

# Guidance on Research Involving FDA-Regulated Investigational Articles: Investigational Drugs and Medical Devices

## Background

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The United States Food and Drug Administration (FDA) enforces the Food, Drug, and Cosmetic Act (FD&C Act) and other laws and regulations governing the use of drugs, biologics, and devices both in research studies and for treatment. FDA regulations governing research with investigational drugs are outlined in [21 CFR 312](#). Those governing investigational devices are in [21 CFR 812](#); regulations for biologics are in [21 CFR 600](#). FDA regulations for the Protection of Human Subjects/Informed Consent ([21 CFR 50](#)) and Institutional Review Boards ([21 CFR 56](#)) also apply.

In general, clinical investigations of investigational drugs or devices require an FDA- and IRB-approved investigational plan, informed consent from all subjects, special labeling of the drug or device, monitoring of the study, and specified record keeping and reporting.

The following sections outline when an Investigational New Drug (IND) application, or an Investigational Device Exemption (IDE) is needed and describe the roles and responsibilities of the FDA, IRBs, sponsors and investigators with respect to human research involving investigational articles.

## Definitions

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FDA regulations define *investigator*, *sponsor*, and *sponsor-investigator* as follows:

### 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 of individuals, is the responsible leader of that team.

### Sponsor

An organization or individual that initiates and takes responsibility for a clinical trial or other FDA-regulated project involving a drug, biologic or device. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator.

### Sponsor-investigator

An individual who both initiates and conducts an investigation of an FDA-regulated drug, biologic or device and under whose immediate direction the drug, biologic or device is administered or dispensed. The term does not include any person other than an individual. A sponsor-investigator must handle the roles and responsibilities for both sponsors and investigators.

# Research requiring INDs and IDEs

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INDs and IDEs are the method by which the FDA grants investigators permission to conduct research using drugs, biologics, or medical devices that are new (unapproved), or that have been FDA-approved, but are being tested for a new indication or use. Sponsors or sponsor-investigators (i.e., principal investigators) are responsible for determining whether their research requires an IND or IDE, and for obtaining the necessary FDA permission (in addition to IRB approval). If there is uncertainty, sponsors or sponsor-investigators should consult with relevant divisions within the FDA for guidance.

## Research involving Investigational Drugs or Biologics

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### IND Requirements

Unless a specific exemption applies, approval of an IND Application from the FDA is required for *clinical investigations* of:

- Unapproved drugs or biologics
- Use of approved drugs or biologics in studies:
  - for new intended uses, or
  - that involve a route of administration or dosage level that may significantly increase risks (or decreases acceptability of risks) associated with use of the product, or
  - that involve use in a new patient population that may significantly increase risks (or decrease acceptability of risks) associated with use
  - that involve requesting an exception for informed consent requirements for emergency use.

### Definition of Key Terms:

A **clinical investigation** is [an] *experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of [the IND regulations], an experiment is any use of a drug [whether approved or unapproved] except for the use of a marketed drug in the course of medical practice* (21 CFR 312.3(b)).

A **biologic** (biological product) is . . . *a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), 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* (42 U.S.C. 262(i)).

A **drug** includes (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 article specified in clause (A), (B), or (C)* (21 U.S.C. 321, Section 201 (g)(1)).

According to [FDA Guidance](#), *the definition of a drug is not limited to compounds intended for therapeutic purpose (i.e., to diagnose, cure, mitigate, treat, or prevent disease)—it also includes compounds intended to affect the structure or function of the body (e.g., compounds administered to healthy persons to prevent pregnancy)* (p. 5).

The definition of a drug excludes the following:

- A dietary supplement that affects the structure or function of the body—but is not intended to diagnose, cure, mitigate, treat, or prevent disease—is NOT a drug ([21 CFR 101.93\(f\)](#) and (g)).

- A food used solely to provide nutrition—and not to affect the structure or function of the body or diagnose, cure, mitigate, treat, or prevent disease—is NOT a drug ([21 U.S.C. 321\(f\)](#) and [\(g\)\(1\)](#)).

## Exemptions from IND Requirements

Investigations meeting specified criteria may be exempt from IND requirements. These criteria are described in [21 CFR 312.2\(b\)](#),<sup>1</sup> and are as follows:

1. Clinical investigations of a drug product that is [lawfully marketed in the US](#), when **all** of the following apply:
  - The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
  - If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;
  - The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
  - The investigation is conducted in compliance with the requirements for institutional review board (IRB) approval for informed consent; and
  - The investigation is conducted in compliance with the requirements that prohibit promoting or marketing the investigational drug, representing it is safe or effective for the purposes being studied, etc.
2. Clinical investigations of in vitro diagnostic biological products when intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established diagnostic procedure, and it is shipped in accordance with [FDA requirements](#).
3. Bioavailability or bioequivalence studies using unapproved versions of drug products, when **all** of the following conditions are met (per [21 CFR 320.31](#)):
  - The drug product does not contain a new chemical entity, is not radioactively labeled, and is not cytotoxic;
  - 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;
  - The investigation is conducted in compliance with the requirements for institutional review board (IRB) approval for informed consent; and
  - The sponsor meets the requirements for retention of test article samples ([21 CFR 320.31\(d\)\(1\)](#)) and safety reporting ([21 CFR 320.31\(d\)\(3\)](#)).

## Obtaining FDA Approval for an Investigational New Drug (IND) Application

Obtaining an IND requires submission of information about the investigation to the FDA. The [FDA Website](#) includes submission information and instructions.

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<sup>1</sup> See also, FDA Guidance [Investigational New Drug Applications \(INDs\)—Determining Whether Human Research Studies can be Conducted Without an IND](#).

# Research with Investigational Devices -- IDE Requirements

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Medical devices range from simple items (bandages and tongue depressors) to complex implanted or surgical devices (pacemakers, lasers, etc.). In-vitro diagnostic products (such as pregnancy test kits), ultrasounds, x-ray machines, etc. are also medical devices.

Unless a specific exemption applies, sponsors and/or sponsor-investigators who conduct clinical investigations with one or more human subjects to assess the safety or effectiveness of investigational medical devices must obtain an Investigational Device Exemption (IDE)—in addition to IRB approval—prior to beginning the research.

In general, an IDE is needed if either of the following applies:

- The device is not approved for marketing in the United States; OR
- The device is approved for marketing, but is being clinically evaluated for a new indication or use.

## Definitions of key terms

According to the Federal Food Drug, and Cosmetic Act (section 201(h)), a **medical 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:*

- *recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,*
- *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*
- *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 any of its primary intended purposes.*

A **clinical investigation** (synonymous with research, clinical study or trial, etc.) is any experiment that involves a test article [i.e. a medical device, drug, etc.] and one or more human subjects, and that either:

- must meet the requirements for prior submission to the FDA under sections 505(i) or 520(g) of the Food, Drug, and Cosmetic Act; or
- 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 50.3\(c\)](#)).

In the context of medical device research, a clinical investigation involves one or more subjects *to determine the safety or effectiveness of a device* ([21 CFR 812.3\(h\)](#)). A **subject** is 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 good health or may have a medical condition or disease. ([21 CFR 812.3\(p\)](#)).

A **transitional device** is a device that the FDA considered to be a new drug or an antibiotic drug before May 28, 1976 (per [21 CFR 812.3\(r\)](#)).

A **custom device** is a device that meets **all** of the following conditions (per Section 520(b) of the [Food, Drug, and Cosmetic Act](#)):

- is created or modified in order to comply with the order of an individual physician or dentist (or any other specially qualified person designated under regulations promulgated by the Secretary after an opportunity for an oral hearing);
- necessarily deviates from an otherwise applicable performance standard [or premarket approval requirement];
- is not generally available in the United States in finished form through labeling or advertising by the manufacturer, importer, or distributor for commercial distribution;
- is designed to treat a unique pathology or physiological condition that no other device is domestically available to treat;
- is intended to meet the special needs of such physician or dentist (or other specially qualified person so designated) in the course of the professional practice of such physician or dentist (or other specially qualified person so designated); OR is intended for use by an individual patient named in such order of such physician or dentist (or other specially qualified person so designated);
- is assembled from components or manufactured and finished on a case-by-case basis to accommodate the unique needs of individuals;
- may have common, standardized design characteristics, chemical and material compositions, and manufacturing processes as commercially distributed devices;
- The device is for the purpose of treating a sufficiently rare condition, such that conducting clinical investigations on such device would be impractical;
- Production of the device is limited to no more than 5 units per year;
- The manufacturer notified the [Federal, DHHS] Secretary on an annual basis of the manufacture of the device.

## Exemption from IDE Requirements

Research on the following types of medical devices are exempt from IDE requirements (per [21 CFR 812.2\(c\)](#)):

1. Legally marketed devices when the devices are used in accordance with their FDA approved labeling (both for use and indication(s));
2. A diagnostic device, if labeling requirements specified in [21 CFR 809.10](#) are met, and the testing:
  - Is noninvasive;<sup>2</sup>
  - Does not require an invasive sampling procedure that presents significant risk;

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<sup>2</sup> *Noninvasive, when applied to a diagnostic device or procedure, means one that does not by design or intention: (1) Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or (2) enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os. For purposes of this part, blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for noninvestigational purposes is also considered noninvasive ([21 CFR 812.3\(k\)](#)).*

- Does not by design or intention introduce energy into a subject; and
  - Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure
3. 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 purposes of assessing safety or effectiveness, and does not put subjects at risk;
  4. A custom device (defined above), unless the device is being used to determine safety or effectiveness for commercial distribution;
  5. A device, other than a transitional device (defined above), in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time;
  6. A device, other than a transitional device (defined above), 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
  7. A device intended solely for veterinary use or shipped solely for research on or with laboratory animals.

## Obtaining an IDE

The process for obtaining an IDE differs depending on whether the medical device is categorized as Significant Risk or Non-Significant Risk.

Research with **Significant Risk (SR) devices** requires [formal submission to and approval of an IDE](#) from the FDA.

Research with **Non-significant Risk (NSR) devices** operate under *Abbreviated IDE Requirements*, where the research is *considered* to have an approved IDE if the IRB determines that the device is NSR. The IRB considers the function of the device and its proposed use in the research study when making this assessment. In effect, the IRB serves as the FDA's surrogate for review of NSR device research.

### Abbreviated IDE requirements for NSR device research include:

- IRB approval must be obtained and maintained throughout the course of the research. The sponsor (or PI, if there is no sponsor) must present the reviewing IRB with an explanation of why the device is not a significant risk device.
- Informed consent must be obtained from each study subject, and documented by a handwritten signature, unless documentation of consent has been waived by the IRB.
- Investigations must be monitored (see [Appendix A.2](#)).
- The device must be labeled in accordance with FDA requirements (see [Appendix B](#)).
- Compliance with the FDA's prohibitions against promotion and other practices ([Appendix C](#))
- All recordkeeping and reporting requirements must be met (see [Appendices D.2 and E.2](#)).

## Distinction between Significant Risk (SR) and Non-Significant Risk (NSR) devices

**Significant Risk Device** -- an investigational device that meets **any** of the following criteria (per [21 CFR 812.3\(m\)](#)):

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- 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;
- 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
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Some general examples:<sup>3</sup>

- Bronchial tubes
- Epidural and Spinal catheters or needles
- CPR devices
- TMJ prostheses
- ENT cements/adhesives
- Contraceptive Devices (IUDs, diaphragms, sponges, condoms made from new materials, etc.)
- Extended wear contact lenses (including single overnight use)

**Non-significant Risk Device** -- A non-significant risk device is any device not considered to be a significant risk device.

Some general examples:

- Electroencephalography
- Jaundice monitors for infants
- Menstrual pads or tampons (cotton or rayon, only)
- MRI devices within FDA specified parameters
- Transcutaneous Electric Nerve Stimulation (TENS) Devices for treatment of pain (except for chest pain/angina)
- Wound dressings, excluding absorbable hemostatic devices and dressings or interactive wound and burn dressings that aid the healing process.

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<sup>3</sup>Examples of significant risk and non-significant risk devices can be found in FDA Guidance [Significant Risk and Non-significant Risk Medical Device Studies](#); Note: Inclusion on either list is not the only factor the IRB must consider; the proposed use of the device must also be taken into account when assessing risk.

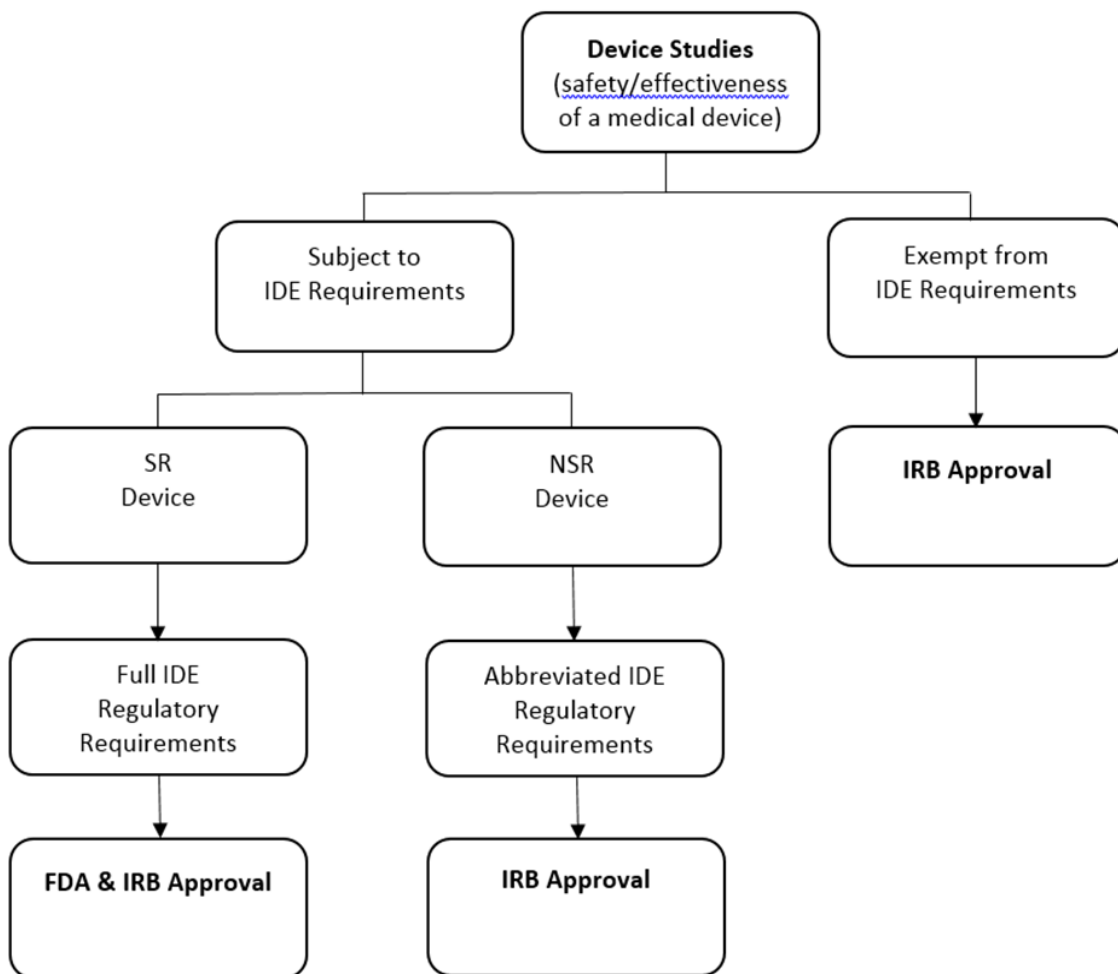
## Who decides whether device research is significant risk (SR) or non-significant risk (NSR)?

Unless the FDA has already made a risk determination, sponsors (or investigators, if there is no sponsor) are responsible for making an *initial* risk assessment and presenting it and corresponding rationale to the IRB. The IRB, at a convened meeting, will review the sponsor's (or investigator's) SR or NSR assessment. The IRB may modify the risk determination if it disagrees.

If the FDA has made the SR or NSR determination, the IRB need not make a determination; the FDA's determination is final.

The IRB is not required to make a SR or NSR determination for studies that are exempt from IDE requirements.

Figure 1: Flowchart of IRB and IDE requirements for device research





# IRB Review of Clinical Investigations involving Investigational Drugs or Biologics or Investigational Devices

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New protocols involving clinical investigations of drugs or biologics will be reviewed by the convened IRB; subsequent reviews (e.g., modifications or continuing reviews) may be reviewed via expedited procedures if allowable under applicable regulations (e.g., minor modifications). An investigational drug or biologic can be used in a human research project only if the study receives IRB approval, and:

- The sponsor or sponsor-investigator obtains an IND from the FDA; OR
- An IND or IDE exemption is granted from the FDA; OR
- The IRB agrees with the assessment of the sponsor or sponsor-investigator that the proposed use of the investigational drug or device meets the IND or IDE exemption criteria; OR
- For device research, the IRB agrees with the rationale provided by the sponsor or sponsor-investigator that the device is non-significant risk (NSR).

Investigators are responsible for providing sufficient information about the research to the IRB to allow it to make the required assessments for approval required by [21 CFR 56.111\(a\)](#) (e.g., risks to subject are minimized, the risk/benefit ratio is acceptable, informed consent will be obtained and documented, etc.). This information includes, among other things:

- Detailed information about the investigational drug or device necessary to assess safety, risk to subjects, and to make the SR/NSR determination (for devices). In general, the IRB application should include:
  - the name of the drug or device, its manufacturer, and directions for use,
  - an investigator's brochure and/or package instructions,
  - a summary of prior research/animal studies, toxicology information (for drugs), any manufacturer warnings or cautions, and
  - any additional information useful for helping the IRB (including lay persons) understand the drug or device, its use, and any risk, discomfort, or safety concerns.
  - Any additional information relevant to the use of the drug or device, such as costs to subjects, whether or not its use is covered by insurance, etc.
- A clear description of the research plan, including provisions to mitigate risk/discomfort, recruit subjects and obtain their informed consent, confidentiality provisions, etc.;
- Qualifications of the investigator(s) and adequacy of the research site(s);<sup>4</sup>
- Plans for monitoring the study data to ensure subject safety;
- Status of IND/IDE, or rationale for exemption or NSR determination (for device studies)

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<sup>4</sup> [FDA Guidance](#) explicitly outlines requirements that the IRB assess the qualifications of investigators. *FDA-Regulated Investigational Drugs and Medical Devices*  
1/21/2019

## Special informed consent requirements

In addition to the typical [elements of informed consent](#), participants in investigational drug or device research should be provided with the following information to help them make an informed decision about participation:

- That the drug or device is investigational, and either has not been approved by the FDA for clinical use, or it has been approved for specific indications, but not for the use being studied.
- A lay person's description of what the drug or device is and what it is intended to do;
- A description of the expected experience or procedures for using the drug or device (e.g., how it is taken/used, what to expect, any discomfort, etc.);
- Any costs the subject may incur while using the investigational drug or device (or any medical treatment related to use of the drug or device);
- Any alternatives to participation, including any standard treatments available with approved drugs or devices;
- That the FDA and sponsor (if applicable) may review study records (including those that may identify subjects);
- For clinical trials of drugs or medical devices, include the following statement, verbatim: *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. At most, the Web site will include a summary of the results. You can search this Web site at any time.*

Consent documents (and any other information shared during the recruitment or consent process) may NOT include the following:

- Any representation that an investigational drug or device is safe or effective for the purposes for which it is being investigated.
- Any exculpatory language where participants waive or appear to waive any of their legal rights, or release or appears to release the investigator, sponsor, the institution or its agents from liability from negligence.
- Any assurance that data will be discarded upon subject withdrawal; FDA requirements mandate retention of data collected up to the point of withdrawal in FDA-regulated clinical trials.<sup>5</sup>

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<sup>5</sup> <https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126489.pdf>  
FDA-Regulated Investigational Drugs and Medical Devices  
1/21/2019

# Appendices

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Page	Title
12	<b>Appendix A.1:</b> Additional Principal Investigator and Sponsor Responsibilities for <b>Investigational New Drug</b> Research
13	<b>Appendix A.2:</b> Additional Principal Investigator and Sponsor Responsibilities for <b>Investigational Device</b> Research
16	<b>Appendix B:</b> <b>Investigational Drug</b> and <b>Device</b> Labeling Requirements
17	<b>Appendix C:</b> Prohibition of promotion and other practices ( <b>Investigational Drugs</b> and <b>Devices</b> )
18	<b>Appendix D.1:</b> Principal Investigator and Sponsor/Sponsor-Investigator Recordkeeping and Retention Requirements – <b>Investigational New Drug</b> Research
19	<b>Appendix D.2:</b> Principal Investigator and Sponsor Recordkeeping and Retention Requirements – <b>Investigational Device</b> Research
21	<b>Appendix E.1:</b> Principal Investigator and Sponsor Reporting Requirements – <b>Investigational Drug</b> Research
26	<b>Appendix E.2:</b> Principal Investigator and Sponsor Reporting Requirements – <b>Investigational Device</b> Research
28	<b>Appendix F:</b> Inspections ( <b>Investigational Drugs</b> and <b>Devices</b> )
29	<b>Resources:</b> Links to Federal Regulations, Guidance, etc.

# Appendix A.1: Additional Principal Investigator and Sponsor Responsibilities for Investigational New Drug Research

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## **Responsibilities of Investigators**

### **General responsibilities of investigators ([21 CFR 312.60](#))**

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation. An investigator shall, in accordance with the provisions of part 50 of this chapter, obtain the informed consent of each human subject to whom the drug is administered, except as provided in §§50.23 or 50.24 of this chapter. Additional specific responsibilities of clinical investigators are set forth in this part and in parts 50 and 56 of this chapter.

### **Control of the investigational drug ([21 CFR 312.61](#))**

An investigator shall administer the drug only to subjects under the investigator's personal supervision or under the supervision of a sub-investigator responsible to the investigator. The investigator shall not supply the investigational drug to any person not authorized under this part to receive it.

### **Assurance of IRB review ([21 CFR 312.66](#))**

An investigator shall assure that an IRB that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study. The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

### **Handling of controlled substances ([21 CFR 312.69](#))**

If the investigational drug is subject to the Controlled Substances Act, the investigator shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

# Appendix A.2: Additional Principal Investigator and Sponsor Responsibilities for Investigational Device Research

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## Responsibilities of Investigators

### General responsibilities of investigators ([21 CFR 812.100](#))

An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation. An investigator also is responsible for ensuring that informed consent is obtained in accordance with [part 50](#).

### Specific responsibilities of investigators ([21 CFR 812.110](#))

- (a) **Awaiting approval.** An investigator may determine whether potential subjects would be interested in participating in an investigation, but shall not request the written informed consent of any subject to participate, and shall not allow any subject to participate before obtaining IRB and FDA approval.
- (b) **Compliance.** An investigator shall conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, this part and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.
- (c) **Supervising device use.** An investigator shall permit an investigational device to be used only with subjects under the investigator's supervision. An investigator shall not supply an investigational device to any person not authorized under this part to receive it.
- (d) **Financial disclosure.** A clinical investigator shall disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements required under [part 54](#). The investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.
- (e) **Disposing of device.** Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.

## Responsibilities of Sponsors (or principal investigators, if there is no sponsor)

### General responsibilities of sponsors ([21 CFR 812.40](#))

Sponsors are responsible for selecting qualified investigators and providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, ensuring that IRB review and approval are obtained, submitting an IDE application to FDA, and ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation. Additional responsibilities of sponsors are described in subparts B and G.

### FDA and IRB approval ([21 CFR 812.42](#))

A sponsor shall not begin an investigation or part of an investigation until an IRB and FDA have both approved the application or supplemental application relating to the investigation or part of an investigation.

- (a) **Selecting investigators and monitors** ([21 CFR 812.43](#))

- (b) **Selecting investigators.** A sponsor shall select investigators qualified by training and experience to investigate the device.
- Control of device.** A sponsor shall ship investigational devices only to qualified investigators participating in the investigation.
- (c) **Obtaining agreements.** A sponsor shall obtain from each participating investigator a signed agreement that includes:
- (1) The investigator's curriculum vitae.
  - (2) Where applicable, a statement of the investigator's relevant experience, including the dates, location, extent, and type of experience.
  - (3) If the investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to termination.
  - (4) A statement of the investigator's commitment to:
    - i. Conduct the investigation in accordance with the agreement, the investigational plan, this part and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA;
    - ii. Supervise all testing of the device involving human subjects; and
    - iii. Ensure that the requirements for obtaining informed consent are met.
  - (5) Sufficient accurate financial disclosure information to allow the sponsor to submit a complete and accurate certification or disclosure statement as required under [part 54](#) of this chapter. The sponsor shall obtain a commitment from the clinical investigator to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study. This information shall not be submitted in an investigational device exemption application, but shall be submitted in any marketing application involving the device.
- (d) **Selecting monitors.** A sponsor shall select monitors qualified by training and experience to monitor the investigational study in accordance with this part and other applicable FDA regulations.
- Informing investigators ([21 CFR 812.45](#))**
- A sponsor shall supply all investigators participating in the investigation with copies of the investigational plan and the report of prior investigations of the device.
- Monitoring investigations ([21 CFR 812.46](#))**
- (a) **Securing compliance.** A sponsor who discovers that an investigator is not complying with the signed agreement, the investigational plan, the requirements of this part or other applicable FDA regulations, or any conditions of approval imposed by the reviewing IRB or FDA shall promptly either secure compliance, or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation. A sponsor shall also require such an investigator to dispose of or return the device, unless this action would jeopardize the rights, safety, or welfare of a subject.
- (b) **Unanticipated adverse device effects.**

- (1) A sponsor shall immediately conduct an evaluation of any unanticipated adverse device effect.<sup>6</sup>
  - (2) A sponsor who determines that an unanticipated adverse device effect presents an unreasonable risk to subjects shall terminate all investigations or parts of investigations presenting that risk as soon as possible. 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.
- (c) **Resumption of terminated studies.** If the device is a significant risk device, a sponsor may not resume a terminated investigation without IRB and FDA approval. 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 paragraph (b)(2) of this section, FDA approval.

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<sup>6</sup> *Unanticipated adverse device effect* means 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\(s\)](#)).

# Appendix B: Investigational Drug and Device Labeling Requirements

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## **Labeling of an investigational new drug ([21 CFR 312.6](#))**

- (a) The immediate package of an investigational new drug intended for human use shall bear a label with the statement “Caution: New Drug—Limited by Federal (or United States) law to investigational use.”
- (b) The label or labeling of an investigational new drug shall not bear any statement that is false or misleading in any particular and shall not represent that the investigational new drug is safe or effective for the purposes for which it is being investigated.
- (c) The appropriate FDA Center Director....may grant an exception or alternative to the provision in paragraph (a) of this section, to the extent that this provision is not explicitly required by statute, for specified lots, batches, or other units of a human drug product that is or will be included in the Strategic National Stockpile.

## **Labeling of investigational devices ([21 CFR 812.5](#))**

All investigational devices, regardless of whether they require a “full” or abbreviated IDE, must meet the following FDA labeling requirements:

- (a) *Contents.* An investigational device or its immediate package shall bear a label with the following information: the name and place of business of the manufacturer, packer, or distributor (in accordance with §801.1), the quantity of contents, if appropriate, and the following statement: “CAUTION—Investigational device. Limited by Federal (or United States) law to investigational use.” The label or other labeling shall describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.
- (b) *Prohibitions.* The labeling of an investigational device shall not bear any statement that is false or misleading in any particular and shall not represent that the device is safe or effective for the purposes for which it is being investigated.
- (c) *Animal research.* An investigational device shipped solely for research on or with laboratory animals shall bear on its label the following statement: “CAUTION—Device for investigational use in laboratory animals or other tests that do not involve human subjects.”
- (d) The appropriate FDA Center Director....may grant an exception or alternative to the provisions in paragraphs (a) and (c) of this section, to the extent that these provisions are not explicitly required by statute, for specified lots, batches, or other units of a device that are or will be included in the Strategic National Stockpile.



## Appendix C: Prohibition of Promotion and Other Practices (Investigational Drugs and Devices)

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### **Investigational Drugs/Biologics (21 CFR 312.7).**

- (a) *Promotion of an investigational new drug.* A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.
- (b) *Commercial distribution of an investigational new drug.* A sponsor or investigator shall not commercially distribute or test market an investigational new drug.
- (c) *Prolonging an investigation.* A sponsor shall not unduly prolong an investigation after finding that the results of the investigation appear to establish sufficient data to support a marketing application

### **Investigational Devices (21 CFR 812.7).**

A sponsor, investigator, or any person acting for or on behalf of a sponsor or investigator shall not:

- (a) *Promote or test market an investigational device,* until after FDA has approved the device for commercial distribution.
- (b) *Commercialize an investigational device* by charging the subjects or investigators for a device a price larger than that necessary to recover costs of manufacture, research, development, and handling.
- (c) *Unduly prolong an investigation.* If data developed by the investigation indicate in the case of a class III device that premarket approval cannot be justified or in the case of a class II device that it will not comply with an applicable performance standard or an amendment to that standard, the sponsor shall promptly terminate the investigation.
- (d) *Represent that an investigational device is safe or effective* for the purposes for which it is being investigated.

# Appendix D.1: Principal Investigator and Sponsor/Sponsor-Investigator Recordkeeping and Retention Requirements – Investigational New Drug Research

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## **Investigator Records ([21 CFR 312.62](#))**

- (a) *Disposition of drug.* An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under [21 CFR 312.59](#).
- (b) *Case histories.* An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.
- (c) *Record retention.* An investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

## **Sponsor/Sponsor-Investigator Records ([21 CFR 312.57](#))**

- (a) A sponsor shall maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug. These records are required to include, as appropriate, the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment.
- (b) A sponsor shall maintain complete and accurate records showing any financial interest in [21 CFR 54.4\(a\)\(3\)\(i\)](#), [\(a\)\(3\)\(ii\)](#), [\(a\)\(3\)\(iii\)](#), and [\(a\)\(3\)\(iv\)](#) of this chapter paid to clinical investigators by the sponsor of the covered study. A sponsor shall also maintain complete and accurate records concerning all other financial interests of investigators subject to [21 CFR 54](#).
- (c) A sponsor shall retain the records and reports required by this part for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.
- (d) A sponsor shall retain reserve samples of any test article and reference standard identified in, and used in any of the bioequivalence or bioavailability studies described in, [21 CFR 320.38](#) or [320.63](#) of this chapter, and release the reserve samples to FDA upon request, in accordance with, and for the period specified in [21 CFR 320.38](#).

# Appendix D.2: Principal Investigator and Sponsor Recordkeeping and Retention Requirements – Investigational Device Research

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## Investigational Device Research ([21 CFR 812.140](#))

- (a) **Investigator records.** A participating investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:
- (1) All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.
  - (2) Records of receipt, use or disposition of a device that relate to:
    - i. The type and quantity of the device, the dates of its receipt, and the batch number or code mark.
    - ii. The names of all persons who received, used, or disposed of each device.
    - iii. Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.
  - (3) Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records shall include:
    - i. Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each individual shall document that informed consent was obtained prior to participation in the study.
    - ii. All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
    - iii. A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.
  - (4) The protocol, with documents showing the dates of and reasons for each deviation from the protocol.
  - (5) Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.
- (b) **Sponsor (or Sponsor-Investigator) records.** A sponsor shall maintain the following accurate, complete, and current records relating to an investigation:
- (1) All correspondence with another sponsor, a monitor, an investigator, an IRB, or FDA, including required reports.
  - (2) Records of shipment and disposition. Records of shipment shall include the name and address of the consignee, type and quantity of device, date of shipment, and batch number or code mark. Records of

disposition shall describe the batch number or code marks of any devices returned to the sponsor, repaired, or disposed of in other ways by the investigator or another person, and the reasons for and method of disposal.

- (3) Signed investigator agreements including the financial disclosure information required to be collected under [21 CFR 812.43\(c\)\(5\)](#) in accordance with [21 CFR 54](#).
  - (4) For each investigation subject to [abbreviated IDE requirements, per [21 CFR 812.2\(b\)\(1\)](#)], the records described in paragraph (b)(5) of this section and the following records, consolidated in one location and available for FDA inspection and copying:
    - (1) The name and intended use of the device and the objectives of the investigation;
    - (2) A brief explanation of why the device is not a significant risk device;
    - (3) The name and address of each investigator;
    - (4) The name and address of each IRB that has reviewed the investigation;
    - (5) A statement of the extent to which the good manufacturing practice regulation in [Part 820](#) will be followed in manufacturing the device; and
    - (6) Any other information required by FDA.
  - (5) Records concerning adverse device effects (whether anticipated or unanticipated) and complaints, and
  - (6) Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.
- (c) **IRB records.** An IRB shall maintain records in accordance with 21 CFR 56.
- (d) **Retention period.** An investigator or sponsor shall maintain the records required by this subpart during the investigation and for a period of 2 years after the latter of the following two dates:  
The date on which the investigation is terminated or completed, or  
The date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.
- (e) **Records custody.** An investigator or sponsor may withdraw from the responsibility to maintain records for the period required in paragraph (d) of this section and transfer custody of the records to any other person who will accept responsibility for them under this part, including the requirements of [§812.145 \[Inspections\]](#). Notice of a transfer shall be given to FDA not later than 10 working days after transfer occurs.

# Appendix E.1: Principal Investigator and Sponsor Reporting Requirements – Investigational Drug Research

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## Definitions

(per [21 CFR 312.32](#))

**Adverse event** means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

**Life-threatening adverse event or life-threatening suspected adverse reaction.** An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

**Serious adverse event or serious suspected adverse reaction.** An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

**Suspected adverse reaction** means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

**Unexpected adverse event or unexpected suspected adverse reaction.** An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. “Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

## Investigator Reports

([21 CFR 312.64](#))

**Progress reports.** The investigator shall furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained. The sponsor is required under [21 CFR 312.33](#) to submit annual reports to FDA on the progress of the clinical investigations.

**Safety reports.** An investigator must immediately report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor. The investigator must record nonserious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol.

**Final report.** An investigator shall provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation.

**Financial disclosure reports.** The clinical investigator shall provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required under [part 54](#) of this chapter. The clinical investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

## Sponsor (or Sponsor-Investigator) Reports

### IND Safety Reporting ([21 CFR 312.32](#))

- (b) **Review of safety information.** The sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.
- (c) **IND safety reports.**
  - (1) The sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under paragraph (c)(1)(i), (c)(1)(ii), (c)(1)(iii), or (c)(1)(iv) of this section. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.
    - i. **Serious and unexpected suspected adverse reaction.** The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:
      - A. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
      - B. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
      - C. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates

those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

- ii. **Findings from other studies.** The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies (other than those reported under paragraph (c)(1)(i) of this section), whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug. Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.
  - iii. **Findings from animal or in vitro testing.** The sponsor must report any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure. Ordinarily, any such findings would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.
  - iv. **Increased rate of occurrence of serious suspected adverse reactions.** The sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.
  - v. **Submission of IND safety reports.** The sponsor must submit each IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. ....The sponsor may submit foreign suspected adverse reactions on a Council for International Organizations of Medical Sciences (CIOMS) I Form instead of a FDA Form 3500A. Reports of overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division in the Center for Drug Evaluation and Research or in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. Upon request from FDA, the sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.
- (2) **Unexpected fatal or life-threatening suspected adverse reaction reports.** The sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.
  - (3) **Reporting format or frequency.** FDA may require a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph. The sponsor may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the director of the FDA review division that has responsibility for review of the IND.
  - (4) **Investigations of marketed drugs.** A sponsor of a clinical study of a drug marketed or approved in the United States that is conducted under an IND is required to submit IND safety reports for suspected adverse reactions that are observed in the clinical study, at domestic or foreign study sites. The sponsor must also submit safety information from the clinical study as prescribed by the postmarketing safety reporting requirements (e.g., §§310.305, 314.80, and 600.80 of this chapter).

(5) **Reporting study endpoints.** Study endpoints (e.g., mortality or major morbidity) must be reported to FDA by the sponsor as described in the protocol and ordinarily would not be reported under paragraph (c) of this section. However, if a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis), the event must be reported under §[312.32\(c\)\(1\)\(i\)](#) as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality).

(d) **Follow-up.**

- (1) The sponsor must promptly investigate all safety information it receives.
- (2) Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such, i.e., "Follow-up IND Safety Report."
- (3) If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable under paragraph (c) of this section is so reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

(e) **Disclaimer.** A safety report or other information submitted by a sponsor under this part (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse event. A sponsor need not admit, and may deny, that the report or information submitted by the sponsor constitutes an admission that the drug caused or contributed to an adverse event.

## Annual reports

[\(21 CFR 312.33\)](#)

A sponsor shall within 60 days of the anniversary date that the IND went into effect, submit a brief report of the progress of the investigation that includes:

- (a) **Individual study information.** A brief summary of the status of each study in progress and each study completed during the previous year. The summary is required to include the following information for each study:
  - (1) The title of the study (with any appropriate study identifiers such as protocol number), its purpose, a brief statement identifying the patient population, and a statement as to whether the study is completed.
  - (2) The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason.
  - (3) If the study has been completed, or if interim results are known, a brief description of any available study results.
- (b) **Summary information.** Information obtained during the previous year's clinical and nonclinical investigations, including:
  - (1) A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system.
  - (2) A summary of all IND safety reports submitted during the past year.



- (3) A list of subjects who died during participation in the investigation, with the cause of death for each subject.
- (4) A list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related.
- (5) A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, information from controlled trials, and information about bioavailability.
- (6) A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings.
- (7) A summary of any significant manufacturing or microbiological changes made during the past year.
- (c) **A description of the general investigational plan for the coming year** to replace that submitted 1 year earlier. The general investigational plan shall contain the information required under [21 CFR 312.23\(a\)\(3\)\(iv\)](#).
- (d) If the investigator brochure has been revised, a **description of the revision and a copy of the new brochure**.
- (e) A description of **any significant Phase 1 protocol modifications** made during the previous year and not previously reported to the IND in a protocol amendment.
- (f) A brief summary of **significant foreign marketing developments** with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country.
- (g) If desired by the sponsor, a log of any outstanding business with respect to the IND for which the sponsor requests or expects a reply, comment, or meeting.

## Appendix E.2: Principal Investigator and Sponsor Reporting Requirements – Investigational Device Research

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(21 CFR 812.150)

- (a) **Investigator reports.** An investigator shall prepare and submit the following complete, accurate, and timely reports:
- (1) **Unanticipated adverse device effects.** An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.
  - (2) **Withdrawal of IRB approval.** An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
  - (3) **Progress.** An investigator shall submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.
  - (4) **Deviations from the investigational plan.** An investigator shall notify the sponsor and the reviewing IRB ... of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB in accordance with 21 CFR 812.35(a) also is required.
  - (5) **Informed consent.** If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.
  - (6) **Final report.** An investigator shall, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.
  - (7) **Other.** An investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.
- (b) **Sponsor (or Sponsor-Investigator) reports.** A sponsor shall prepare and submit the following complete, accurate, and timely reports:
- (1) **Unanticipated adverse device effects.** A sponsor who conducts an evaluation of an unanticipated adverse device effect under 21 CFR 812.46(b) [Monitoring] shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.
  - (2) **Withdrawal of IRB approval.** A sponsor shall notify FDA and all reviewing IRB's and participating investigators of any withdrawal of approval of an investigation or a part of an investigation by a reviewing IRB within 5 working days after receipt of the withdrawal of approval.

- (3) **Withdrawal of FDA approval.** A sponsor shall notify all reviewing IRB's and participating investigators of any withdrawal of FDA approval of the investigation, and shall do so within 5 working days after receipt of notice of the withdrawal of approval.
- (4) **Current investigator list.** A sponsor shall submit to FDA, at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. The sponsor shall submit the first such list 6 months after FDA approval.
- (5) **Progress reports.** At regular intervals, and at least yearly, a sponsor shall submit progress reports to all reviewing IRB's. In the case of a significant risk device, a sponsor shall also submit progress reports to FDA.

A sponsor of a *treatment IDE* shall submit semi-annual progress reports to all reviewing IRB's and FDA in accordance with 21 CFR 812.36(f) and annual reports in accordance with this section.

- (6) **Recall and device disposition.** A sponsor shall notify FDA and all reviewing IRB's of any request that an investigator return, repair, or otherwise dispose of any units of a device. Such notice shall occur within 30 working days after the request is made and shall state why the request was made.
- (7) **Final report.** In the case of a *significant risk device*, the sponsor shall notify FDA within 30 working days of the completion or termination of the investigation and shall submit a final report to FDA and all reviewing the IRB's and participating investigators within 6 months after completion or termination.

In the case of a device that is *not a significant risk device*, the sponsor shall submit a final report to all reviewing IRB's within 6 months after termination or completion.

- (8) **Informed consent.** A sponsor shall submit to FDA a copy of any report by an investigator under paragraph (a)(5) of this section of use of a device without obtaining informed consent, within 5 working days of receipt of notice of such use.
- (9) **Significant risk device determinations.** If an IRB determines that a device is a significant risk device, and the sponsor had 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.
- (10) A sponsor shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

## Appendix F: Inspections (Investigational Drugs and Devices)

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Investigational drug and medical device research is subject to inspections by the FDA (in addition to audit by the IRB, post-approval monitoring, etc.

FDA requirements for **Investigational Drug Research** ([21 CFR 312.68](#)) are as follows:

An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to [21 CFR 312.62](#). The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.

FDA requirements for **Investigational Device Research** ([21 CFR 812.145](#)) are as follows:

- (a) Entry and inspection. A sponsor or an investigator who has authority to grant access shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept).
- (b) Records inspection. A sponsor, IRB, or investigator, or any other person acting on behalf of such a person with respect to an investigation, shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation.
- (c) Records identifying subjects. An investigator shall permit authorized FDA employees to inspect and copy records that identify subjects, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, 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.

# Resources

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## General

[FDA Regulations – Protection of Human Subjects \(21 CFR 50\)](#)

[FDA Regulations – Institutional Review Boards \(21 CFR 56\)](#)

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

[IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and Determination of Whether an IND/IDE is Needed](#)

[Financial Disclosure by Clinical Investigators](#)

[Questions and Answers on Informed Consent Elements](#)

[Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring](#)

[Computerized Systems Used in Clinical Investigations](#)

## Medical Devices

[FDA Regulations – Investigational Device Exemptions \(21 CFR 812\)](#)

[Device Advice: Investigational Device Exemption \(IDE\)](#)

[FAQs about IDE](#)

[FDA Decisions for Investigational Device Exemption Clinical Investigations](#)

[In Vitro Diagnostic \(IVD\) Device Studies – Frequently Asked Questions](#)

[Mobile Medical Applications](#)

[Significant Risk and Nonsignificant Risk Medical Device Studies](#)

[Suggested Format for IDE Progress Report](#)

## Investigational Drugs

[FDA Regulations—Investigational New Drug Application \(21 CFR 312\)](#)

[Charging for Investigational Drugs under an IND—Questions and Answers](#)

[Safety Reporting Requirements for INDs and BA/BE Studies](#)

[Treatment Use of Investigational Drugs](#)

### Document History

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