", Attachment 1, at <https://www.fda.gov/media/72429/download>). For substantial (i.e., impacting the risk/benefit assessment) protocol changes under an IDE

(excluding protocols with an NSR determination), FDA approval of an IDE supplement is needed prior to the implementation of the protocol amendment. For other – typically more minor<sup>1</sup> - protocol changes, the FDA may require notification within 5 working days after the implementation of the change, or at the time of annual progress report.

For a protocol amendment of a study under an IDE, the PI must provide to the NINDS CTU: 1) a description of the change (cross-referenced to the appropriate sections of the original protocol); 2) an assessment whether the change significantly impacts the trial design or planned statistical analysis; and 3) a summary of the information for determining whether the changes affect the rights, safety, or welfare of the subjects.

#### **5.14. IDE SIGNIFICANT RISK DEVICE ADDITIONAL REPORTING**

List of Investigators: The PI is required to keep the SAR and the NINDS CTU informed of the current list of all investigators, including names and addresses. The SAR must submit to FDA a current list of all investigators participating in a significant risk device investigation every six months. A waiver of this requirement can be requested.

Progress Reports (or Annual Reports): At regular intervals, and at least yearly, the SAR must provide progress reports to all reviewing IRBs and the FDA for a significant risk device.

#### **5.15. MONITORING OF STUDY CONDUCT**

NINDS as Sponsor, together with the PI, will ensure that the clinical investigation is performed in accordance with the general investigational plan and protocol, NIH regulations and policy, the International Conference on Harmonization (ICH) Good Clinical Practices (GCP), and the Code of Federal Regulations (21 CFR and 45 CFR Part 46).

- External monitoring for NINDS sponsored IND and IDE (potentially including NSR device protocols) trials will be conducted through a Contract Research Organization (CRO) or by the NINDS Quality Assurance and Data Management Office.
- The NINDS CTU will notify the CRO of new applicable clinical investigations. The monitoring of the clinical investigation will be conducted in compliance with the NINDS Monitoring SOP, the NINDS/CRO Clinical Monitoring Plan, and the Protocol Monitoring Plan.

---

<sup>1</sup> Prior FDA approval is not required (but subject to the 5-day rule) for developmental changes in the device (including manufacturing changes) that do not constitute a significant change in design or basic principles of operation and that are made in response to information gathered during the course of an investigation, as well as changes to clinical protocol that do not affect the validity of the data or information in the approved protocol, or the patient risk to benefit relationship relied upon to approve the protocol, the scientific soundness of the investigational plan, and the rights, safety, or welfare of the human subjects involved in the investigation. Minor changes that fulfil these criteria and affect study purpose, risk analysis, monitoring procedures, labeling, or informed consent materials may be reported to FDA in the annual progress report for the IDE.



- In addition to all regulatory requirements being met, a clinical investigation can only be initiated at NINDS after all study startup requirements have been met per the NINDS CTU Study Startup Checklist, and NINDS CTU provides approval to start recruiting. A study can start enrolling participants only after the NINDS CTU issues a formal “ok to enroll” letter from CTU to the study investigators. This “ok to enroll” letter supersedes a “study may proceed” determination from the FDA.
- In special circumstances (e.g., gene therapy clinical trials), additional requirements may have to be met before a study can initiate recruitment (e.g., IBC approval).
- The frequency of Interim Monitoring Visits may be driven by enrollment milestones, (e.g., after the first subject is administered a study drug, after the first cohort completes specific study time points, etc.), as directed by the NINDS CTU and/or as outlined in the IRB approved protocol. The PI will be responsible for notifying the CRO via the NINDS CTU when enrollment milestones are met which trigger monitoring visits.
- If deficiencies are identified during monitoring visits, the PI (or his/her designee) and the Sponsor will be notified at the time of the monitoring summary meeting.

#### **5.16. EXPEDITED SAFETY REPORTING**

Unless otherwise agreed upon between PI and sponsor, as documented in the IRB approved protocol, the PI will immediately report serious adverse events that are at least temporally associated with the use of the medicinal product under investigation (whether assumed to be related or not) and adverse device effects to the designated DSM entity and to the NINDS CTU. The Form 3500 (MedWatch) may be used for all potential SUSARs submitted to the CTU. The PI should provide a determination of the relatedness and expectedness of the event to the Sponsor (as represented here by the NINDS CTU). The NINDS CTU/SAR reserves the right of final determination of relatedness for all safety events reported to the FDA.

For intramural clinical trials under an IND/IDE, NINDS designates the role of Sponsor’s Safety Monitor to the protocol’s designated DSM entity (see sections 5.2 and 5.3), to fulfill the safety monitoring requirements per the following regulations:

- 21 CFR 312.32 and 21 CFR 312.64b (for IND).
- 21 CFR 812.150(b)(1) (for IDE).

These regulations describe the sponsor’s roles and responsibilities, including reporting requirements, to the FDA. In addition, the PI should reference the NIH OHSRP Policy 801 (reporting requirements), as well as SOP 24 (reporting requirements in the context of FDA regulated research). Refer to the protocol if the sponsor requires more stringent reporting requirements.

The NINDS CTU, as the regulatory support office of the sponsor (NINDS), will be notified by the PI or the DSM entity in writing of an event or new information that may require

expedited safety reporting to prepare the submission documents and complete the submission process.

#### **5.16.1. IND Safety Reporting**

*(Refer to 21 CFR 312.32 for more detailed information)*

Depending on severity, seriousness, unexpectedness, and relatedness to the investigational product, as determined by the Sponsor's Safety Monitor, an IND event must be reported to the FDA within 7 (death or life-threatening) or 15 calendar days (all other related and unexpected SAEs), from the time the Sponsor's Safety Monitor learned of the event and made a determination. An event occurring in conjunction with a device under an IDE, and if qualifying as unanticipated adverse device effect, must be reported to the FDA within 10 working days after the sponsor first received notice of the effect. The processes are as follows:

- Determination of relatedness is reviewed and final determination whether the event qualifies for expedited reporting to the FDA is made by the Sponsor based on initial assessment by the PI and the Sponsor's Safety Monitor (DSM entity).
- If the event qualifies for expedited reporting, the NINDS CTU will prepare a safety report for FDA submission, which will be submitted by the SAR.
- If the IRB makes a different determination warranting immediate reporting to the FDA, the sponsor will inform the FDA accordingly.

The sponsor must notify the FDA and all participating investigators (i.e., all investigators to whom NINDS is providing drug under its IND or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source.

In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

- Serious and unexpected suspected adverse reaction (SUSAR)
  - The sponsor must report any suspected adverse reaction that is both serious and unexpected in an expedited fashion. The sponsor must report an adverse event expeditiously as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event.
  - SUSARs will be reported to the FDA and all participating investigators as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting. For an unexpected fatal or life-threatening suspected adverse reaction, the FDA should be notified as soon as possible but no later than 7 calendar days after the sponsor's initial receipt of the information.
- Findings from other studies

- The sponsor must report any findings from epidemiological studies, pooled analyses of multiple studies, or clinical studies (other than those reported under 21 CFR 312.32 (c)(1)(i)), whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.
  - Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.
- Findings from animal or in vitro testing
  - The sponsor must report any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure.
    - Ordinarily, any such findings would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.
- Increased rate of occurrence of serious suspected adverse reactions
  - The sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.
- Submission of IND safety reports.
  - The sponsor must submit each IND safety report in either:
    - A narrative format, OR
    - On FDA Form 3500A, OR
    - In an electronic format that FDA can process, review, and archive.
- FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files).
- The sponsor may submit foreign suspected adverse reactions on a Council for International Organizations of Medical Sciences (CIOMS) I Form instead of an FDA Form 3500A.
- Reports of overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format.
- Each notification to the FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the appropriate review division that has responsibility for review of the IND.
- Upon request from the FDA, the sponsor must submit to the FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

### **5.16.2. IDE Safety/Expedited Reporting**

*(Refer to 21 CFR 812.150 for more detailed information)*

- Unanticipated Adverse Device Effects (UADE) Reporting
  - The sponsor must report the results of an evaluation of an unanticipated adverse device effect to the FDA and all reviewing IRBs and investigators within 10 working days after the sponsor first receives notice of the adverse effect.
- Withdrawal of IRB Approval
  - The sponsor must notify the FDA and all reviewing IRBs and participating investigators of the withdrawal of IRB approval of an investigation (or any part of an investigation) within 5 working days of receipt of the withdrawal of approval.
- Recalls and Device Disposition
  - The sponsor must notify the FDA and all reviewing IRBs of any request that an investigator return, repair, or dispose of any unit of an investigational device within 30 working days after the request is made, and must state why the request was made.
- Failure to obtain informed consent under an IDE
  - The sponsor must submit a copy of any report by an investigator of the use of a device without first obtaining informed consent within 5 working days after receipt of the notice of such use.
- Significant Risk Device Determination
  - If an IRB determines that the device is a significant risk device and not a nonsignificant risk device as the sponsor had proposed to the IRB, a report must be submitted to the FDA within 5 working days after the sponsor learns of the IRB's determination.

## **5.17. IND/IDE TERMINATION, INACTIVATION, WITHDRAWAL, AND CLOSURE**

### **5.17.1. IND Termination**

- An IND can only be terminated by the FDA. Refer to 21 CFR 312.44 for procedures by which termination may occur.

### **5.17.2. IND Inactivation**

Below are the circumstances by which an IND can be inactivated. For more information refer to 21 CFR 312.45.

- If no subjects are entered into the clinical trial(s) for a period of 2 years or more under an IND, or if all investigations under an IND remain on clinical hold for 1 year or more, the IND may be placed by the FDA on inactive status. This action may be taken by the FDA either on request of the SAR or on the FDA's own initiative.
  - If the FDA seeks to act on its own initiative under this section, it shall first notify the sponsor in writing of the proposed inactive status. Upon receipt of the notification, the sponsor will have 30 days to respond as to why the

IND should remain active.

- If the sponsor wishes to place the IND on inactive status, the submission to the FDA should be done through the NINDS CTU.

If an IND is placed on inactive status, all investigators shall be informed and all drug supply shall be returned or disposed of (21 CFR 312.59).

A sponsor is not required to submit annual reports to an IND that is in inactive status. However, the inactive IND is still in effect for purposes of public disclosure of data and information under 21 CFR 312.130.

A sponsor who intends to resume clinical investigation under an IND placed on inactive status shall submit a protocol amendment under 21 CFR 312.30 containing the proposed general investigational plan for the coming year and appropriate protocols.

- Clinical investigations under an IND on inactive status may only resume:
  - 30 days after the FDA receives the protocol amendment, unless the FDA notifies the sponsor that the investigations described in the amendment are subject to a clinical hold under 312.42; or
  - On earlier notification by the FDA that the clinical investigations described in the protocol amendment may begin.
- An IND that remains on inactive status for 5 years or more may be terminated under 312.44.

#### **5.17.3. IND Withdrawal**

- Communication regarding the completion or closure of an intramural trial under IND should be initiated with the NINDS CTU in advance of the desired withdrawal of the regulatory application.
- For IND trials, the SAR must notify the NINDS CTU of the intent to withdraw the IND application, to prepare a withdrawal submission to the FDA. If an IND is closed early, the PI must provide information regarding the rationale for early withdrawal. If the clinical investigation has ended per protocol, the IND withdrawal submission should include a final annual report with final data and journal publication, if applicable.

#### **5.17.4. IDE Withdrawal**

- Communication regarding the completion or closure of an intramural trial under IDE should be initiated with the NINDS CTU in advance of the desired withdrawal of the regulatory application.
- For significant risk IDE trials, the PI must notify the NINDS CTU of the intent to withdraw the IDE application. The procedure for closing an IDE may vary depending on the time point in which the decision to close the IDE occurs. If the IDE is closed early, the PI should provide information regarding the rationale for early withdrawal. If the clinical investigation has ended per protocol, the IDE

submission should include a final progress report with final data and journal publication, if applicable. Refer to 21 CFR 812.30(b) for more information.

- If after closure of IDE has occurred, the sponsor decides to pursue an investigation of the device, a new IDE would need to be submitted; however, the closed IDE may be referenced in the new application.
- Below are the circumstances by which an IDE can be withdrawn or disapproved by the FDA (21 CFR 812.30(b):
  1. There has been a failure to comply with any requirement of this part or the act, any other applicable regulation or statute, or any condition of approval imposed by an IRB or FDA.
  2. The application or a report contains an untrue statement of a material fact, or omits material information required by this part.
  3. The sponsor fails to respond to a request for additional information within the time prescribed by FDA.
  4. There is reason to believe that the risks to the subjects are not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained, or informed consent is inadequate, or the investigation is scientifically unsound, or there is reason to believe that the device as used is ineffective.
  5. It is otherwise unreasonable to begin or to continue the investigation owing to the way in which the device is used or the inadequacy of:
    - i. The report of prior investigations or the investigational plan;
    - ii. The methods, facilities, and controls used for the manufacturing, processing, packaging, storage, and, where appropriate, installation of the device; or
    - iii. Monitoring and review of the investigation.

**5.17.5. Final Report of an IDE**

- For a significant risk device, the sponsor must notify the FDA and all reviewing IRBs within 30 working days of the completion or termination of the investigation. The sponsor must also submit a final report to the FDA and all reviewing IRBs and participating investigators within 6 months after the completion or termination of the investigation. A suggested format is provided in 21 CFR 812.150. For a non-significant risk device, the PI must submit a final report to all reviewing IRBs within 6 months after completion or termination.

**5.18 EXPANDED ACCESS TO INVESTIGATIONAL DRUGS OR DEVICES FOR TREATMENT USE**

NINDS serves as IND/IDE sponsor for all expanded access submissions to the FDA. The PI who will oversee the planned expanded access use must work with the NINDS CTU to determine which expanded access criteria apply. The PI will work with the CTU to prepare the expanded access submission under an IND or IDE as applicable, and throughout the period of the expanded access use.

Expanded access use or compassionate use INDs and IDEs will follow all applicable regulations (e.g., 21 CFR 312 Subpart I, 21 CFR 812.36, 21 USC 360bbb, 21 CFR 812.35(a), 21 CFR 56.104(c), 21 CFR 50.23, 21 CFR 812.150(a)(4)).

## 6. LIST OF REFERENCES/APPENDICES

A. FDA Form 1572:

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf>

B. IDE Approval:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046164.htm>

C. FDA regulations -- IND annual reports (21 CFR 312.33):

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=312.33>

D. FDA regulations -- IND safety reports (21 CFR 312.32):

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=312.32>

E. FDA IDE regulations (21 CFR part 812):

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=812>

F. FDA IND regulations 21 CFR part 312 (exemptions from these regulations provided at 312.2):

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312>

G. FDA IDE regulations, "Abbreviated Requirements" (21 CFR 812.2(b)):

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?FR=812.2>

H. FDA regulations -- Exception from general requirements for informed consent (21 CFR 50.23):

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.23>

I. FDA regulations -- Exemptions from IRB requirement (21 CFR 56.104):

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=56.104>

J. FDA regulations -- Exception from informed consent for emergency research (21 CFR 50.24):

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.24>

K. FDA regulations -- Institutional Review Boards (21 CFR part 56):

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56>

L. FDA Regulations -- "Protection of Human Subjects" (21 CFR part 50):

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50>

M. FDA Device Advice:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm>

N. Comparison of FDA's regulations at 21 CFR parts 50 and 56 and HHS Human Subject Protection Regulations:

<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/EducationalMaterials/ucm112910.htm>

O. HHS Human Subject Protection Regulations 45 CFR 46:

<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>

P. Medical devices:

[http://www.fda.gov/RegulatoryInformation/Guidances/ucm258946.htm#\\_Toc294261435](http://www.fda.gov/RegulatoryInformation/Guidances/ucm258946.htm#_Toc294261435) and

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051512.htm>

Q. Biological Product, 21 CFR 600.3(h):

<http://www.fda.gov/RegulatoryInformation/Legislation/ucm149278.htm>

R. 21 CFR 50.3 Definitions:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50&showFR=1&subpartNode=21:1.0.1.1.19.1>

S. 21 CFR 56.102 Definitions:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=56.102>

T. Guidance for Sponsors, Clinical Investigators, and IRBs: Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials:

<http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126489.pdf>

U. SOP 15: Research Regulated by the Food and Drug Administration (FDA): General Procedures for Both IND and IDE Applications

V. SOP 15A: Research Regulated by the Food and Drug Administration (FDA): Information and Policies Specific to Research Involving Investigational New Drugs (Including Biological Products)

W. SOP 15B: Research Regulated by the Food and Drug Administration (FDA): Information and Policies for Investigational Device Exemption (IDE)



X. Policy 801: HRPP Standard Operating Procedure/Policy Approval & Implementation: Reporting Research Events

Y. FDA Expanded Access for Medical Devices: <https://www.fda.gov/medical-devices/investigational-device-exemption-ide/expanded-access-medical-devices>

Z. Emergency Use and Compassionate Use of Unapproved Devices: <https://www.fda.gov/media/77477/download>

AA. Introduction to Master Files for Devices (MAFs): <https://www.fda.gov/medical-devices/premarket-approval-pma/master-files>

NOTE: definitions are available on the "[Glossary](#)" page of the CTU intranet.