7 FDA Regulated Research

The CMU IRB does not review research involving Investigational New Drug (IND) Applications to the FDA.

FDA regulations apply to any research that involves a "test article" in a "clinical investigation" involving "human subjects" as defined by the FDA regulations. For FDA regulated research, the IRB must apply the FDA regulations at 21 CFR 50 and 21 CFR 56, as well as, where appropriate, 45 CFR 46.

Use of investigational drugs must be conducted according to FDA IND regulations, 21 CFR Part 312, and other applicable FDA regulations. Use of an investigational device in a clinical trial to obtain safety and effectiveness data must be conducted according to FDA's IDE regulations, 21 CFR Part 812, and other applicable FDA regulations.

The following definitions and procedures describe the review of FDA-regulated research conducted under the auspices of CMU.

7.1 Definitions

Investigational Drug – An investigational drug for clinical research use is one for which the PI or a sponsor has filed an IND application (21 CFR Part 312) or an approved drug that is being studied for an unapproved or approved use in a controlled, randomized, or blinded clinical trial.

Investigational Device – A medical device that is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device. As further stated, a device is any healthcare product that does not achieve its primary intended purpose by chemical action or by being metabolized.

IND – An investigational new drug application in accordance with 21 CFR Part 312.

IDE – An investigational device exemption in accordance with 21 CFR 812.

Significant Risk (SR) – A significant risk device is an investigational device that

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

Non-Significant Risk (NSR) – An investigational device other than a significant risk device.

7.2 Procedures

At initial submission, the PI must indicate whether the research involves a test article and is a clinical investigation involving human subjects on the application form. The PI may use the FDA Determination Checklist to assist in making this determination.

During the pre-review process, the DRC will confirm whether FDA regulations are applicable using the FDA Determination Checklist. If FDA regulations apply and the research is not exempt, the IRB Administrator will indicate on the agenda that the protocol is an FDA-regulated study.

7.3 Investigational Drugs and Devices

Studies of drugs that require an IND will not be conducted at CMU. Drug studies that are exempt from IND requirements and medical device studies may be conducted at CMU and may be overseen either by the CMU IRB or an external IRB (per Sec 0). The PI must indicate on the IRB application whether the research involves investigational drugs or devices. If so, the PI must indicate if there is an IND Exemption/IDE for the research and provide documented assurance from the sponsor that the manufacture and formulation of investigational or unlicensed test articles conform to federal regulations. Documentation of the IND Exemption/IDE could be :

1. an industry-sponsored protocol with IND Exemption/IDE.
2. a letter from FDA.
3. a letter from industry sponsor.
4. other document and/or communication verifying the IND Exemption/IDE.

For investigational devices, NSR device studies follow abbreviated IDE requirements and do not have to have an IDE application approved by the FDA. If a sponsor has identified a study as NSR, then the investigator must provide an explanation of the determination. If the FDA has determined that the study is NSR, documentation of that determination must be provided.

If the research involves drugs or devices and there is no IND Exemption/IDE, the PI must provide a rationale as to why it is not required.

The IRB will review the application and determine:

1. whether there is an IND Exemption/IDE and if so, whether there is appropriate supporting documentation;
2. if the research involves drugs or devices with no IND/IDE and whether the research meets the criteria below.

7.4 IND Exemption

For drugs, an IND is not necessary if the research falls in <u>one</u> of the following categories:

1. The drug being used in the research is lawfully marketed in the United States and <u>all</u> of the following requirements are met:
   a. The research is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug.
   b. The research is not intended to support a significant change in the advertising for the product.

c. The research does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
d. The research is conducted in compliance with the requirements for IRB review and informed consent [See 21 CFR parts 56 and 50, respectively].
e. The research is conducted in compliance with the requirements concerning the promotion and sale of drugs [See 21 CFR 312.7].
f. The research does not intend to invoke FDA regulations for planned emergency research [See 21 CFR 50.24].

2. The research only involves one or more of the following: (i) Blood grouping serum, (ii) Reagent red blood cells, or (iii) Anti-human globulin.
3. For clinical investigations involving an in vitro diagnostic biological product, an IND is not necessary if (i) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and (ii) it is shipped in compliance with 312.160.

7.5 Medical Devices

7.5.1 IDE Requirements

The PI must indicate on the IRB application whether the research involves investigational devices. If so, the PI must indicate if there is an IDE for the research and provide documented assurance from the sponsor that the manufacture and formulation of investigational or unlicensed test articles conform to federal regulations. Documentation of the IDE could be:

1. an industry-sponsored protocol with IDE.
2. a letter from FDA.
3. a letter from industry sponsor.
4. other document and/or communication verifying the IDE.

For investigational devices, NSR device studies follow abbreviated IDE requirements and do not have to have an IDE application approved by the FDA. If a sponsor has identified a study as NSR, then the investigator must provide an explanation of the determination. If the FDA has determined that the study is NSR, documentation of that determination must be provided.

If the research involves devices and there is no IDE, the PI must provide a rationale as to why it is not required.

The IRB will review the application and determine

1. whether there is an IDE and if so, whether there is appropriate supporting documentation;
2. if the research involves drugs or devices with no IDE and whether the research meets the criteria below.

7.5.2 Exempted IDE Investigations

For devices, an IDE is not necessary if

1. The research involves a device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
2. The research involves a device other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of 21 CFR 807 in determining substantial equivalence.
3. The research involves a diagnostic device and if the sponsor complies with applicable requirements in 21 CFR 809.10(c), and if the testing
   a. is noninvasive,
   b. does not require an invasive sampling procedure that presents significant risk,
   c. does not by design or intention introduce energy into a subject, and
   d. is not used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure.
4. The research involves a device undergoing consumer-preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.
5. The research involves a device intended solely for veterinary use.
6. The research involves a device shipped solely for research on/or with laboratory animals and labeled in accordance with 21 CFR 812.5(c).
7. The research involves a custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

7.6 Responsibilities

7.6.1 Principal Investigator

1. The PI is responsible for ensuring that the research is conducted according to all regulatory guidelines and CMU policies and procedures.
2. The PI must obtain approval from the IRB before initiating any research activities.
3. The PI proposing the drug/device research will be required to provide a plan – to be evaluated by the IRB – that includes storage, security, and dispensing of the (test items (drug/device).
   a. The PI is responsible for the investigational drug/device accountability, which includes storage, security, dispensing, administration, return, disposition, and records of accountability.
   b All test items received for a study must be stored in a controlled environment under secure control with limited access. The area must be within an area of PI's control. A log must be kept regarding the receipt, use, and/or dispensing of the test items and the disposition of remaining test items at the conclusion of the investigation.
4. The PI shall report all unanticipated problems involving risk to subjects or others to the IRB according to the procedures outlined in Section 8.
5. For research involving investigational drugs, the PI will maintain the following:
   a. Current curriculum vitae (CV).

b. Protocol.
c. Records of receipt and disposition of drugs.
d. List of any co-investigators with their curricula vitae.
e. Certification that all physicians, dentists, and/or nurses responsible in the study have appropriate valid licenses for the duration of the investigation.
f. Case histories with particular documentation on evidence of drug effects. Emphasis is on toxicity and possible untoward happenings. All unexpected adverse effects are reportable, even if the investigator considers that the event is not related to the drug. All unexpected adverse effects must be reported immediately to the IRB in the manner defined by the protocol.
g. IRB letters of approval.
h. Other documents as outlined in the Human Subject Protection Program – Standard Operating Procedures.

6. For research involving investigational devices,
   a. If a device is considered NSR by the PI or sponsor, but after review the IRB determines the device to have significant risk, upon receipt of written notice from IRB, the PI is responsible for notifying the sponsor of the IRB's determination. The PI must provide the IRB with confirmation of this action.
   b. If the PI is storing the devices, he/she must maintain a log indicating the identification/serial number of the device, name of subject, date dispensed, by whom it was dispensed, and amount remaining; and
   c. The PI will maintain the following:
      i. Current curriculum vita (CV).
      ii. Protocol of the study.
      iii. Records of animal study reports.
      iv. Records of receipt and disposition of devices.
      v. List of any co-investigators with their curricula vitae.
      vi. Certification that all physicians, dentists, and/or nurses responsible in the study have appropriate valid licenses for the duration of the investigation.
      vii. Case histories with particular documentation on evidence of effects. Emphasis is on safety and possible untoward happenings. All adverse device effects are reportable.
      viii. IRB letters of approval.
      ix. Device training.
      x. Other documents as outlined in the Human Subject Protection Program – Standard Operating Procedures.
7. Following completion of the study, the log must be completed regarding the receipt, use and/or dispensing of the test items and the disposition of remaining test items at the conclusion of the investigation.
8. If, after use, the PI keeps the test items, he/she must maintain a log regarding the receipt, use, and/or re-dispensing of the devices and the disposition of remaining test items at the conclusion of the investigation.
9. The PI will submit to the sponsor and to the IRB a report of any unanticipated adverse effects occurring during an investigation as soon as possible, but in no event later than ten (10) working days after the investigator first learns of the effect.

10. When a PI files an IDE, the PI is considered the sponsor and as such is accountable for all of the FDA regulatory responsibilities and reporting obligations of both the PI and the sponsor, as described in the FDA regulations. The Research Plan asks the PI if he/she also acts as the sponsor of the research and, if so, asks him/her to affirm that he/she has reviewed the **Guidance Document on Requirements of the Sponsor and the Investigator as a Sponsor** and will comply with the regulatory responsibilities of a sponsor. The investigator is responsible for arranging any necessary education or training required to make the regulatory filings and conduct the study. The Office of Research Compliance will conduct random audits of PIs holding an IDE as per the Research Quality Improvement Program (per Sec 1.12).

7.6.2 IRB

1. The IRB will review the research in accordance with the following requirements and the same criteria it would use in considering approval of any research involving an FDA-regulated product. [See 21 CFR 56.111]
2. For research involving investigational devices,
   a. The IRB will review the control plan and determine whether it is adequate. If the Chair determines that the IRB does not have the necessary expertise to evaluate the plan, outside consultation will be used.
   b. Unless the FDA has already made a risk determination for the study, the IRB will review NSR studies and determine if the device represents significant or non-significant risk and report the findings to the PI in writing. The IRB will consider the risks and benefits of the medical device compared to the risks and benefits of alternative devices or procedures. NSR device studies do not require submission of an IDE application but must be conducted in accordance with the abbreviated requirements of IDE regulations. If IRB considers the study that has been submitted as NSR to be considered SR, then IRB may approve the study, but the study cannot begin until an IDE is obtained.
   c. The IRB will not review protocols involving SR devices under expedited review.
   d. The IRB will document in the minutes and provide written documentation to the PI of the rationale for determining whether a device is classified as NSR/SR.
   e. If the FDA has already made the SR or NSR determination for the study, the agency's determination is final, and the IRB does not need to make a risk determination.