

The Food and Drug Administration (FDA) regulates drugs, biologics, devices, food or color additives and electronic products used in the diagnosis, mitigation, treatment, or prevention of disease in humans. When reviewing research or clinical investigations involving these products (test articles), the IRB applies additional FDA requirements to protect the safety and welfare of research participants. The FDA also charges sponsors and investigators with specific responsibilities in the conduct of such research.

#### 1.0 Applicability.

Research or clinical investigations involving a test article and one or more human subjects must comply with additional FDA regulations to protect the safety and welfare of research participants. Test articles regulated by the FDA include:

- drugs for human use
- biological products for human use
- medical devices for human use
- human food additives
- color additives
- electronic products
- any other articles subject to regulation under the Food and Drug Act

#### 2.0 Drugs and biologics.

Research projects involving administration of a drug or biologic to human subjects are applicable to FDA regulations. These requirements apply whether or not the drug or biologic is being studied for safety and effectiveness, and regardless of the investigator's intention to submit data to FDA in support of a change in marketing or labeling.

Applicable research includes projects involving:

- FDA approved drugs and biologics administered solely for research purposes
- drugs and biologics not yet approved for marketing by the FDA
- botanical or natural products (e.g., food or dietary supplements) being tested for the prevention, cure, or treatment of a specific disease or class of diseases, or to affect the structure or function of the body

Research projects involving orally ingested dietary supplements are not applicable when being tested:

- for benefits related to a classical nutrient deficiency disease
- to affect the structure or function of the human body, and
- to promote general well-being.

In the IRB protocol submission, the investigator includes additional drug information: FDA status, approved indications, risks, proposed use, and results of any prior lab or animal studies.

### 2.1 Investigational new drug application (IND).

Research involving new drugs not previously approved, as well as drugs under evaluation for a new indication require an investigational new drug application (IND) from the FDA. Sponsors, or sponsor-investigators, are responsible for submitting the application to the agency, and complying with specific responsibilities in the conduct of the research, as described in FDA regulations at 21 CFR 312. The FDA Center for Drug Evaluation and Research (CDER) may be contacted for assistance with this process. The investigator submits documentation of IND approval (FDA letter or sponsor letter listing IND#) in the IRB protocol application.

### 2.2 Exempt from IND requirement.

Research involving FDA approved drugs or biologics are exempt from the IND requirement provided that the investigation:

- is not intended to be reported to the FDA to support a new indication for use or a significant change in labeling
- is not intended to support a significant change in advertising for the product
- does not involve a route of administration, dosage level, patient population, or other factor that significantly increases the risks associated with use of the product, AND
- complies with requirements for IRB review and informed consent, and requirements prohibiting promotion and sale of investigational drugs.

Research projects involving *in vitro* diagnostic biological products are exempt from the IND requirement as long as the product is:

- intended to be used in a diagnostic procedure that confirms the diagnosis made by another medically established diagnostic product or procedure, or
- blood grouping serum, reagent red blood cells and anti-human globulin.

Research exempt from the IND requirement is not exempt from the requirements for IRB review and informed consent. When uncertainty or disagreement exists regarding IND requirements, the investigator contacts the FDA Center for Drug Evaluation and Research for a final determination.

### 2.3 IRB review.

The IRB performs initial and continuing review of research involving drugs or biologics at a convened meeting including the presence of a physician member, unless eligible for expedited review. Applicable categories of expedited review include:

- (1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
  - (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
  - (b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the

medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

- (8) Continuing review of research previously approved by the convened IRB as follows:
- (a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or
  - (b) where no subjects have been enrolled and no additional risks have been identified; or
  - (c) where the remaining research activities are limited to data analysis.
- (9) Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

#### 2.4 Treatment use or emergency use of investigational new drugs or biologics.

Under limited circumstances, a physician may use an investigational new drug or biologic to provide emergency patient care, when the drug may be the only possible life-saving alternative. NDSU has no procedures for IRB review of such use, however, as the scope of NDSU functions does not include provision of emergency medical care.

#### 3.0 Medical devices.

Research involving investigational use of a medical device is applicable to FDA regulations for protection of the welfare of participants. 'Investigational use' involves studies performed to establish safety and effectiveness of a device. Medical devices may come in a variety of forms; the FDA defines medical devices on the basis of the product's intended use: diagnosis, cure, mitigation, treatment, or prevention of human disease, or to affect the structure or any function of the human body. This definition encompasses a diverse array of products including: implantable heart valves, catheters, wheelchairs, contact lenses, orthopedic pins, surgical gloves, and diagnostic instruments or test kits.

These requirements apply whether or not the data is intended to be submitted to the FDA to support a new indication or marketing. Applicable research includes projects involving:

- unapproved devices studied for safety and effectiveness
- approved devices studied for a new, previously unapproved indication

FDA requirements do not apply when the safety or effectiveness of a device is not the purpose of the research, and the device is used in accordance with approved FDA indications. For example, an approved ECG is used in a research project to monitor heart rhythm, to obtain data for research of a new cardiac medication.

In the IRB protocol submission, the investigator includes additional device information: FDA status, approved indications, risks, proposed use, and results of any prior lab , animal or clinical studies.

### 3.1 Risk determination.

Medical device studies are classified on the basis of significant risk (SR), or non-significant risk (NSR). The sponsor, or sponsor-investigator, makes the initial determination of risk and provides this assessment to the IRB. At a convened meeting, the IRB evaluates the level of risk based on information provided by the investigator in the protocol attachment form, including a detailed description of the device, reports of previous studies of the device, proposed research use, subject selection criteria and monitoring plan.

The risk determination is based on the type of device, as well as considerations of:

- proposed use of the device
- nature of harm that may result from use of the device
- whether the subject will need to undergo an additional procedure for the study

#### 3.1.1 Significant risk device studies.

FDA defines a significant risk (SR) device as one that presents the potential for serious risk to the health, safety, or welfare of a subject and:

- is intended as an implant
- is purported or represented to be for a use in supporting or sustaining human life
- is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health, or
- otherwise presents a potential for serious risk to the healthy, safety or welfare of a subject

Several examples of SR devices include:

- Collagen implant material for ear, nose and throat surgery, dental applications
- Surgical lasers for various medical specialties
- Tissue adhesives
- Breathing gas mixers
- Bronchial or tracheal tubes
- Epidural and spinal catheters
- Respiratory ventilators
- Artificial hearts, cardiac bypass devices
- Cardiac pacemaker
- CPR devices
- Organ storage/transport units
- Pacing leads
- Endosseous implants and associated bone filling and augmentation materials

- TMJ prostheses
- Absorbable gelatin sponge
- ENT cements/adhesives
- Injectable Teflon paste
- Dialysis delivery systems
- Sutures
- Infusion pumps
- Contraceptive devices
- Extended wear contact lenses
- Bone growth stimulators
- Computer guided robotic surgery

### 3.1.2 Non-significant risk device studies.

A device not meeting criteria as a significant risk device is considered to be a NSR device. Several examples of NSR devices include:

- Contact lens solutions and daily wear contact lenses
- Digital mammography
- Denture repair kits
- Conventional implantable vascular access devices (ports)
- Electroencephalography
- External monitors for insulin reactions
- Non-invasive electrical neuromuscular stimulators
- Low power lasers for pain treatment
- MRI devices
- Menstrual pads or tampons
- Non-implantable electrical incontinence devices
- Wound dressings

Inclusion of a device on the NSR list is not a final determination of risk, as the evaluation must consider the proposed use of a device, and other factors. When uncertainty or disagreement exists regarding a risk determination, the sponsor or sponsor-investigator submits an application to the FDA Center for Devices and Radiological Health for a final determination.

## 3.2 Investigational Device Exemption (IDE) requirements.

Research involving investigational use of medical devices requires an investigational device exemption (IDE) from the FDA, unless exempt from the IDE requirement. The process to obtain an approved IDE depends on the risk classification of the study.

### 3.2.1 SR device studies.

Significant risk device studies require FDA approval of an IDE. The sponsor, or sponsor-investigator, of an SR device study is responsible for submitting an IDE application to the Agency, as outlined in federal regulations at 21 CFR Part 812, Investigational Device Exemptions. The FDA Center for Devices and Radiological Health (CDRH) may be contacted for assistance with the process. Upon approval, the sponsor and investigator(s) agree to comply with their responsibilities, as outlined in 21 CFR Part 812 ('full' IDE requirements). The

investigator submits documentation of IDE approval (FDA letter or sponsor letter listing IDE#) in the IRB protocol application.

### 3.2.2 NSR device studies.

Non-significant risk device studies do not require submission of an IDE application to the FDA. Such studies are considered to hold an approved IDE once approved by the IRB, provided that the investigator and sponsor comply with their responsibilities, as outlined in 21 CFR Part 812.2 ('abbreviated' IDE requirements).

### 3.3 Exempt from IDE requirements.

Research involving investigational use of any of the following devices is not applicable to IDE requirements:

- a device, other than a transitional device, in commercial distribution before May 28, 1976, when used in accordance with indications in labeling
- a device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined is substantially equivalent to a device in commercial distribution before May 28, 1976, and used in accordance with indications in labeling
- an *in vitro* diagnostic device, if the testing is:
  - noninvasive
  - does not require an invasive sampling procedures that presents significant risk
  - does not by design or intention introduce energy into a subject, and
  - is not used as a diagnostic procedure without confirmation of diagnosis by another established product or procedure
- a device undergoing consumer preference testing, testing of a modification, or testing of a combination of 2 or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk
- a device intended solely for veterinary use
- a device shipped solely for research on or with lab animals, and labeled appropriately, OR
- a custom device, unless the device is being used to determine safety or effectiveness for commercial distribution

Such device studies do not require an approved IDE, or compliance with the full or abbreviated IDE requirements as described above. However, these studies are not otherwise exempt from the requirements for IRB review and informed consent.

### 3.4 IRB review.

The IRB performs initial and continuing review of research involving investigational use of a device at a convened meeting, including the presence of a physician member. Occasionally, projects may be eligible for expedited review. Applicable categories of expedited review include:

- (1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

- (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
  - (b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
- (4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples:
- (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;
  - (b) weighing or testing sensory acuity;
  - (c) magnetic resonance imaging;
  - (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;
  - (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.
- (8) Continuing review of research previously approved by the convened IRB as follows:
- (a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or
  - (b) where no subjects have been enrolled and no additional risks have been identified; or
  - (c) where the remaining research activities are limited to data analysis.
- (9) Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

### 3.5 *In vitro* diagnostic devices.

Research involving investigational use of an *in vitro* diagnostic device is also applicable to FDA regulations. Such devices are used to collect, prepare and examine specimens (e.g., blood, serum, urine, spinal fluid, tissue samples) after removal from the body.

### 3.5.1 IRB review.

Studies on the safety and effectiveness of these types of devices, known as *in vitro* diagnostic devices, require IRB review when the testing is performed on human specimens. The requirement for review applies regardless of the nature of the collection process (prospective or retrospective) and the presence or absence of identifiers. The risk determination for IVD studies is based on the impact of the performance of the device on patient health; particularly with respect to the impact of false negative or false positive results.

### 3.5.2 Informed consent.

Informed consent is also required from individual donors for FDA regulated research, unless the research is limited to use of 'leftover specimens' that are not individually identifiable. Research utilizing human specimens for an investigational IVD study qualifies for a waiver of the requirement for informed consent when:

- the study is exempt from IDE requirements
- specimens (and any associated clinical information) are provided to researchers without identifiers; supplier has policies to prevent release of personal information
- only 'leftover' specimens are used (e.g., repositories, or remnants of specimens collected for routine clinical care that would have been discarded)
- individuals caring for the patients are different from, and do not share information about the patient with those conducting the investigation; and
- study has been reviewed by an IRB

IVD studies do not qualify for waiver of informed consent if:

- specimens were collected specifically for the study (were not 'left-over' from routine clinical care or other research)
- test results will be reported to a subject's health care provider.

### 3.6 Emergency use of unapproved devices.

Under limited circumstances, a physician may use an investigational medical device to provide emergency patient care, when the device may be the only possible life-saving alternative. NDSU has no procedures for IRB review of such use, however, as the scope of NDSU functions does not include provision of emergency medical care.

## 4.0 Significant differences between FDA and HHS requirements.

NDSU human subjects research applicable to FDA regulations must comply with both HHS and FDA requirements, using the more stringent standard where applicable. While the FDA regulations for protection of research subjects are practically identical to those of HHS, several significant exceptions exist.

#### 4.1 Applicability.

FDA regulations apply to clinical investigations involving a test article and one or more human subjects, regardless of the presence or absence of identifiable information (see section 1.0). HHS regulations apply more broadly to projects defined as 'human subjects research'; refer to SOP 2.1 *Human Subjects Research* for more information.

#### 4.2 Exemptions from IRB review.

Under FDA regulations, the categories of research eligible for exemption from IRB review are limited to:

- taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the FDA or approved by the EPA or the USDA.
- emergency use of a test article, provided that such use is reported to the IRB within 5 working days. Subsequent use of the test article is subject to IRB review

#### 4.3 Informed consent.

Under FDA regulations, requirements for informed consent are identical to those of HHS, with several additional requirements:

- participants must be informed that representatives of the FDA may inspect their medical records pertaining to the research
- participants must be informed of the experimental nature of the applicable drug, biologic or device
- consent forms must be dated, as well as signed
- the signature on the consent form may only be waived for minimal risk research in which a signature would not otherwise be required
- the IRB should assure the accurate written translation of any consent documents presented to participants in another language.

In general, FDA regulations do not permit waiver or alteration of informed consent. Limited exceptions include planned emergency research (see SOP 11.7 *Review of Emergency Research*) and research involving use of leftover, de-identified specimens to evaluate the safety and effectiveness of *in vitro* diagnostic devices.

#### 5.0 Sponsor and investigator responsibilities.

FDA regulations require sponsors and investigators of drug and device studies to comply with additional responsibilities regarding the storage, control and labeling of the test article, as well as study monitoring, reporting and recordkeeping.

#### 5.1 Sponsor.

The sponsor is typically an entity that initiates, but does not conduct an investigation. FDA specifies their responsibilities for the drug or device in the following areas:

- manufacturing

- labeling
- assessment of safety
- prohibition of promotion
- obtaining an IND or IDE, as applicable
- ensuring qualifications of investigators
- study monitoring
- record keeping
- reporting, including reporting adverse events

A complete description of sponsor responsibilities is outside the scope of this SOP; refer to 21 CFR 312, Subpart D (drug and biologic studies), or 21 CFR 812.40 (medical device studies) for more information.

### 5.2 Investigator.

An investigator is an individual who conducts or directs the study involving administration or use of a test article. FDA specifies their responsibilities in the conduct of the study:

- obtaining IRB approval
- ensuring compliance with the protocol
- maintaining control of the test article
- record keeping and reporting
- communicating FDA or sponsor audits and findings to the IRB

A complete description of investigator responsibilities is outside the scope of this SOP; refer to 21 CFR 312.60 (drug and biologic studies), or 21 CFR 812.100 (medical device studies) for more information.

### 5.3 Sponsor-Investigator.

A sponsor-investigator is an individual who fulfills the responsibilities of both sponsor and investigator. Such studies may be referred to as 'investigator-initiated' research.

## 6.0 Clinical trial registration.

Various entities, including the FDA, funding agencies, and journal organizations, require clinical trials (as defined below) to be registered prior to enrollment of subjects. The requirement does not apply to purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator). Registration of IRB-approved trials is the responsibility of the sponsor, investigator, or sponsor-investigator; refer to ClinicalTrials.gov for more information.

## **DEFINITIONS:**

**Biologic:** any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product or analogous product applicable to the prevention, treatment or cure of disease or injuries to man.

**Clinical investigation (drugs and biologics):** any experiment in which a drug is administered to, dispensed to, or used involving, one or more human subjects. An experiment is considered to be any use of a drug except for the use of a marketed drug

in medical practice. (Synonymous with the terms 'research', 'clinical research', 'clinical study', and 'study')

Clinical investigation (medical devices): an investigation or research involving one or more human subjects to determine the safety and effectiveness of a device.

(Synonymous with the terms 'research', 'clinical research', 'clinical study', and 'study')

Clinical trial (as defined by WHO): any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events.

Custom device: a device that: necessarily deviates from devices available from an applicable performance standard or premarket approval requirement in order to comply with the order of an individual physician or dentist; is not available to other physicians and dentists; is not available in finished form for purchase upon prescription; is not offered for commercial distribution through labeling or advertising; and is intended for use by an individual patient named in the order of a physician or a 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.

Disease: damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension). Diseases resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) are not included in this definition.

Drug: an article recognized in the US Pharmacopeia (USP), National Formulary (NF) or Homeopathic Pharmacopeia of the US, and intended for diagnosis, cure, mitigation, treatment or prevention of disease in man or animal, or intended to affect the structure or function of the body.

Electronic product: 1) any manufactured or assembled product which, when in operation: (i) contains or acts as part of an electronic circuit and (ii) emits (or in the absence of effective shielding or other controls would emit) electronic product radiation, or 2) any manufactured or assembled article that is intended for use as a component, part, or accessory of an electronic product (as in 1 above) and which, when in operation, emits (or in the absence of effective shielding or other controls would emit) such radiation.

Emergency use: the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.

Human subject (FDA): an individual who is or becomes a participant in research, either as a recipient of a test article, or as a control; also includes someone on whom, or on whose specimen, an investigational device is used, or who participates as a control.

Investigator: an individual who actually 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, is the responsible leader of that team.

In-vitro diagnostic devices: those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the act), and may also be biological products subject to section 351 of the Public Health Service Act.

Medical device: A device is: an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: i) recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them, ii) 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 iii) intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of 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 any of its primary intended purposes.

Off-label use: use of a marketed drug, biologic or device outside of the FDA approved labeling in order to provide patient care. Off-label use in the practice of medicine is not considered research, and does not require an IND or IRB approval.

Sponsor: an individual or entity that initiates a clinical investigation, but that does not actually conduct the investigation.

Sponsor-investigator: an individual who initiates, as well as conducts, alone or with others, a clinical investigation; must fulfill the responsibilities of both investigator and sponsor.

## **REFERENCES:**

[21 CFR Part 50](#) Protection of Human Subjects

[21 CFR Part 56](#) Institutional Review Boards

[21 CFR Part 312](#) Investigational New Drug Application

[21 CFR Part 600](#) Biological Products

[21 CFR Part 809](#) In Vitro Diagnostic Products for Human Use

[21 CFR Part 812](#) Investigational Device Exemptions

[21 CFR Part 1000 Subchapter J](#) Radiological Health

[21 CFR Part 814 Subpart H](#) Humanitarian Use Devices

FDA Information Sheet [Guidance documents](#)

FDA Guidance [Investigator Responsibilities – Protecting the Rights, Safety and Welfare of Study Subjects](#)

Clinical Trials Registration, [ClinicalTrials.gov](#)

FDA [Center for Drug Evaluation and Research](#)

FDA [Center for Devices and Radiological Health](#)

FDA Information Sheet Guidance, [Significant Risk and Nonsignificant Risk Device Studies](#)

FDA Guidance [Informed Consent for \*In Vitro\* Diagnostic Studies using Leftover Human Specimens that are not Individually Identifiable](#)

[21 CFR 101.93](#) Certain types of statements for dietary supplements

FDA Guidance [Botanical Drug Products](#)

FDA Guidance [The Establishment and Operation of Clinical Trial Data Monitoring Committees](#), Food and Drug Administration

FDA Guidance [Monitoring Clinical Investigations](#)

[Definition of 'Clinical Trial'](#), World Health Organization (WHO)

#### **RELATED [FORMS](#):**

IRB Protocol Form

Investigational Use of Medical Devices

Use of Drugs and Biological Products

#### **RELATED HRPP SECTIONS AND STANDARD OPERATING PROCEDURES:**

2.1 Human Subjects Research

3.1 Roles and Responsibilities - Investigator

Section 7 – IRB Review Process

8.3 Data Safety Monitoring

Section 9 – Requirements for Informed Consent