“Clinical investigation means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that must meet the provisions of part 58, regarding nonclinical laboratory studies. The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part.” (21 CFR 56.102(c))

“Test article means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act.” (21 CFR 56.102(l))

Investigators involved in clinical investigations on test articles (e.g., investigational new drugs, investigational devices) must obtain Institutional Review Board (IRB) review and approval and must comply with federal and local regulations and legal and regulatory requirements that apply to use of investigational test articles and govern such clinical investigations.

When an investigational new drug or device is being used in a clinical investigation, the U.S. Food and Drug Administration (FDA) requires an application for an Investigational New Drug (IND) or Investigational Device Exemption (IDE) and authorization from the FDA unless the clinical investigation meets the criteria for exemption or is considered to have an approved IDE. Exemption from the IND or IDE requirement is not an exemption from IRB review or from informed consent requirements.

A sponsor may choose, but is not required, to conduct a foreign clinical study under an IND. When a foreign clinical study is conducted under an IND, all FDA IND requirements must be met unless waived. When the foreign clinical study is not conducted under an IND, the sponsor must ensure that the study complies with the requirements in 21 CFR 312.120 in order to use the study as support for an IND or application for marketing approval. Under 21 CFR 312.120, FDA will accept a well-designed, well-conducted, non-IND foreign study as support for an IND or application.
for marketing approval if the study was conducted in accordance with GCP and if FDA is able to validate the data from the study through an onsite inspection, if necessary. See FDA Guidance, “FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND Frequently Asked Questions” for more information. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294729.pdf

Investigators participating in clinical investigations of investigational new drugs or devices must provide documentation of FDA authorization to the IRB, e.g., drug name, IND or IDE number, name of manufacturer or holder of the IND or IDE.

The HRPP staff will verify the IND or IDE submitted by the investigator in the IRB application. Methods of verification may include determining that the IND or IDE number matches the sponsor protocol, communication from the sponsor, or communication from the FDA. In cases where the investigator holds the IND or IDE, the number should match with the information provided by the FDA. The investigator brochure should not be used because one investigator brochure may serve multiple INDs or IDEs.

If there is not an IND or IDE, the investigator must provide the IRB with documentation of the rationale for the exemption (see section below on IND and IDE determination). Such documentation may include a determination by the FDA. For abbreviated IDE requirements, see below and HRPP Manual Section 7-2, “Significant Risk and Nonsignificant Risk Medical Devices.”

To assist in the determinations for clinical investigations of drugs or devices, the Compliance office is assigned when applications are submitted to the MSU IRB that involve drugs or devices

**Handling, Storage, and Control**
The investigator is responsible for storing and handling the test article appropriately as well as for control of the inventory.

> “An investigator shall permit an investigational device to be used only with subjects under the investigator's supervision.” 21 CFR 812.110(c).

> “An investigator shall administer the drug only to subjects under the investigator's personal supervision or under the supervision of a subinvestigator responsible to the investigator” 21 CFR 312.61.

Investigators must be qualified by training and experience for their research role, including the storage and handling of test articles. IRB members may request additional information about qualifications, if necessary. The investigator is responsible for assuring that the individuals administering the drug and device are appropriately trained (e.g., radiation, chemical or biological safety, occupational health). See the Human Research Protection Program (HRPP) Manual 11-1-A “Education – Investigators and Research Staff” for education requirements.
The investigator must describe the plan for storage, handling, and control of the test article. If the clinical investigation is being conducted at a clinical facility, the facility's procedures for control of pharmaceuticals, medical devices, and controlled substances should be followed. For additional guidance for investigators on developing an accountability plan for proper storage, handling, and control of test articles, see HRPP Manual 12-2 “Guidance Document: Storage and Handling of Investigational Drugs and Devices.” A sample log is available on the HRPP website (hrpp.msu.edu).

IRB members will evaluate the investigator’s plan, including assessment of the following:
- Storage and security of test article
- Administration by appropriate individuals
- Plans for documentation and maintenance of records

Proper handling and storage may also be assessed during site visits by the Compliance office.

**Sponsor-Investigator**
If an MSU investigator is also assuming the sponsor function of an investigational drug or device, then the investigator must provide the IRB a copy of the application submitted to the FDA or documentation of FDA exemption for the clinical investigation of the test article. The investigator must also complete the sponsor-investigator worksheet and assure the IRB that they will adhere to all requirements of FDA regulations regarding fulfilling the sponsor function, e.g., 21 CFR 812, subpart C for devices, or 21 CFR 312, subpart D for drugs. Guidance for conducting clinical investigations is provided by FDA, e.g., E6 Good Clinical Practice. Based on the investigator's responses, the IRB will evaluate whether the investigator meets the sponsor requirements. Consultation with MSU Office of the General Counsel, the Office or Regulatory Affairs, and the Institutional Official may also occur. The Compliance office will also assist the investigator regarding the regulatory requirements for conducting research when the PI is responsible for both the sponsor and investigator requirements.

**IND and IDE Determination**
When an investigational new drug or device is being used in a clinical investigation, an IND or IDE is required prior to conducting the research unless the clinical investigation meets the criteria for exemption. Exemption from the IND or IDE requirement is not an exemption from IRB review or from informed consent requirements.

An investigational drug is determined to be exempt from requiring an IND if it meets an exemption category listed in 21 CFR 312.2 (see “Regulatory Language: Investigational New Drug” below).

An investigational device is determined to be exempt from requiring an IDE if it meets one of the seven exemption categories listed in 21 CFR 812.2(c) (see “Regulatory Language: Investigational New Device” below). An investigational device is considered to have an abbreviated IDE if the IRB determines that the clinical investigation meets
the abbreviated IDE requirements listed in 21 CFR 812.2(b). See HRPP Manual 7-2 “Significant Risk and Nonsignificant Risk Medical Devices” for additional information on the IRB determination of whether the device represents a significant risk.

Investigational New Drugs
An IND must be submitted to the FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug unless the investigation is exempt from the IND requirements. 21 CFR 312.20(a).

A clinical investigation is “any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.” 21 CFR 312.3(a)(b)

An investigational new drug is a “new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms "investigational drug" and "investigational new drug" are deemed to be synonymous for purposes of this part.” 21 CFR 312.3(a)(b)

The following are exemptions to the requirements for an IND:

“(1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:”

“(i) 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,”

“(ii) 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,”

“(iii) 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,”

“(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and”

“(v) The investigation is conducted in compliance with the requirements of § 312.7”

(2)  

“(i) A clinical investigation involving an in vitro diagnostic biological product listed in paragraph (b)(2)(ii) of this section is exempt from the requirements of this part if (a) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and (b) it is shipped in compliance with § 312.160.”

“(ii) In accordance with paragraph (b)(2)(i) of this section, the following products are exempt from the requirements of this part: (a) blood grouping serum; (b) reagent red blood cells; and (c) anti-human globulin.”

“(3) A drug intended solely for tests in vitro or in laboratory research animals is exempt from the requirements of this part if shipped in accordance with § 312.160.”
“(4) FDA will not accept an application for an investigation that is exempt under the provisions of paragraph (b)(1) of this section.”

“(5) A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.”

“(6) A clinical investigation involving an exception from informed consent under § 50.24 of this chapter is not exempt from the requirements of this part.”

“(c) Bioavailability studies. The applicability of this part to in vivo bioavailability studies in humans is subject to the provisions of § 320.31.”

“(d) Unlabeled indication. This part does not apply to the use in the practice of medicine for an unlabeled indication of a new drug product approved under part 314 or of a licensed biological product.”

When an IND is submitted, it may be submitted for one or more phases of an investigation.

“Phase 1 includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug’s pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies. The total number of subjects and patients included in Phase 1 studies varies with the drug, but is generally in the range of 20 to 80.” (21 CFR 312.21(a)(1))

“Phase 1 studies also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes.” (21 CFR 312.21(a)(2))

“Phase 2 includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects.” (21 CFR 312.21(b))

“Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects.” (21 CFR 312.21(c))

Investigational Devices
An IDE must be submitted to the FDA if the sponsor intends to conduct a clinical investigation with an investigational new device to determine safety and effectiveness unless the investigation is considered to have an approved application for an IDE or is exempt from the IDE requirements. 21 CFR 812.2.

An investigation is “a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.” 21 CFR 812.3(h)
An investigational device is “a device, including a transitional device, that is the object of an investigation.” 21 CFR 812.3(g)

The following categories of investigations are considered to have approved applications for IDEs, unless the FDA has notified a sponsor under § 812.20(a) that approval of an application is required: 21 CFR 812.2(b)

“(1)  An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor.”

“(i)  Labels the device in accordance with § 812.5;”

“(ii)  Obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;”

“(iii)  Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator’s care, informed consent under part 50 and documents it, unless documentation is waived by an IRB under § 56.109(c);”

“(iv)  Complies with the requirements of § 812.46 with respect to monitoring investigations;”

“(v)  Maintains the records required under § 812.140(b) (4) and (5) and makes the reports required under § 812.150(b) (1) through (3) and (5) through (10);”

“(vi)  Ensures that participating investigators maintain the records required by § 812.140(a)(3)(i) and make the reports required under § 812.150(a) (1), (2), (5), and (7); and”

“(vii)  Complies with the prohibitions in § 812.7 against promotion and other practices.”

“(2)  An investigation of a device other than one subject to paragraph (e) of this section, if the investigation was begun on or before July 16, 1980, and to be completed, and is completed, on or before January 19, 1981.”

The following categories of investigations are exempt from the IDE requirements (with the exception of 21 CFR 812.119).

“(1)  A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.”

“(2)  A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.”

“(3)  A diagnostic device, if the sponsor complies with applicable requirements in § 809.10(c) and if the testing:

“(i)  Is noninvasive;”

“(ii)  Does not require an invasive sampling procedure that presents significant risk;”

“(iii)  Does not by design or intention introduce energy into a subject, and”
“(iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.”

“(4) A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk”

“(5) A device intended solely for veterinary use”

“(6) A device shipped solely for research on or with laboratory animals and labeled in accordance with § 812.5(c)”

“(7) A custom device as defined in § 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.”

“(d) Limit on certain exemptions. In the case of class II or class III device described in paragraph (c)(1) or (2) of this section, this part applies beginning on the date stipulated in an FDA regulation or order that calls for the submission of premarket approval applications for an unapproved class III device, or establishes a performance standard for a class II device.”

“(e) Investigations subject to IND’s. A sponsor that, on July 16, 1980, has an effective investigational new drug application (IND) for an investigation of a device, shall continue to comply with the requirements of part 312 until 90 days after that date. To continue the investigation after that date, a sponsor shall comply with paragraph (b)(1) of this section, if the device is not a significant risk device, or shall have obtained FDA approval under § 812.30 of an IDE application for the investigation of the device.”

Additional Considerations
For related policies and procedures on investigational drugs and devices, see the following sections of the HRPP Manual:

2-4 International Conference on Harmonization Good Clinical Practice (E6)
7-2 Significant Risk and Nonsignificant Risk Medical Devices
7-3 Emergency Use of Investigational Drugs and Devices
7-4 Charging for Investigational Drugs
7-5 Investigational Use with Approved Drugs
7-7 Humanitarian Use Device