

HRPP POLICY APPROVAL & IMPLEMENTATION
OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS

Policy Number: 501

SOP Title: Research Involving FDA Regulated Devices

**Distribution: Scientific Directors; Clinical Directors; Clinical Investigators,
IRB Chairs, IRB Administrators, Protocol Navigators**

Revision Approval:

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**Deputy Director for Intramural
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Implementation date: 10-26-2020

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POLICY

A. PURPOSE

1. Describes the responsibilities of NIH investigators, non-NIH investigators, NIH sponsors and the NIH Institutional Review Board (IRB) when conducting or reviewing human subjects research that involves the use of devices regulated by the Food and Drug Administration (FDA) and the Department of Health and Human Services (HHS).

B. SCOPE

1. This policy applies to NIH investigators when conducting FDA-regulated research involving the use of devices.
2. This policy applies to non-NIH investigators when conducting FDA-regulated research involving the use of devices when the NIH IRB is the Reviewing IRB.
3. This policy applies to the NIH IRB when it is the Reviewing IRB.

C. POLICY

1. NIH Principal Investigators (PIs) NIH investigators conducting human subjects research involving investigational device(s) must comply with applicable FDA regulations including, but not limited to, 21 CFR parts [50](#), [56](#), [809](#), [812](#), and [814](#) as applicable, as well as those set forth in HHS regulations at [45 CFR part 46](#).
2. When reviewing and approving research involving investigational devices, the NIH IRB must apply the applicable FDA regulations including, but not limited to, 21 CFR parts [50](#), [56](#), [809](#), [812](#), and [814](#) as applicable, as well as those set forth in HHS regulations at [45 CFR part 46](#).
3. By NIH policy, NIH investigators may not be Sponsors, effective January 15, 2018. However, investigators may have sponsor responsibilities when required by regulation.

D. DEFINITIONS

1. *Device* – The term “device” (except when used in paragraph (n) of this section and in sections 331(i), 343(f), 352(c), and 362(c) of this title) means 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,

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- (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. ([21 USC 321\(h\)](#))
2. *Exempt Investigational Device Study* – This part [21 CFR part 812], with the exception of §812.119, does not apply to investigations of the following categories of devices:
- (1) A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
 - (2) A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.
 - (3) A diagnostic device, if the sponsor complies with applicable requirements in §809.10(c) and if the testing:
 - (i) Is noninvasive,
 - (ii) Does not require an invasive sampling procedure that presents significant risk,
 - (iii) Does not by design or intention introduce energy into a subject, and
 - (iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
 - (4) A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two 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.
 - (5) A device intended solely for veterinary use.
 - (6) A device shipped solely for research on or with laboratory animals and labeled in accordance with §812.5(c).
 - (7) A custom device as defined in §812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution. ([21 CFR 812.3\(b\)](#))
3. *Human Subject (2018 Common Rule definition)* – In the context of investigators conducting HSR:
- (1) A living individual about whom an investigator (whether professional or student) conducting research:

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- (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
 - (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.
- (2) Intervention – includes both physical procedures by which information or biospecimens are gathered (e.g. venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.
 - (3) Interaction – includes communication or interpersonal contact between investigator and subject.
 - (4) Private information – includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g. a medical record).
 - (5) Identifiable private information – is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.
 - (6) Identifiable biospecimen – is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen. ([45 CFR 46.102\(e\) 2018 Common Rule](#)) (See also the FDA definition of Subject below.)
4. *Human Subject (Pre-2018 Common Rule definition)* – A living individual about whom an investigator (whether professional or student) conducting research obtains: 1) Data through intervention or interaction with the individual, or 2) Identifiable private information. ([45 CFR 46.102\(f\) pre-2018 Common Rule](#)) (See also the FDA definition of Subject below.)
 5. *Humanitarian Device Exemption (HDE)* – A premarket approval application submitted pursuant to this subpart [21 CFR 814] seeking a humanitarian device exemption from the effectiveness requirements of sections 514 and 515 of the act as authorized by section 520(m)(2) of the act [[FD&C Act](#)]. ([21 CFR 814.3\(m\)](#))
 6. *Humanitarian Use Device (HUD)* – Means a medical device intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect or is manifested in not more than 8,000 people in the United States per year. (21st Century Cures Act, [Public Law 114-255, 130 Stat. 1033 \(2016\)](#) and [21 CFR 814.3\(n\)](#))
 7. *Implant* – A device that is placed into a surgically or naturally formed cavity of the human body if it is intended to remain there for a period of 30 days or more. FDA may, in order to protect public health, determine that devices placed in subjects for shorter periods are also “implants” for purposes of this part. ([21 CFR 812.3\(d\)](#))

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8. *Investigation (Clinical investigation of a device)* – A clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device. ([21 CFR 812.3\(h\)](#))
9. *Investigational Device* – A device, including a transitional device, that is the object of an investigation. ([21 CFR 812.3\(g\)](#))
10. *In vitro diagnostic (IVD) products* – Are 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. ([21 CFR 809.3\(a\)](#))
11. *NIH Investigator* – An NIH federal employee (intramural or extramural), Special Volunteer, Intramural Research Training Awardee (IRTA) and Cancer Research Training Awardee (CRTA) who is conducting human subjects research on behalf of the NIH. This may include a contractor in accordance with policy.
12. *Non-Significant Risk (NSR) Device* – Means an investigational device that is not a significant risk device as defined at [21 CFR 812.3\(m\)](#)
13. *Significant Risk (SR) Device* – Means an investigational device that:
 - (1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
 - (2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
 - (3) 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; or
 - (4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. ([21 CFR 812.3\(m\)](#))
14. *Sponsor (for devices)* – A person who initiates, but who does not actually conduct, the investigation, that is, the investigational device is administered, dispensed, or used under the immediate direction of another individual. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators. ([21 CFR 812.3\(n\)](#))
15. *Sponsor-Investigator (for devices)* – An individual who both initiates and actually conducts, alone or with others, an investigation, that is, under whose immediate direction the investigational device is administered, dispensed, or used. The term does not include

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any person other than an individual. The obligations of a sponsor-investigator under this part include those of an investigator and those of a sponsor. ([21 CFR 812.3\(o\)](#))

16. *Subject (FDA for study of investigational devices)* – 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 subject may be in normal health or may have a medical condition or disease. ([21 CFR 812\(p\)](#))
17. *Transitional Device* – A device subject to section 520(l) of the Food, Drug & Cosmetic Act, that is, a device that FDA considered to be a new drug or an antibiotic drug before May 28, 1976. ([21 CFR 812.3\(r\)](#))
18. *Unanticipated adverse device effect (UADE)* – Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. ([21 CFR 812.3\(s\)](#))

E. RESPONSIBILITIES AND REQUIREMENTS

1. Principal Investigator Responsibilities

- a. When the research involves the study of the safety or efficacy of an investigational device, the Principal Investigator (PI) will provide documentation supporting the sponsor's assessment of whether the device is exempt ([21 CFR 812.2\(c\)](#)), non-significant risk (NSR) or significant risk (SR) to the reviewing IRB.
 - I. If a determination by the FDA has already been made as to whether the device is exempt, NSR or SR, documentation from the FDA must be provided to the reviewing IRB.
 - II. The IRB or IRBO may require the PI to submit to the FDA for a determination prior to reviewing any device study. FDA is the final arbiter as to whether a device study is Exempt, SR or NSR.
 - III. The PI will submit the report of prior investigations (or device labeling information) to the IRB for review.
- b. The PI must confirm that there is IRB and FDA approval, when required, prior to enrolling subjects in the protocol.
- c. The PI is responsible for:

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- IV. Conducting the investigation according to the signed agreement with the sponsor, the investigational plan, and applicable FDA regulations. ([21 CFR 812 subpart E](#)).
 - V. Ensuring requirements for obtaining informed consent are met.
 - VI. Storing, controlling, and accounting of the investigational device.
 - VII. Limiting investigational device use to only subjects under the investigator's supervision.
 - VIII. Disclosing to the sponsor sufficient accurate financial information to allow the sponsor to submit complete and accurate certification or disclosure statements required under [21 CFR part 54](#) and promptly updating this information if any relevant changes occur during the course of the investigation and for one (1) year following completion of the study.
 - IX. Reporting Unanticipated Adverse Device Events (UADEs) promptly to the sponsor, to the reviewing IRB if required, and performing evaluation/investigation for all UADEs. (See [Policy 801 Reporting Research Events](#).)
 - X. Keeping accurate, complete and current records as specified in [21 CFR 812.140](#).
 - XI. Returning to the sponsor any remaining supply of the device or otherwise disposing of the device as the sponsor directs when the investigation is completed or terminated.
 - XII. Submitting complete, accurate, and timely reports as specified in [21 CFR 812.150](#).
- d. The PI must cooperate with Sponsor monitoring and audits.
 - e. The PI must cooperate with FDA inspections: Permit authorized FDA employees, at reasonable times and in a reasonable manner to:
 - I. Enter and inspect any establishment where devices are held;
 - II. Inspect and copy all records relating to an investigation;

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- III. Inspect and copy records that identify subjects, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, if required by the IRB, or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.
2. Sponsor Responsibilities (when the sponsor is the NIH or an NIH investigator)
 - a. The Sponsor is responsible for:
 - I. Submitting an IDE application to the FDA, when applicable.
 - II. Selecting qualified investigators and providing them with the information they need to conduct the investigation properly, including providing the investigational plan and reports of prior investigations. ([21 CFR 812 subpart C](#) and [21 CFR 812.27](#))
 - III. Obtaining signed sponsor agreements from each investigator that included the information as noted in [21 CFR 812.43\(c\)](#).
 - IV. Providing the IRB with a risk assessment and the rationale used in making its SR, NSR or exempt determination (*See [E.1.a.](#)* above);
 - i. If an IRB determines that a device is a significant risk device, and the sponsor has proposed that the IRB consider the device not to be a significant risk device, the sponsor shall submit to FDA a report of the IRB's determination within 5 working days after the sponsor first learns of the IRB's determination. ([21 CFR 812.150\(b\)\(9\)](#))
 - V. Ensuring that IRB and, as applicable, FDA review and approval are obtained prior to beginning an investigation.
 - VI. Ensuring requirements for obtaining informed consent are met.
 - VII. Maintaining control of the device: Ship investigational devices only to qualified investigators participating in the investigation.
 - VIII. Ensuring proper monitoring of the investigation by qualified individuals.
 - IX. Ensuring that any reviewing IRB and the FDA are promptly informed of significant new information about an investigation.
 - X. Conducting evaluation of any Unanticipated Adverse Device Events (UADEs):

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- i. If a UADE presents an unreasonable risk to subjects, the sponsor shall terminate all investigations or parts of investigations presenting that risk as soon as possible.
 - ii. 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.
 - iii. If the device is a significant risk device, a sponsor may not resume a terminated investigation without IRB and FDA approval.
 - iv. If the device is not a significant risk device, a sponsor may not resume a terminated investigation without IRB approval and, if the investigation was terminated under [E.2.a.X.i.](#) above, without FDA approval.
 - XI. Maintaining accurate, complete, and current records relating to an investigation as required by [21 CFR 812.140](#):
 - XII. Submitting complete, accurate, and timely reports as required by [21 CFR 812.150](#).
- 3. Sponsor Investigator
 - a. By NIH policy, IDEs shall be held by the IC, rather than by the NIH Principal Investigator on the clinical protocol.
 - I. Investigators may serve as the sponsor for expanded access protocols or when the device has been determined to be non-significant risk.
 - b. When a PI holds the IDE (Sponsor-Investigator), s/he assumes all responsibilities of both the Investigator (*see E.1. above*) as well as the Sponsor (*see E.2. above*). (*See [21 CFR 812 subpart E](#) and [21 CFR 812 subpart C.](#) (See *Policy 502 Expanded Access, Including Emergency Use of Investigational Drugs, Biologics, and Medical Devices (Test Articles).*)*)
- 4. IRB Responsibilities
 - a. When the NIH IRB is the Reviewing IRB, the NIH IRB is responsible for the review and approval of research involving devices under [21 CFR 812 subpart D](#) and according to *Policy 204 Levels of IRB Review and Criteria for IRB Approval of Research*.
 - b. Prior to considering whether the research may be approved, the office of IRB Operations (IRBO) will first review the IRB application to confirm that one of the following is true:

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- I. The study is an exempt investigational device study.
 - II. The study has an approved IDE issued by the FDA.
 - III. The study sponsor has provided sufficient justification that the investigation is an NSR device study.
- c. If the IRBO determines that none of the above conditions are met (*see E.4.b.* above), the study will be returned to the PI, to ensure these requirements are met.
- d. During the pre-review of the research, the IRBO will evaluate the sponsor’s justification. If the Director, IRBO, the Director, OHSRP or the Executive Chair of the IRB, disagree with the sponsor’s assessment that a study is exempt or NSR, they may require submission to the FDA prior to further review of the research.
- e. When the neither the Sponsor, nor the FDA has provided an assessment that the investigational device is exempt, an NSR or an SR, then only the convened IRB may make and document the SR or NSR determination by reviewing relevant information including:
- I. Description of the device;
 - II. Reports of prior investigations conducted with the device;
 - III. Proposed investigational plan including the proposed use of the device in the study, not just the device alone;
 - IV. As well as any protocol related procedures and tests (e.g., surgery for an implant), and any potential for serious risk to the health, safety or welfare of the subject; and
 - V. Subject selection criteria.
- f. If the FDA has already determined that the investigation is an NSR or an SR device study, then the IRB does not need to make a determination, and the FDA determination is final.
- g. If the IRB determines the study is NSR or is an exempt device investigation, and the IRB otherwise approves the study, the study may begin without submission to the FDA.
- h. If the IRB disagrees with the sponsor’s initial NSR assessment and decides the study is SR, the IRB must tell the clinical investigator and the sponsor (decision may be conveyed via investigator to the sponsor), and an IDE application must be submitted and approved by the FDA before research may commence.

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5. General Requirements for Humanitarian Use Devices:
 - a. Before use of a Humanitarian Use Device (HUD) in the course of routine clinical care to treat or diagnose patients at the NIH, IRB approval must be obtained. ([21 CFR 814.124](#))
 - b. Initial review of a HUD will be performed by the convened NIH IRB. Subsequent reviews may be conducted by expedited procedures.
 - I. The IRB may require either informed consent from the patient or require that the treating physician provide the patient with a patient information sheet describing the HUD.
 - II. An IRB does not have to make a SR/NSR determination when it receives a request to review a clinical investigation of a HUD (e.g., collection of safety and effectiveness data) when that clinical investigation concerns the HDE-approved indication(s) only. FDA does not consider such investigations to require an IDE under [21 CFR part 812](#). (See [Humanitarian Device Exemption \(HDE\) Program – Guidance for Industry and Food and Drug Administration Staff](#).)
 - c. The Humanitarian Device Exemption (HDE) holder is responsible for ensuring that a (HUD) under an HDE is administered only in facilities having IRB oversight in accordance with the Agency’s regulation governing IRBs. ([21 CFR 814 subpart H](#))
 - d. The HDE holder shall notify FDA of any withdrawal of approval for the use of a HUD by a reviewing IRB within 5 working days after being notified of the withdrawal of approval.
 - e. Emergency use: If a physician in an emergency situation determines that IRB approval for the use of the HUD at the facility cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be used without prior approval. In this situation:
 - I. The HDE holder may ship the HUD, based on the physician’s certification of the emergent need.
 - II. FDA regulations require that physicians provide such notification to the chairperson of the IRB in writing within 5 days of the emergency use of the device. Such written notification shall include the identification of the patient involved, the date on which the device was used, and the reason for the use.

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- f. The HDE holder is required to submit annual reports, including the applicant’s clinical experience with the device and the number of devices shipped or sold. ([21 CFR 814.126\(b\)](#))
- g. When used in a clinical investigation evaluating the safety or effectiveness of a HUD for an indication other than the approved HDE, the investigation is subject to all applicable investigational device and human subjects protections regulations.
- h. Off-label clinical or treatment use of a HUD, where no safety and effectiveness data is collected, does not require IRB review.

F. REFERENCES

1. Federal Regulations

HHS: [45 CFR part 46](#)

FDA: 21 CFR parts [50](#), [56](#), [809](#), [812](#) and [814](#)

2. NIH Policy

[Policy 204 Levels of IRB Review and Criteria for IRB Approval of Research](#)

Policy 502 Expanded Access, Including Emergency Use of Investigational Drugs, Biologics, and Medical Devices (Test Articles)

[Policy 801 Reporting Research Events](#)

3. Guidance

[IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risks to Human Subjects: Guidance for Sponsors, Investigators and IRBs \(July 2017\)](#)

[Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors Significant Risk and Nonsignificant Risk Medical Device Studies \(January 2006\)](#)

[Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions Guidance for Investigational Device Exemption Sponsors, Sponsor-Investigators and Food and Drug Administration Staff \(Document issued on January 13, 2017\)](#)

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[Decisions for Investigational Device Exemption Clinical Investigations Guidance for Sponsors, Clinical Investigators, Institutional Review Boards, and Food and Drug Administration Staff \(January 2006\)](#)

[Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors Frequently Asked Questions About Medical Devices \(January 2006\)](#)

[Guidance for Industry and FDA Staff In Vitro Diagnostic \(IVD\) Device Studies - Frequently Asked Questions \(Document issued on: June 25, 2010\)](#)

[Overview of IVD Regulation \(Content current as of 9/16/2019\)](#)

Presentation by Robert ‘Skip’ Nelson, MD PhD - [IRB Oversight of Humanitarian Use Devices \(What’s an IRB to do?\) \(January 8, 2014\)](#)

[Guidance for HDE Holders, Institutional Review Boards \(IRBs\), Clinical Investigators, and Food and Drug Administration Staff: Humanitarian Use Device \(HUD\) Designations \(Document issued on: January 24, 2013\)](#)

G. APPENDICES: NA

H. REVISION HISTORY: NA

I. SUPERSEDES DATE: 10/26/2020

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

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