## OBJECTIVE

To describe policies and procedures related to how the Institutional Review Board (IRB) and IRB Office apply Food and Drug Administration (FDA) Drug and Device regulations to clinical investigations.

## GENERAL DESCRIPTION

FDA regulations are a separate set of regulations that apply to studies beyond the general Office for Human Research Protection (OHRP) regulations. FDA-regulated studies (hereafter referred to as "FDA clinical investigations") apply to studies in human participants that meet certain requirements for the use of drugs or medical devices. These requirements under 21 CFR 312 (drugs) and 812 (devices) impose additional responsibilities and review standards on investigators, institutions, and IRBs.

## RESPONSIBILITY

Execution of standard operating policy and procedure (SOPP): Principal Investigator (PI)/Research Personnel, IRB Office Staff, IRB Members, IRB Chairs.

## DEFINITIONS

FDA Clinical Investigation: any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the FDA under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the FDA under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit. (21 CFR 56.102(c))

Investigator: an individual who conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject) or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team. (21 CFR 56.102(h))

Participant (FDA Drug): an individual who is or becomes a participant in research as either a recipient of a test article or as a control, or as an individual on whose specimen a device is used. A participant may be either a healthy individual or a patient. [21 CFR 56.102(e)] (Drug, Food, Biologic).

Participant (FDA Device): a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A participant may

be in normal health or may have a medical condition or disease. [21 CFR 812.3(p)] (Medical Devices). This definition includes the use of tissue as specimens, even if they are unidentified.

Drug: a drug is defined as:

(A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and

(B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and

(C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and

(D) articles intended for use as a component of any articles specified in clause (A), (B), or (C).

Device: a device is defined as an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—

(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,

(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

(3) intended to affect the structure or any function of the body of man or other animals,

and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

Supplement: a product intended for ingestion that, among other requirements, contains a "dietary ingredient" intended to supplement the diet. The term "dietary ingredient" includes vitamins and minerals; herbs and other botanicals; amino acids; "dietary substances" that are part of the food supply, such as enzymes and live microbials (commonly referred to as "probiotics"); and concentrates, metabolites, constituents, extracts, or combinations of any dietary ingredient from the preceding categories.

Cosmetic: articles except for soap intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance.

Biologics/Biological Product: a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (consisting of 40+ amino acids), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

## PROCEDURES

I. General Determinations and Process

A. Clinical Investigation Determination
   a. The IRB Office reviews submissions to the IRB involving Drugs or Devices to determine if the submissions are FDA Clinical Investigations.
      i. An FDA Clinical Investigation is:
         1. Research involving human participants.
         2. A test article (drug or device) that either:
            a. Has received approval from the FDA, or
            b. Has not received approval from the FDA but data from the investigation may be used in a future FDA application.
   b. The IRB Office may consult with researchers and regulatory consultants in making the preliminary determination of a Clinical Investigation.

B. FDA Clinical Investigation submissions require NSU Biomedical Consent Form templates.
   a. Exception: the IRB Office may grant permission to use a sponsor's consent form template after review.
      i. Under NO circumstances can an informed consent form also serve as a HIPAA Authorization form.
   b. Regardless of template, the consent form must include the following FDA-specific items:
      i. FDA statement that the drug/device is not FDA approved as being used.

      "This research involves an [investigational drug and/or device] that is not approved by the U.S. Food and Drug Administration or has not been approved for the purpose being used in this research study."

      ii. Statement that the FDA may inspect research records:

> Only people who need to review your information will have access to study files. Organizations or people that may review and copy your information include:
> …
> The U.S. Food and Drug Administration (FDA)

iii. Injury Compensation language, per NSU institutional requirements, unless otherwise dictated by sponsored agreement:

> Nova Southeastern University does not have a program to pay you if you are hurt or have other bad results from being in this study. Medical care at Nova Southeastern University is open to you as it is to all sick or injured people. The cost for such care will be billed to you or your insurance company.
> If you sign this form, you do not give up your right to seek additional compensation if you are harmed because of participation in this study.

iv. Posting of a study on clinicaltrials.gov (see below for more information):

> A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. The Web site will include a summary of the results. You can search this Web site at any time.

C. FDA Clinical Investigations must register with clinicaltrials.gov.
   a. The FDA's guidance on registration is here: https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/fdas-role-clinicaltrialsgov-information. See Division of Research (DoR) Policy for specific information on the process.

D. Good Clinical Practice requirements.
   a. These requirements are the responsibility of the investigator overseeing the clinical investigation. Delegation of any of these responsibilities must be documented properly. Researchers should contact Office of Clinical Research (OCR) at ocr@nova.edu or visit https://www.nova.edu/ocr/policies-for-gcp/index.html for further requirements and guidance on best practices.

b. Investigators must contact the Office of Clinical Research (OCR) at ocr@nova.edu with the sponsor's protocol, research documents, and agreements. This action should conducted separately from the IRB submission.

E. Review Process
   a. Upon initial submission, the IRB Office reviews all materials in the submission form and makes a recommendation about the FDA Clinical Investigation status, IND/IDE status, and exemptions or waivers under FDA determinations.
      i. The IRB Office will request further information or clarification as needed for the submission.
   b. IRB Policy 2-1 outlines review conditions for IND and IDE convened review; studies found to be exempt from IND and IDE requirements may be Expedited.
   c. Chair recommendations will be sought if the IRB Office is unable to make a preliminary recommendation.

II. Investigational Device Specific Determinations and Process

A. All clinical investigations of devices must have an approved IDE (Investigational Device Exemption) from the FDA or be exempt from the IDE regulations before beginning clinical investigation activities. An investigational device exemption (IDE) allows the investigational device to be used in a clinical study to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification 510(k) submission to FDA.
   a. In accordance with FDA regulations, preliminary or pilot research studies with limited scope or scale require review by the IRB.

B. The IRB Office will provide guidance on whether an IDE will be required after the submission of a consultation request. The DoR may also provide support in this process. To request a consultation, PI should contact the IRB:
   a. Prior to any studies activities and prior to IRB New Protocol submission.
   b. By email, providing an up-to-date version of protocol and any supporting documents describing the planned investigation.
   c. IRB can provide guidance on probable need for an IDE application, but the final determination will be made by the FDA per 21 CFR 812.

C. Exemptions from Device Regulations (Device Exemptions):
   a. Device Exemptions under FDA regulations are different from Exempt Categories under OHRP regulations.

b. FDA Device Exemption: If the investigator or sponsor has correspondence with the FDA on the topic of a Device Exemption, the investigator must attach it in the New Protocol Submission.
c. Requests for Device Exemptions are made by the investigator to the IRB as part of the New Protocol Submission form. The determination of a Device Exemption is made by the IRB as outlined in "General Determinations and Procedures" above.
d. Device Exemptions:
    i. Require a New Protocol Submission form to the IRB, reviewed under Policy 2-1 and OHRP regulations.
    ii. May involve FDA regulations at 21 CFR 50 and 56.
    iii. Do not involve FDA regulations at 21 CFR 812.
e. The specific Exemptions considered by the IRB are:
    i. Use of a legally marketed device used according to its labeling.
    ii. Diagnostic Devices that are:
        1. Noninvasive or does not require invasive sampling procedures that present significant risk.
        2. Does not introduce energy into a subject, ex: ionizing radiation.
        3. Is not used for actual diagnosis unless that diagnosis is confirmed by another established procedure or device.
    iii. Consumer Preference Testing, including modifications or testing combinations of devices if:
        1. The devices are legally marketed.
        2. The testing is not for determining safety or efficacy and participants are not at risk.
f. FDA Device Waiver/Alteration: The FDA may grant, at its discretion, a waiver or alteration from the regulations at 21 CFR 812. The sponsor of the study must make the request.
    i. The IRB Office STRONGLY recommends that investigators seek the waiver or alteration AS SOON AS POSSIBLE.

D. Investigational Device Exemptions (IDEs): All studies not qualifying for a Device Exemption must abide by the requirements under 21 CFR 812, which includes obtaining an IDE for a specific study of a given device.

E. There are two pathways for obtaining an IDE: full IDEs obtained from the FDA for Significant Risk Devices and abbreviated IDEs for Not-Significant Risk Devices obtained either from FDA or from an IRB.
    a. Not Significant Risk Devices:
        i. NSR Devices are defined as devices which do not present a significant risk.
        ii. NSR devices may use an approved IRB submission as their abbreviated submission to the FDA.
        iii. The NSR determination may be made by:
            1. A written determination by the study sponsor, including justification, that is attached to the IRB submission. The convened IRB reviews the sponsor's determination to decide whether to endorse the determination.
            2. The convened IRB if the study sponsor has not made the determination.
            3. A prior FDA determination, which is final. The investigator must attach the correspondence with the FDA to their submission.
    b. Significant Risk (SR) Devices: Significant Risk devices are devices that present a serious risk to health, safety, or welfare of participants. Typically, these are devices that are implanted, sustain/support human life, or are substantially important in healthcare, but carry a potential for significant risk.
        i. All SR device studies require an IDE submission to the FDA and FDA approval of the IDE submission.
        ii. The IRB cannot approve a SR device study without:
            1. The approval document from the FDA, including IDE number issued by the FDA.
            2. The IDE submission to the FDA, including the specific protocol approved by the FDA as part of the IDE submission.
            3. All correspondence with the FDA as part of the IDE process.
        iii. If the IRB determines that a device study does not qualify for a NSR determination, then the IRB will require that the study sponsor and the investigator undergo the IDE process.

III. Drug Specific Determination and Processes:

A. All clinical investigations of drugs must either have an approved IND (Investigational New Drug) from the FDA or qualify as exempt from the INfD regulations.

a. These requirements apply regardless of the scope or scale of the study. Pilot and feasibility studies are still research studies requiring review by the IRB under FDA regulations.

B. Guidance on whether an IND will be required can be obtained through consultation with IRB by submitting a consultation request. DoR may also provide support in this process. To request a consultation, PI should contact the IRB:
   a. Prior to any studies activities and prior to IRB New Protocol submission.
   b. By email, providing an up to date version of protocol and any supporting documents describing the planned investigation.
   c. IRB can provide guidance on probable need for an IND application, but final determination will be made by the FDA per 21 CFR 312.

C. Exemptions from Drug Regulations (Drug Exemptions):
   a. Drug Exemptions under FDA regulations are different from Exempt Categories under OHRP regulations.
   b. The investigator must submit all correspondence with the FDA as part of the New Protocol Submission along with all materials submitted to the FDA.
   c. Requests for Drug Exemptions are made by the investigator as part of the New Protocol Submission form. The determination of a Drug Exemption is made by the IRB as outlined in "General Determinations and Procedures" above.
   d. Drug Exemptions:
      i. Require a New Protocol Submission and IRB review under Policy 2-1 and OHRP regulations.
      ii. Do not require IRB review under FDA regulations for 21 CFR 312.
      iii. May be subject to the general FDA regulations at 21 CFR 50 and 56.
   e. The FDA may grant an exemption from IND requirements or may waive or alter the requirements under 21 CFR 312. The sponsor of the study must make the request.
      i. The IRB Office STRONGLY recommends that investigators seek the waiver or alteration AS SOON AS POSSIBLE.
   f. The specific Exemptions are:
      i. Use of a legally marketed drug used according with its labeling which meet ALL the following:
         1. The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any significant change in the labeling for the drug.

2. The drug that is undergoing investigation is lawfully marketed as a prescription drug.
3. The investigation is not intended to support a significant change in the advertising for the product.
4. The investigation does not involve a route of administration or dosage level or use in a patient population or other factors that significantly increase the risks (or decreases the acceptability of the risks) associated with the use of the drug.
5. The investigation is conducted in compliance with the requirement for institutional review set forth in 21CRF 56 and with the requirements for informed consent set forth in 21CFR 50.
6. The investigation is conducted in compliance with the requirements of 21CRF 312.7 - meaning that the drug may not be represented as safe or effective for the purposes for which it is under investigation, nor may it be commercially distributed or test marketed or sold.

ii. Bioavailability/Bioequivalence Studies (typically generic drug testing):
1. The drug product does not contain a new chemical entity (21 CFR 314.108), is not radioactively labeled, and is not cytotoxic.
2. The dose (single dose or total daily dose) does not exceed the dose specified in the labeling of the approved version of the drug product.
3. The sponsor meets the requirements for retention of test article samples (21 CFR 320.31(d)(1)) and safety reporting (21 CFR 320.31(d)(3)).

g. If an IND is required, either from clear application of the regulations or by specific IRB determination, the investigator must submit the IND paperwork, FDA correspondence, and IND number as part of their IRB submission to obtain IRB approval.

IV. Supplements/Cosmetics

A. Supplements: Supplements may only be taken orally, including vitamins, minerals, herbs/botanicals, amino acids, and naturally occurring substances including extracts and concentrates.
B. Cosmetics: Cosmetics are topically applied products and use the same “structural” vs. “disease” claim evaluation. Cosmetics cannot include any soaps or disinfectants.

C. Determinations:
   a. The IRB or Chair will review any submissions using supplements or cosmetics for structural vs. disease claims under 21 CFR 101.93(f) and (g).
   b. Studies involving disease claims will be reviewed as drugs possibly requiring an IND as outlined above.
   c. Studies involving ONLY structural claims will be reviewed under Expedited Review per Policy 2-1.
   d. Investigators may contact the FDA with a protocol to ask for a determination. The FDA determination is final, and all correspondence must be attached to the IRB submission.

## REFERENCES

**21 CFR 50, 56, 312, 812**