



**Nova Southeastern University
Standard Operating Procedure for GCP**

Title: <u>Differentiation between "Off-Label" Use and Need for IND/IDE</u>		Version # 1
SOP Number: OCR-IIV-001	Effective Date: August 2013	Page 1 of 7

PURPOSE: Good medical practice and the best interests of the patient require that physicians and health care providers use legally available drugs, biologics and devices according to their best knowledge and judgment. If health care providers use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale as well as sound medical evidence, and to maintain records of the product's use and effects. Use of a marketed product in this manner when the intent is the "practice of medicine" does not require the submission of an Investigational New Drug Application (IND), Investigational Device Exemption (IDE) or review by an Institutional Review Board (IRB). However, the institution at which the product will be used may, under its own authority, require IRB review or other institutional oversight.

POLICY:

1. In order for research to be done with a drug or biologic that does not have NDA approval by the FDA, the test article must have an Investigational New Drug application on file with the FDA. In order for research to be done on medical devices that does not have 510(k), PMA, HUD or HDE approval, an IDE is required.
2. Even for products with NDA/510(k)/PMA/HUD/HDE approval, an IND or IDE is usually required if the research pertains to one of the following:
 - 2.1. New indication not on the label
 - 2.2. Manufacturer's intention to change product label
 - 2.3. Intended to support a significant change in advertising
 - 2.4. Uses a new route of administration
 - 2.5. Uses a new dosage level
 - 2.6. The product is used in new patient population that either significantly increases the risks or decreases the acceptability of the risks associated with the use of the product.

3. Supportive documentation is submitted to the IRB with a New Protocol Submission Form

Investigator-Initiated Clinical Trial

Investigator may wish to act as a sponsor and investigator of a clinical study. Acting as a sponsor-investigator, the investigator accepts all the responsibilities as an individual or organization initiating a clinical investigation. These responsibilities are:

- a) writing the protocol and designing the case report forms
- b) monitoring the study and reviewing the source documents
- c) drug/device accountability
- d) submitting safety reports to the FDA
- e) complying with all FDA regulations

NOTE: Investigators who wish to act as a sponsor-investigator are strongly recommended to contact the Office of Clinical Research for consultation. The Investigator will be provided with university specific documents and checklists that will assist with application process.

Procedure for an “Investigational New Drug Application” (IND) submission

A sponsor-investigator should follow the principles of the IND submission set forth in §312.22-312.23 of 21 CFR.

IND application includes:

- 1) Cover sheet (Form FDA-1571) that includes following
 - (i) The name, address and telephone number of the sponsor, the date of application, and the name of investigational new drug.
 - (ii) Identification of the phase of clinical investigation to be conducted.
 - (iii) A commitment not to begin investigation until an IND is in effect.
 - (iv) A commitment that IRB will be responsible for the initial, continuing review, and approval. Investigator will report to IRB all proposed changes to investigation.
 - (v) A commitment to conduct investigation in accordance with all applicable regulatory requirements.
 - (vi) The name and title of person responsible for monitoring the conduct and progress of the clinical investigation.

- (vii) The name and title of the person(s) responsible under §312.32 (IND safety reports) for review and evaluation of information relevant to the safety of the drug.
 - (viii) The information about contract research organization and statement regarding all transferring obligations.
 - (ix) Signature of authorized representative.
- 2) A table of contents.
 - 3) Introductory statement and general investigational plan.
 - 4) Investigator's brochure.
 - 5) Protocols.
 - 6) Chemistry, manufacturing, and control information.
 - 7) Previous human experience with the investigational drug.
 - 8) Additional information may be needed such as drug dependence and abuse potential, radioactive drugs, pediatric studies.
 - 9) Relevant information, if requested by FDA, such as previously submitted information.

Contacts and Submissions for FDA

Procedure for oral and written correspondence with the FDA

1. The Investigator contacts the FDA early in the planning process to find out the name of the administrative reviewer (Consumer Safety Officer- CSO) to get information about correspondence and submissions.
2. The date, time, parties and discussion summary of all oral conversations with the FDA personnel must be documented on a "Telephone Contact Log" (See Forms Section).
3. If the FDA requests a written response in its correspondence, the Investigator submits responses by due date or obtains an extension in advance from the agency.
4. Investigator Binder is where all FDA correspondence, including copies of all oral contact summaries, electronic mail, and written correspondence must be maintained current by the Investigator.
5. The Investigator should contact Office of Clinical Research for the guidelines on conducting a meeting with the FDA.
6. For meeting specified in the FDA regulations (end-of- phase 2, pre-NDA, pre-IDE) the Investigator must verify additional requirements by calling the Consumer Safety Officer at the FDA.

7. All meeting materials and correspondence must be collected in the appropriate section of the Investigator Binder.

Procedure for IND Development

1. The Investigator must follow the guidance for preparing the content of a new IND and collect all required forms and documents following the principles of the IND submission set forth in §312.22-312.23 of 21CFR (IND Form and Instructions- See Forms Section) .
2. By accessing the Internet, the Investigator should obtain all current versions of FDA-required forms. (See "IND Forms and Instructions" in the Forms Section of this manual).
3. Before submitting the IND to the FDA, the Investigator needs to provide the Office of Clinical Research with a full copy of the submission.
4. The Investigator should keep a copy of the full IND submission and related materials in the appropriate section of the Investigator Binder.
5. The Investigator may conduct the clinical trial after he or she received the IRB approval and the FDA's determination letter that grants the IND or an exemption from filing the IND.
6. In case the FDA requested supplementary information, the Investigator should provide it as soon as possible and within specified timeframes.
7. The Investigator should provide for the IRB a review of all changes in the study protocol and file IND amendments as required by the FDA.
8. The Investigator cannot progress with changes to the IND until it has been submitted to the FDA and approved by the IRB.
9. The Investigator should ensure reporting of all significant safety issues discovered during the study to the FDA, the IRB, OCR, and other applicable authorities.
10. If any regulatory authority (FDA, IRB, and University Administration) requested a clinical hold, the Investigator may not proceed until all issues are resolved.
11. If the clinical hold was issued after the study had already begun, the enrollment of new study participants must be ceased, and the Investigator must determine how to treat currently enrolled participants (e.g., stop study medication etc.).
12. If the FDA issued the clinical hold letter and specified the study may proceed after certain corrections are made without its prior approval, then the Investigator may proceed after the corrections are made. If

the clinical hold requires the FDA notification to proceed with the study, then that notification is required to proceed with the study after all terms of the clinical holds are satisfied.

13. If the FDA orders a termination of all or part of the IND, the Investigator must stop the clinical study and arrange for disposal of unused investigational drug/product.

The following regulations apply to the IND application process:

21CFR Part 312	Investigational New Drug Application
21CFR Part 314	INDA and NDA Applications for FDA Approval to Market a New Drug (New Drug Approval)
21CFR Part 316	Orphan Drugs
21CFR Part 58	Good Lab Practice for Nonclinical Laboratory [Animal] Studies
21CFR Part 50	Protection of Human Subjects
21CFR Part 56	Institutional Review Boards
21CFR Part 201	Drug Labeling
21CFR Part 54	Financial Disclosure by Clinical Investigators

Procedure for IDE Development

1. The Investigator must determine whether the investigational medical device is a Significant Risk (SR) or Non-Significant (NSR).
1. The Investigator should verify on the FDA website (www.fda.gov/cdrh/ or www.fda.gov/cber/) if there is a device-specific written guidance on content for required submission that already exist.
2. For NSR devices, submission to the FDA may be required for marketing (See 510(k) notification). The Investigator should consult with the FDA Consumer Safety Officer regarding submission, protocol, and clinical data requirements.
3. For a SR device study, the Investigator must contact the FDA to schedule for possible pre-IDE meetings or FDA pre-IDE protocol review.
4. After the investigational plan and clinical protocol are approved, the author should prepare the IDE submission content following the principles of the IND submission set forth in Part 812 of 21CFR.
5. The Investigator must provide OCR with a full copy of the submission before submitting the IDE to the FDA.
6. The Investigator should keep a copy of the full IDE submission and related materials in the appropriate section of the Regulatory Master File.
7. The Investigator may initiate the investigational medical device study after the receipt of the FDA's IDE determination letter that assigns an IDE number or grants an exemption from filing the IDE, and approval from the IRB.
8. In case the FDA requests supplementary information before granting the approval, the Investigator should provide it as soon as possible and within the specified timeframes.
9. The Investigator should use additional guidance for providing added information or changes in the study that must be reported to the FDA in an IDE supplement (See IDE Supplement Checklist).
10. The Investigator should ensure that the IRB reviews and approves all additions or changes of the study.
11. The Investigator must file IDE supplements as required by the FDA.
12. The Investigator may not proceed with changes to the IDE until it has been submitted to the FDA and approved by the IRB.
13. The Investigator should submit all required IDE reports to the FDA.

14. If safety issues arise during the clinical study conduct, the Investigator is responsible to ensure reporting and notification to the FDA, the IRB, OCR and other applicable authorities.
15. If the FDA disapproves an IDE, the Investigator cannot initiate the study until all questions identified by the FDA are resolved, and an approval is granted.
16. If the FDA withdraws an IDE after the study has begun, the Investigator must cease enrolling study participants and determine how to treat currently enrolled participants (e.g., stop study treatment etc.).
17. If the Investigator receives a disapproval letter from the FDA that specifies that the study can proceed after corrections are made, without its approval, then the Investigator may begin the study after corrections are put in place.
18. If the FDA's disapproval letter requires a FDA notification to proceed with the study, then that notification is required to proceed after all terms of the disapproval letter are satisfied.
19. The Investigator must stop study if the FDA orders a termination of all or part of the IDE, and the Investigator must arrange for disposal of all unused investigational product.

Procedure to Document IND Filing

1. When an IND is determined to be needed, the Center/College should obtain documentation of either:
 - 1.1. The IND approval from the FDA (the IND number will suffice)
 - 1.2. Dated copy of IND filing and a written attestation from the investigator that the FDA has not responded within 30 days.
 - 1.3. The 510K or IDE approval from the FDA
2. Any question to the validity of the claim shall be verified with the FDA.
3. Documentation shall be given to the IRB and OCR.