



The University of Georgia requires its researchers and its IRB to comply with all applicable regulations of the Food and Drug Administration (FDA) when conducting research with drugs, devices, supplements, botanicals, or biologics (collectively referred to as “items”) that are regulated by the FDA. This includes the research use of items that have already received FDA approval as well as the research use of investigational items.

The FDA has its own definitions of “human subject” and “research” (called “clinical investigation” by the FDA), which the University of Georgia IRB applies when it considers whether a proposed activity requires IRB review. Researchers who have the roles of both “investigator” and “sponsor”, as defined by the FDA, have additional FDA-specified responsibilities which University of Georgia IRB expects them to fulfill.

This guidance document describes the requirements and procedures for research that is subject to the regulations of the FDA.

### A. DEFINITIONS (per FDA)

1. **Biologic:** Also called a biological product. Defined as a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product which is applicable to the prevention, treatment, or cure of a disease or condition of human beings. Also includes immunoglobulin products, products containing cells or microorganisms, somatic cells, gene therapy, tissues, recombinant therapeutic proteins, and most protein products. Biologics can be composed of sugars, proteins or nucleic acids or complex combinations of these substances, or may be living entities such as cells or tissues. Most biologics meet the FDA’s definition of “drug”. Investigational biologics are generally subject to the investigational drug regulations (i.e., 21 CFR 312). However, depending in part on its intended use, a biologic may be a drug or device.
2. **Botanical:** A finished, labeled product that contains vegetable matter, which may include plant materials, algae, macroscopic fungi, or combinations of these. Depending in part on its intended use, a botanical product may be a food, drug, medical device, or cosmetic.
3. **Classes of devices:** The FDA has established three regulatory classes for devices, based on the level of control necessary to assure the safety and effectiveness of the device. Device classification determines which type of premarketing submission or application is required in order to obtain FDA clearance to market a device.
  - a) **Class I:** Very low risk devices that are generally exempt from FDA regulations. All Class I medical devices are exempt from the requirement of premarket notification (510(k)) unless the device is intended for a use that is of substantial importance in preventing impairment to human health or presents a potentially unreasonable risk of illness or injury. Examples: tongue depressors; stethoscopes; elastic bandages.
  - b) **Class II:** Moderate risk devices that are generally subject to 510(k) clearance. Clinical investigations are not required in most cases. However, if clinical data are necessary to

demonstrate “substantial equivalence” to another device, the clinical study must comply with the IDE regulations. Subject to labeling requirements, mandatory performance standards, and post-market surveillance. Typically non-invasive. Examples: MRIs; software; powered wheelchairs; surgical needles.

- c) **Class III:** Higher risk devices that require Premarket Approval (PMA). Clinical investigations are necessary to establish the safety and efficacy of the device. Insufficient information exists to assure safety and effectiveness solely through the general or special controls sufficient for Class I or Class II devices, or is of substantial importance in preventing impairment to human health or presents a potential unreasonable risk of illness or injury. Class III devices are usually “significant risk” devices, but also include a few “non-significant risk” devices such as continuous glucose monitors and PSA tests. Examples of Class III devices: nonroller cardiovascular blood pumps; hemoperfusion systems for the treatment of hepatic coma and metabolic disturbances; and nonthermal shortwave diathermal devices.
4. **Custom device:** A device that is not being used to determine safety or effectiveness for commercial distribution, and which has all of the characteristics described below. Data are not collected on its use for submission to the FDA. Custom devices are not subject to FDA regulations. The concept of “custom device” should not be used to circumvent the FDA regulations. Use of custom devices may still require IRB review, however, if the use meets the Health and Human Services definition of “human subjects research”.

Required characteristics of custom device:

- a) Necessarily deviates from devices generally available or from an applicable performance standard or premarket approval requirement in order to comply with the order of an individual physician or dentist;
  - b) Is not generally available to, or generally used by, other physicians or dentists;
  - c) Is not generally available in finished form for purchase or for dispensing upon prescription;
  - d) Is not offered for commercial distribution through labeling or advertising; and
  - e) Is intended for use by an individual patient named in the order of a physician or dentist, and is to be made in a specific form for that patient, or is intended to meet the special needs of the physician or dentist in the course of professional practice.
5. **Device:** An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article which is recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement, and is:
- a) Intended:
    - i. 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
    - ii. To affect the structure of any function of the body of man or other animals;

- b) And which does not achieve its primary intentional purposes through chemical action and which is not dependent upon being metabolized for the achievement of its primary intended purposes.
  - c) Can include investigational software, whether it is “standalone” software meant for use on a general-purpose computer/other device, or it is a component of or accessory to another medical device (such as a MRI machine or CT scanner).
6. **Drug:** A drug is defined by the FDA as:
- a) A substance recognized by an official pharmacopoeia or formulary, or
  - b) A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, or
  - c) A substance (other than food) intended to affect the structure or any function of the body, or
  - d) A substance intended for use as a component of a medicine but not a device or a component, part, or accessory of a device.
  - e) Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process).
7. **Humanitarian Device Exemption (HDE):** A type of application to the FDA for an investigational device that, if approved, means that the device can be used clinically without having first demonstrated to the FDA its effectiveness. Clinical use of investigational devices under a HDE is not considered research, but the FDA nonetheless requires IRB review prior to use. The term HDE is also used to refer to FDA approval for a physician to use a HUD for research.
8. **Humanitarian Use Device (HUD):** A device that is intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year.
9. **Investigational:** This term is used to refer to an item that is not FDA-approved for marketing in the United States, or to an item that is being evaluated for a new and not-yet-approved indication, dosage, or formulation.
10. **Investigational Device Exemption (IDE):** An IDE application is the document submitted to the FDA for permission to conduct a clinical study using a significant risk device that is new or not approved for a given use. When the FDA approves an IDE application, it assigns an IDE number to the specific use of the device.
11. **Investigational New Drug (IND):** An IND application is the document submitted to the FDA for permission to conduct a clinical study using a drug or biologic that is new or not approved for a given dosage, formulation, or indication. When the FDA approves an IND application, it assigns an IND number to the specific use of the item.
12. **Investigator:** The individual conducting the research. The term “researcher” is used in this document in place of “investigator”, so as to be consistent with other UGA IRB SOPs.

13. **Investigator's Brochure:** A comprehensive document summarizing the body of information about an investigational product. The purpose of it is to compile data relevant to studies of the investigational item in human subjects, gathered during preclinical and clinical trials. It contains a "Summary of Data and Guidance for the Investigator" section, of which the overall aim is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. The sponsor is responsible for keeping the information up-to-date.
14. **Non-significant risk device:** An investigational device that does not meet the definition of a significant risk device. This is not the same as the concept of "minimal risk" as used elsewhere in federal human subjects regulations. An IDE is not required for studies involving a non-significant risk device. For this reason, the FDA is usually not aware of the existence of these studies even after they receive IRB approval.
15. **Phase:** Clinical trials involving new drugs are commonly classified into phases. Each phase has a different purpose.
  - a) **Phase 0:** Pharmacodynamics and Pharmacokinetics. These are "first-in-human" trials. Typically, single sub-therapeutic doses of the drug are given to a small number of individuals (10-15) to gather preliminary data about pharmacodynamics (what the drug does to the body) and pharmacokinetics (what the body does to the drug).
  - b) **Phase 1:** Screening for safety. The drug is tested in a small group of people (20-80) to evaluate its safety, determine a safe dosage range, and identify side effects.
  - c) **Phase 2:** Establishing efficacy. The drug is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety. It may be compared against a placebo or against an approved drug designed to treat the same condition.
  - d) **Phase 3:** Final confirmation of safety and efficacy. The drug is given to large groups of people (1000-3000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely.
  - e) **Phase 4:** Sentry studies during sales. These post-marketing studies gather additional information, including the drug's risks, benefits, and optimal use.
16. **Premarket Approval (PMA):** A type of application to the FDA, for high risk Class III devices. In most cases, an IDE is required to clinically evaluate devices subject to PMA regulations.
17. **Premarket Notification (510(k)):** A type of application to the FDA, used for Class I, Class II, and some Class III devices which the sponsor believes have "substantial equivalence" to the safety and effectiveness of an already-approved device.
18. **Protocol:** A complete written description of a research activity involving human subjects. Often includes the scientific rationale as well.
19. **Significant risk device:** An investigational device that meets any of the following criteria. An IDE is required before the study can begin.

- a) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
  - b) Is purported or represented to be for use in supporting or sustaining human life and presents a potential for serious risk to the health, safety or welfare of a subject;
  - c) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject;
  - d) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject, OR
  - e) Is classified by the FDA as a significant risk device.
20. **Sponsor:** The person, company, organization, or other entity that initiates and takes responsibility for a clinical investigation using an FDA-regulated item. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. The item is administered, dispensed, or used under the immediate direction of another individual. The sponsor is almost always the holder of an IND or IDE when the research involves an item that the FDA considers investigational.
21. **Sponsor-Investigator:** An individual who both initiates and actually conducts, alone or with others, a clinical investigation; that is, under whose immediate direction the test item is administered, dispense or used. This term does not include any entity other than an individual. A sponsor-investigator has the responsibilities of both a sponsor and an investigator.
22. **Supplement (dietary supplement):** A product (other than tobacco) that is:
- a) Intended to supplement the diet, and that bears or contains one or more of the following dietary ingredients: (a) a vitamin; (b) a mineral; (c) an herb or other botanical; (d) an amino acid; (e) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (f) a concentrate, metabolite, constituent, extract, or combination of these ingredients,
  - b) Not represented for use as a conventional food or a sole item of a meal of the diet, and
  - c) Is labeled as a dietary supplement.

## B. RESPONSIBILITIES

Specific responsibilities for researchers, staff, and the UGA IRB are described throughout this document. However, the researcher responsibilities described here are limited to those associated with IRB review and approval. Researcher responsibilities to the FDA (whether as a sponsor, an investigator, or a sponsor-investigator) or to a sponsor are not described here.

Determining whether FDA regulations apply. Human Subjects Office (HSO)/IRB staff determines which FDA regulations, if any, apply to a research study during pre-review of the IRB application materials provided by the researcher, in the absence of specific information from the FDA. The assessment may require obtaining additional information from the researcher, the sponsor, and/or the FDA.

If the FDA has indicated that the research involving the specific use of the item is subject to its regulations, the UGA Human Research Protection Program applies the relevant FDA regulations for the IRB review.

IND or IDE requirement. The FDA requires sponsors and sponsor-investigators to determine whether an IND or IDE is required for a study.

Though it is not the responsibility of HSO staff or the IRB to determine whether an IND or IDE is necessary, the FDA has stated that the IRB's role is to ask the researcher whether an IND or IDE is required and the basis for that determination. This is accomplished by the UGA IRB through the researcher's completion of the Drugs and Devices page of the IRB submission.

UGA researchers who are sponsor-investigators and who think they need an IND or IDE are strongly encouraged to submit their IND or IDE application to the FDA before or at the same time as submitting the IRB application to the IRB, to reduce delays in initiating the study.

The investigator is required to wait 30 calendar days after submitting the IND application to the FDA before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk. The IRB will not provide final approval to the study until the 30 day time period has passed. Investigators conducting studies with an IND are required to submit documentation (either a letter or email from the FDA or sponsor, or indication on the commercial sponsor's protocol) of the IND number assigned by the FDA. If the IND is an investigator-held IND, the entire IND application and the FDA Form 1571 (IND application cover page) are required. This documentation must be uploaded with the IRB submission.

The role of the IRB. The IRB has neither the responsibility nor authority to determine whether an IND or IDE is necessary. The FDA has specified that the IRB's role is to ask the researcher whether an IND or IDE is required and the basis for that determination.

If the IRB believes that the study requires an IND or IDE but the researcher and/or sponsor does not, the IRB has the authority to require the researcher and/or sponsor to provide or obtain confirmation from the FDA that an IND or IDE is not required.

Device risk assessment. For studies with an investigational device, the convened IRB must determine whether the use of the device involves "significant risk" or "non-significant risk". The risk determination is specific to the use of the device in the proposed study. The researcher is responsible for providing the IRB with any information relevant to this determination, including a copy of the FDA's determination (if one has been made).

Consent form elements. The FDA has additional requirements for consent processes and forms. The IRB confirms that these requirements have been met. The IRB does not approve the research until any missing elements have been provided. The requirements are:

- FDA review. A statement indicating that the FDA may review subject medical records and research records which identify the subjects.

- Clinical trial registration. For applicable clinical trials: A statement informing subjects that the clinical trial has been registered with the ClinicalTrials.gov database, and that some research data will be submitted to the database. The FDA regulation (21 CFR 50.25(c)) specifying this requirement provides the exact statement that must be used ad verbatim.
- Data retention after subject withdrawal. FDA has a policy on the withdrawal of subjects from clinical investigations which must be considered and the appropriate language included in the consent form; see <https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126489.pdf>.

Waiver of documentation of Informed Consent. FDA regulations allow the waiver of a signed written consent form if the IRB determines that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context. In the event that an IRB waives the requirement for written documentation of informed consent, FDA recommends that the elements of informed consent be reviewed verbally with the subject or the subject's legally authorized representative. Additionally, the IRB may require the investigator to provide subjects with a written statement regarding the clinical investigation. FDA recommends that when an IRB waives the documentation requirement for informed consent in circumstances where there is minimal risk of harm, the consent process and discussion be described and noted in the records relating to the clinical investigation.

Waiver or alteration of Informed Consent. FDA has recently issued guidance allowing IRBs to waive the requirement to obtain consent, or to make alterations to, or omission of, some or all elements the informed consent under circumstances that mirror those currently found in the Common Rule at 45 CFR 46.116(d). Specifically, an IRB may waive or alter informed consent if it finds and documents that:

1. The clinical investigation involves no more than “minimal risk” to subjects;
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
3. The clinical investigation could not practicably be carried out without the waiver or alteration; and.
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

### **C. Questions**

Please contact the Human Subjects Office (706-542-3199 or [irb@uga.edu](mailto:irb@uga.edu)) for any questions or assistance.