Federal Regulations Governing Subject-Specific Clinical Research Activities

Food and Drug Administration (FDA)

Conflict of Interest	42 CFR Part 50, Subpart F
Electronic Records; Electronic Signatures	21 CFR Part 11 sections 1-300
HIPAA Privacy and HITECH Rule	42 CFR Parts 160, 162 and 164
Financial Disclosure by Clinical Investigator	21 CFR Part 54 sections 1-6
International Council on Harmonization/Good Clinical Practice	**ICH** E6, E2A, and E8
Investigational Medical Device & Reporting	21 CFR Part 803 section 1-58 21 CFR Part 812 section1-150 21 CFR Part 814 section 1-126
Investigational New Drug & Safety Reporting	21 CFR Part 312 sections 1- 320 21 CFR Part 314 section 1-650
Protection of Human Subjects/Informed Consent	21 CFR Part 50 sections 1-56

Department of Health and Human Services (DHHS)

Basic HHS Policy for Protection of Human Research Participants	45 CFR 46 Subpart A
Protections for Pregnant Woman, Human Fetuses & Neonates	45 CFR 46 Subpart B
Protections Pertaining to Biomedical/Behavioral Research Involving Prisoners	45 CFR Subpart C
Additional Protections for Children Involved as Subjects in Research	45 CFR Subpart D

Research Billing Regulations

Centers for Medicare and Medicaid Services	42 CFR Parts 405 & 411
Medicare Secondary Payor Rule	42 USC 1395y(b)(5)

Federal Regulations and Requirements Governing Clinical Trials

In addition to human subject protection regulations, there are regulations that govern the approvals and oversight required before a drug or device can be tested and approved for market. These regulations give the Food and Drug Administration (FDA) the authority to oversee the safety of drugs, biologics and devices.

Current federal law requires that an investigational drug and device be subject to an approved marketing application before it is transported or distributed for clinical investigation purposes. The **Investigational New Drug (IND) Application** and **Investigational Device Exemption (IDE)** are means by which an exemption to this requirement is obtained from the FDA. Specifically, the IND allows a drug or biologic to be used in a clinical trial to collect safety and efficacy/effectiveness data notwithstanding the fact that the drug has not been approved by the FDA. Similarly, the IDE allows a device to be used in a clinical trial to collect safety and efficacy/effectiveness data notwithstanding the fact that the device has not been approved by the FDA.

Investigational New Drug (IND) Applications

There are three IND Application types:

(1) An Investigator IND Application is submitted by an investigator who both initiates ***and*** conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. For example, a researcher might submit an IND to study an unapproved drug or to study an approved drug for a new indication or in a new patient population.

(2) An Emergency Use IND Application seeks the FDA's authorization to use an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21 CFR §312.23 or §312.34. It is also used in cases where study participants do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.

(3) A Treatment IND Application is submitted for experimental drugs showing promise in clinical testing for serious or immediate life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

The FDA has the authority to require pre-clinical test results, data reports, and other relevant information before approving the IND application. The FDA may also seek guarantees that only qualified investigators will be part of the investigational study, as well as ensure the protection of human participants in the investigational study before approving the IND application.

An IND is deemed approved if not acted upon by the FDA within 30 calendar days of the IND application submission. Accordingly, the investigator must wait thirty (30) calendar days after submission of IND application before initiating the clinical trial. However, the FDA may place a "clinical hold" during the 30-day period, or after the IND has been approved. Reasons for placing a

clinical hold include but are not limited to (a) failure to provide sufficient investigator documentation, (b) clear deficiencies in the protocol, (c) unreasonable and significant risk to study participants, and (d) failure to provide sufficient information to evaluate risks to study participants.[1]

> **Investigator's Responsibilities Under an IND**: An investigator conducting a clinical investigation under an IND application is responsible for ensuring that the investigation is conducted according to the signed investigator's statement Form 1572 (PDF - 718KB), the investigational plan, and the applicable regulations as referenced in this document. In addition, an investigator is responsible for protecting the rights, safety, and welfare of subjects under the investigator's care and for the control of drugs under investigation. Such responsibilities also include record retention, reporting, inspection, and assurance of IRB review. For a list of investigator's responsibilities, please see https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-procedures-investigators-responsibilities

[1] 21 CFR §312.42.

Investigational Device Exemption (IDE)

An Investigational Device Exemption (IDE) is required prior to the initiation and enrollment of study participants in an investigational device study[2]. The IDE must be supplied by the sponsor (if the study is sponsored) or requested and obtained by the Principal Investigator. An IDE must contain, among other information, (a) an investigational plan that includes the study's purpose and protocol, (b) a description of the methods, facilities, and controls used for manufacturing the device, and (d) an example of the agreements to be entered into with clinical investigators.

Upon receipt of the IDE application, the FDA assigns an IDE number. The IDE application is considered "approved" thirty (30) calendar days after the FDA receives the IDE application, unless the FDA informs the IDE submitter otherwise prior to that date[3]

With an approved IDE, the Principal Investigator can use[4] and/or ship the device lawfully for the purpose of conducting a clinical study without complying with most regulations applicable to devices in commercial distribution[5].

The FDA regulates medical devices according to their risk. Accordingly, the FDA has established the following three classes of risk for devices:

> **Class I Devices**: Class I Devices are subject to the least regulatory control because they are viewed by the FDA as presenting a low risk of potential harm to patients/study participants than Class II or Class III devices. Examples of Class I devices include orthopedic blades and tongue depressors.
>
> **Class II Devices**: Devices that present a moderate risk to injury to patients/study participants. Examples of Class II devices are powered wheelchairs, infusion pumps and surgical drapes.
>
> **Class III Devices**: Class III Devices are the highest risk devices, and includes life-supporting or life-sustaining devices. Examples of Class III devices include cardiac ablation catheters and coronary stents.

Additional information on device classes can be found at https://www.fda.gov/medical-devices/overview-device-regulation/classify-your-medical-device

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[2] 21 CFR §812.20.

[3] 21 CFR §812.30(a)(1).

[4] Please note investigational uses include clinical evaluation of certain modifications or new intended uses of legally marketed devices.

[5] Please note that all investigational device studies require approval from the Medicare Administrative Center (MAC) and local carrier before Medicare can be billed for participants enrolled in the clinical trial.

Significant Risk Device Studies: Studies of devices that pose "significant risk" require approval from both the FDA and the Institutional Review Board (IRB) prior to commencement of a clinical study[6]. A *significant risk device*[7] is defined as an investigational device that:

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

Non-Significant Risk Device Studies: Examples of non-significant risk devices include contact lens, urethral stents, and denture repair kits[8]. An IDE application is *not* required to be submitted to the FDA for non-significant risk device studies. Rather, non-significant risks studies are considered to have an IDE approval if/when IRB approval is obtained for the study[9], and other specific requirements are met such as (i) the investigator obtaining consent from study participants, (ii) monitoring of the study, and (iii) adherence to the prohibition against, among things, promotion or test marketing of the investigational device[10].

***Comprehensive instructions on the required forms and documentation for IDE study planning, and the application submission and approval process can be found on the FDA website at https://www.fda.gov/media/87607/download

Investigator's Responsibilities Under an IDE: Although specific investigator responsibilities in drug and biologics clinical trials are not identical to the investigator responsibilities in medical device clinical trials, the general responsibilities are essentially the same. Specifically, an investigator's responsibilities in conducting clinical investigations of a medical device are provided in 21 CFR Part 812. Note: the medical device regulations do not require use of a specific form for an investigator's statement (FDA Form 1572). Investigators should refer to

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[6] *See* 21 CFR §56.102(g).
[7] 21 CFR §812.3(m).
[8] Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies *See* https://www.fda.gov/science-research/guidance-documents-including-information-sheets-and-notices/information-sheet-guidance-institutional-review-boards-irbs-clinical-investigators-and-sponsors
[9] The IDE holder must include in the IRB submission an explanation of why the device does not pose a significant risk. If the IRB disagrees with the IDE holder's non-significant risk determination, then the IDE holder must report the IRB's findings to the FDA within five (5) working days. The FDA makes the final determination as to whether the device is significant or non-significant risk.
[10] 21 CFR §812.2(b).

21 CFR Parts 11, 50, 54, 56, and 812 for a more comprehensive listing of FDA's requirements for the conduct of device studies.

Updating the IND/IDE

Once the clinical trial is initiated, the investigator has an obligation to update the IND/IDE to ensure the clinical trial is being conducted consistent with the IND/IDE application.

For investigational drug trials, the investigator must generally submit a "*protocol amendment"* to the FDA to: (1) conduct any clinical trial that is not covered by a protocol in the IND application, (2) make changes to existing protocols if the changes affect the safety of study participants or the scope of the investigation[11], or (3)add a new investigator. Except for the addition of a new investigator, the trial can begin only after FDA submission and IRB approval of the amendment.

Annual reports must also be submitted to update the FDA on the progress of the investigation.[12] The reports generally include information such as a summary of current and recently completed clinical trials, information obtained during the investigation (including information relating to the safety and efficacy of the drug), a description of plans for upcoming investigations, and information on changes to the drug, clinical trial, or clinical trial documents.

For investigational device trials, the investigator must generate a supplemental IDE and obtain FDA approval before significantly changing an investigational plan or clinical protocol.[13] Significant changes to the plan include increasing the number of clinical sites or study participants, changing the device indication, changing the type or nature of the study control, changing the method of statistical evaluation, or terminating the trial early. Significant changes also include protocol revisions that affect the validity of the data, and/or the rights, safety, welfare of study participants.

Notice to the FDA is required within five (5) working days of some IDE changes that do not qualify as significant, while other minor changes to the IDE, such as changes to the purpose of the clinical trial, the risk analysis, monitoring procedures, informed consent materials, or IRB information may be submitted in an annual report.[14]

[11] An increase in the drug dosage or the duration of exposure, as well as significant increase in the number of study participants would constitute a change for which an amendment is required. See 21 CFR § 312.30.
[12] 21 CFR § 312.33.
[13] 21 CFR § 812.35.
[14] 21 CFR § 812.35.

IND and IDE Frequently Asked Questions

Investigational New Drug Application (IND)

Q: How do I know if an Investigational Product is a "Drug" Subject to FDA Regulations and Approval?

A: *For most, "drugs" are products obtained from pharmacists via prescription or over-the-counter (in a pharmacy or retailer) that require special packaging, formulaic warnings and instructions that do something to our bodies to address illness or dysfunction. However, the reality is most of these factors do not cause a product's classification as a drug—they are consequences of it.*

The Food, Drug and Cosmetics Act (FDCA) provides the following four criteria for determining whether a product is a drug:

1. *It is an article recognized in the United States Pharmacopoeia, the official Homeopathic Pharmacopoeia of the United States or the official National Formulary, or a supplement to any of them.*

2. *It is an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals.*

3. *It is an article (other than food) intended to affect the structure or any function of the body of man or other animals.*

4. *It is an article intended for use as a component of any of the previous articles above (1,2, or 3).*

********* *In many cases, the most important criteria are (2) and (3) above as these reflect the legal concept of "intended use," which leads most frequently to their categorization as drugs.*

Q: What is the Purpose for Submitting an IND Application?

A: *The IND application allows a drug or biologic to be used in a clinical trial to collect safety and efficacy/effectiveness data notwithstanding the fact that the drug has not been approved by the FDA.*

Q: Who is Required to Submit an IND Application?

A: *The IND application is submitted by an investigator who <u>both</u> initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed.*

Q: How Long Does It Take for Approval After the Submission of an IND Application?

A: *An IND is deemed approved if not acted upon by the FDA within 30 calendar days of the IND application submission. However, the FDA may place a "clinical hold" during the 30-day period, or after the IND has been approved. Reasons for placing a clinical hold include but are not limited to (a) failure to provide sufficient investigator documentation, (b) clear deficiencies in the protocol, (c) unreasonable and significant risk to study participants, and (d) failure to provide sufficient information to evaluate risks to study participants.*

Q: Can I Begin to Enroll Patients/Study Participants in a Study/Clinical Trial While the IND Application is Pending?

A: *Unless the FDA has placed a "clinical hold" during the 30-day period (for reasons referenced above), the investigator must wait thirty (30) calendar days after submission of the IND application before enrolling patients/study participants in a study/clinical trial.*

Q: What are the Investigator's Responsibilities under an IND?

A: *An investigator conducting a clinical investigation under an IND application is responsible for ensuring that the investigation is conducted according to the signed investigator's statement Form 1572 (PDF - 718KB), the investigational plan, and the applicable regulations. For a list of investigator's responsibilities, see https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-procedures-investigators-responsibilities*

Q: When must an IND be Amended?

A: T*he investigator must generally submit a "protocol amendment" to the FDA to: (1) conduct any clinical trial that is not covered by a protocol in the IND application, (2) make changes to existing protocols if the changes affect the safety of study participants or the scope of the investigation[15], or (3) add a new investigator.*

[15] An increase in the drug dosage or the duration of exposure, as well as significant increase in the number of study participants would constitute a change for which an amendment is required. See 21 CFR § 312.30.

Investigational Device Exemption (IDE)

Q: When Does a Product Constitute a Device Subject to FDA Regulations and Approval?

A: *The FDCA defines a Device as an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is---*

1. *Recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them.*
2. *Intended for use in the diagnosis or 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.*

******* *However, the question of whether or not a product is a device is not always straightforward. Often times, whether a product is a device will depend on the claims made about the product or its performance. Hence, products that would not otherwise fall within the definition of devices may be regulated as such by the FDA solely on the basis of the labeling claims made for the product. For example, a treadmill is not typically considered a device; however, if the manufacturer makes therapeutic claims for the treadmill like, "it helps to prevent heart disease," then the FDA would likely regulate the treadmill as a device.*

Q: What is the Purpose for Submitting an IDE?

A: *An Investigational Device Exemption (IDE) is required prior to the initiation and enrollment of study participants in an investigational device study. An IDE must contain, among other information, (a) an investigational plan that includes the study's purpose and protocol, (b) a description of the methods, facilities, and controls used for manufacturing the device, and (c) an example of the agreements to be entered into with investigators*.

An approved IDE allows the investigator to use and/or ship the investigational device lawfully for the purpose of conducting a clinical study without complying with most regulations applicable to devices in commercial distribution.

Q: Who is Required to Submit an IDE?

A: *The IDE is submitted by an investigator who <u>both</u> initiates and conducts an investigation, and under whose immediate direction the investigational device is administered.*

Q: How Long Does It Take for Approval After the Submission of an IDE?

A: *The IDE is considered "approved" thirty (30) calendar days after the FDA receives the IDE application, unless the FDA informs the IDE submitter otherwise prior to that date.*

Q: Can I Begin to Enroll Patients/Study Participants in a Study/Clinical Trial While the IDE is Pending?

A: *The investigator must wait thirty (30) calendar days after submission of the IDE before enrolling patients/study participants in a study/clinical trial.*

Q: What are the Investigator's Responsibilities under an IDE?

A: A*n investigator's responsibilities in conducting clinical investigations of a medical device are provided in 21 CFR Part 812. Investigators should refer to 21 CFR Parts 11, 50, 54, 56, and 812 for a more comprehensive listing of FDA's requirements for the conduct of device studies****.***

Q. How Do I Find and/or Determine the Risk Classification for a Device?

A: To find the classification, as well as whether any exemptions may exist, you need to find the regulation number that is the classification regulation for the device. There are two methods for accomplishing this: go directly to the classification database and search for a part of the device name, or, if you know the device panel (medical specialty) to which the device belongs, go directly to the listing for that panel and identify the device and the corresponding regulation.

If you already know the appropriate panel you can go directly to the CFR and find the classification for the device by reading through the list of classified devices, or if you're not sure, you can use the keyword directory in the PRODUCT CODE CLASSIFICATION DATABASE. In most cases this database will identify the classification regulation in the CFR.

Q: Who Determines Whether a Device is a Significant or Non-Significant Risk Device?

A: *The IDE holder must include in its submission to the IRB an explanation of why the device does not pose a significant risk. If the IRB disagrees with the IDE holder's non-significant risk determination, then the IDE holder must report the IRB's findings to the FDA within five (5) working days. The FDA makes the final determination as to whether the device is significant or non-significant risk.*

Q: When must a supplemental IDE be submitted?

A*: The investigator must generate a supplemental IDE and obtain FDA approval before significantly changing an investigational plan or clinical protocol.*[16] *Significant changes to the plan include increasing the number of clinical sites or study participants, changing the device indication, changing the type or nature of the study control, changing the method of statistical evaluation, or terminating the trial early. Significant changes also include protocol revisions that affect the validity of the data, and/or the rights, safety, welfare of study participants.*

[16] 21 CFR § 812.35.