



Investigational or Unlicensed Test Articles

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1.0 Purpose

The purpose of this policy is to determine when an Investigational New Drug (IND) or Investigational Device Exemption (IDE) is required and establish procedures for investigators and those who may be investigator-sponsors holding an IND or IDE for the test article under study.

2.0 Scope

The SOP applies to all human subject research falling under the purview of the Institutional Review Board.

3.0 Policy/Procedure

Use of any investigational or unlicensed test articles must comply with all federal, state, or local regulations. The Food and Drug Administration (FDA) regulates clinical investigations (research) conducted on drugs, biologics, devices, diagnostics, infant formulas and, in some cases, dietary supplements and food additives, hereinafter referred to as "FDA regulated test articles." All such investigations must be conducted in accordance with FDA requirements for informed consent and IRB review, regardless of funding source or sponsor.

When an FDA regulated test article is used in research being done at the University of Missouri-Columbia or funded by another federal agency, more than one set of regulations may apply. For example, clinical trials involving FDA regulated test articles that are supported by the U.S. Department of Health and Human Services (DHHS), (e.g., the National Institutes of Health (NIH)) fall under the jurisdiction of both the FDA and the DHHS Office for Human Research Protections (OHRP). Such trials must comply with the FDA and the DHHS human subject regulations.

The DHHS regulations include specific additional protections for pregnant women, human fetuses, and neonates (Subpart B); prisoners (Subpart C); and children (Subpart D). In April 2004, FDA issued revised regulations to protect children in research (21 CFR 50 Subpart D).

In addition to regulations governing human subject protection, the FDA also has regulations governing the investigational use of drugs and biological drugs (21 CFR 312 and 21 CFR 314) and devices (21 CFR 812 and 21 CFR 814).

Research Involving Investigational FDA Regulated Test Articles

New medical products that have not yet been approved for marketing by the FDA require a special status so they can be legally shipped for the purpose of conducting clinical investigations to establish safety and efficacy.

Drugs

IND refers to an Investigational New Drug application. ***Investigational New Drug*** means a new drug or biological drug used in a clinical investigation. An investigational drug must have an IND before it can be shipped, unless one of the exemptions outlined in 21 CFR 312.2 is met. (See [FDA Investigational New Drug \(IND\) Application](#))

312.2 (b) Exemptions.

(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.

Studies involving the use of an investigational drug will be conducted in compliance with [21 CFR 312](#) Subchapter D, Drugs for Human Use / Investigational New Drug Application (IND). An IND is required for experimental drugs if the drugs are used for the purpose of developing information about their safety or efficacy. Approved, marketed drugs may also require an IND if the proposed use in research is different from its previously FDA-approved use or administered by an unapproved route or method of delivery or an altered dosage.

1. An IND is NOT REQUIRED when all of the following are TRUE for a clinical investigation involving a drug or biologic: (21 CFR 312.2(b)(1))

- The drug product is lawfully marketed in the United States.
- 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 set forth in part 56 and with the requirements for informed consent set forth in part 50; and
- The investigation is conducted in compliance with the requirements of §312.7.

2. An IND is NOT REQUIRED when all of the following are TRUE for a clinical investigation involving a drug or biologic: (21 CFR 312.2(b)(2))

- The clinical investigation involves one of the following in vitro diagnostic biological product:
 - (1) blood grouping serum;
 - (2) reagent red blood cells; and
 - (3) anti-human globulin.
- The clinical investigation is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and
- The drug or biologic is shipped in compliance with §312.160.

IND Determination:

The investigator will need to determine if an IND is necessary. This decision will be confirmed by the IRB. Prior to IRB approval, the IRB office will ensure there is valid documentation of the determination (copy of letter from the FDA, FDA application, or IND number included in the protocol from the sponsor) of an IND.

Investigational Pharmacy:

Investigators are required to use the investigational pharmacy for the control and accountability of research related drugs. Investigators, who arrange with the investigational pharmacy to be exempt from this requirement or are not within the hospital system, are required to submit a plan for drug accountability and storage to the IRB.

Devices

An approved **Investigational Device Exemption (IDE)** permits a device not approved by the FDA to be shipped to conduct clinical investigations of that device. Not all investigational devices need an IDE, if they satisfy the FDA criteria for non-significant risk devices or are determined to be Exempt (see [Device Exemptions](#) below).

Significant Risk (SR) Device vs. Non-Significant Risk (NSR) Device Determinations:

The sponsor makes the initial determination of SR or NSR for the device. However, the IRB will make the final determination for NSR devices. If the IRB disagrees with the sponsor and designates the device as SR, the sponsor will be required to submit to the FDA for an IDE. The study will not be approved by the IRB until the IDE is obtained. The investigator will be informed of the IRB's determination in writing and the investigator must inform the sponsor.

(See [FDA Information Sheet on Significant Risk \(SR\) and Non-Significant Risk \(NSR\) Medical Device Studies](#))

Risk Assessment:

In assessing the risk level of a device, the IRB will consider information such as a description of the device and its proposed use, nature of the harm that may result from the use of the device or from procedures required for use of the device, e.g. surgical implants, reports of prior investigations conducted with the device, the proposed investigational plan, a description of subject selection criteria and monitoring procedures. The IRB should be provided with the sponsor's risk assessment and rationale for its determination as NSR. The sponsor must provide the IRB with the FDA's assessment of the device's risk if such an assessment has been made. The IRB may also choose to consult with the FDA.

FDA considers a device to have an IDE (without the FDA granting the IDE) when all of the following are TRUE: (21 CFR 812.2(b)(1))

- The device is not a significant risk device;
- The device is not a banned device;
- The sponsor labels the device in accordance with §812.5;
- The sponsor 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;
- The sponsor 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);
- The sponsor complies with the requirements of §812.46 with respect to monitoring investigations;
- The sponsor 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);
- The sponsor 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
- The sponsor complies with the prohibitions in §812.7 against promotion and other practices.

Device Exemptions:

A device is exempt from the requirements of an IDE when it falls into one or more of the following categories:

- (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:
 - Is noninvasive,
 - Does not require an invasive sampling procedure that presents significant risk,
 - 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.
- (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.

IRB Review of FDA-Regulated Test Articles:

With only a few exceptions, most clinical research being done on FDA-regulated test articles with either an IND or IDE will need initial and continuing review at a convened IRB meeting. (One exception is IRB continuing review of HUD submissions). (See [IRB Review of Humanitarian Use Device \(HUD\)](#) below)

Research involving FDA-regulated test articles will be approved *only* after the IRB:

- Has received documentation that the research will be conducted under an applicable IND or IDE; or
- Has formally determined that satisfactory justification has been provided by the investigator as to why an IND or IDE is not required; or
- Has formally determined and documented that the proposed use of any unapproved device satisfies the FDA criteria for non-significant risk devices.

The IRB will use the guidance provided by 21 CFR 312.2(b) and 21 CFR 812.2(b) in determining if an IND or IDE is required.

Advertisement

The IRB will determine that advertisements do not:

- Make claims, either explicitly or implicitly, about the drug, biologic, or device under investigation that are inconsistent with FDA labeling.
- Use terms, such as “new treatment,” “new medication,” or “new drug,” without explaining that the test article is investigational.
- Allow compensation for participation in a trial offered by a Sponsor that includes a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

Investigators

Under FDA regulations and guidance, investigators (and investigator-sponsors) are responsible for the conduct of the study and for leading the team of individuals conducting the study. Their responsibilities include the following:

- Ensuring informed consent of each subject is obtained
- Ensuring the investigation is conducted according to the investigational plan
- Personally conducting or supervising the investigation

- Protecting the rights, safety, and welfare of participants
- Preparing and maintaining, adequate, current, and complete case histories or records
- Retaining records for two years following the date the marketing application is approved or withdrawn
- Furnishing the required reports to the sponsor, including reports of adverse events and study completion
- Providing timely reports to the IRB, including reports of changes in the research activity needed to avoid immediate hazards to participants or other unanticipated problems involving risks to participants or others, including adverse events to the extent required by the IRB
- Ensuring changes are not implemented without prospective IRB approval, unless required to eliminate immediate hazard to participants
- Complying with the requirements of the Controlled Substances Act
- Complying with all FDA test article requirements
- Adequately maintaining control of test articles, including appropriate tracking documentation for test articles to the extent that such control and documentation are not centrally administered
- Supervising the use and disposition of the test article
- Disclosing relevant financial information
- Ensuring that all associates, colleagues, and employees assisting in the conduct of the investigation(s) are informed about their obligations in meeting the above commitments.

Sponsors:

The sponsor takes responsibility for initiating the clinical investigation and holding the IND or IDE, but does not usually conduct the investigation. Although the sponsor is usually a pharmaceutical, biotech, or medical device company, an individual or group of individuals or medical center can also be considered a sponsor for an investigation. The sponsors' responsibilities include the following:

- Selecting qualified investigators
- Providing investigators with the information they need to conduct the investigation properly
- Ensuring proper monitoring of the investigation
- Ensuring that the FDA and (for devices) any reviewing IRBs or (for drugs) all participating investigators are promptly informed of significant new information about an investigation.

Investigator-Sponsors

In reviewing research involving FDA regulated articles, the IRB determines if the study involves an investigator-sponsor. If so, the IRB informs the investigator that sponsor responsibilities including reporting requirements to the FDA, (as well as the investigator responsibilities) are his/her responsibility as required by this Section.

1. Investigator-sponsors who submit protocols to the IRB involving FDA test articles must include all supporting FDA documentation for their IND or IDE and any other required approvals for applying for an IND or IDE. Additionally, if the IND or IDE product will be manufactured at this institution, the Principal Investigator must submit documentation that:
 - The product preparation and manufacture meets the standards for current Good Manufacturing Practice (GMP), or any modification to those standards approved by the FDA in issuing the IND or IDE.
 - The GMP plan has been approved by the applicable Institutional Official.
2. A plan for the IND or IDE product storage, security, and dispensing must be documented and submitted to the IRB.
3. An investigator-sponsor for an IDE protocol must follow the FDA regulations in 21 CFR 812 applicable to sponsor responsibilities, particularly Subpart C. This includes:
 - the record keeping requirements of 21 CFR 812.140(b), and
 - the required notification under 21 CFR 812.150(b)(1) to the FDA and all participating investigators of any evaluation of an unanticipated device effect within ten (10) working days of first receiving notice of the effect.
4. An investigator-sponsor for an IND protocol must follow the FDA regulations in 21 CFR 312 applicable to sponsor responsibilities, particularly Subpart D. This includes:
 - the record keeping requirements of 21 CFR 312.57, and
 - promptly reporting as required in 21 CFR 312.55(b) to the FDA and all participating investigators of significant new adverse effects or risks with respect to the drug or biologic.

The IRB must perform a site visit with the investigator-sponsor before initiation of the research to determine compliance with these FDA regulatory requirements. If compliance has been demonstrated, the investigator-sponsor may begin the research. The audit will be repeated periodically by the IRB.

IRB Review of Humanitarian Use Device (HUD)

For an HUD to be used in treatment, diagnosis, or research at MU, the IRB and the FDA must approve it and a Humanitarian Device Exemption (HDE) must be issued by the FDA. While the effectiveness of the device does not have to be demonstrated, the IRB will verify that the device does not pose an unreasonable risk of illness or injury to the recipient, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. The IRB approval must verify that the use of the HUD, as proposed, is consistent with current labeling of the device and does not exceed the scope of the FDA approved indication. The device's labeling must state that the device is a humanitarian use device and that, although the device is authorized by Federal Law, the effectiveness of the device for the specific indication has not been proven or demonstrated.

The initial review of an HUD is to be completed by a convened IRB. The IRB may approve use of the HUD without any further restrictions, or under a protocol, or on a case-by-case basis. The convened Board may make the determination at initial review that continuing review may occur using the expedited procedure if the HUD is not being used in the course of a research study.

Criteria the IRB may use to grant continuing review using the expedited procedure include:

- initial use of the HUD was approved without any further restrictions, and
- the continuing review period was not less than 1 year.

Criteria for subsequent continuing review using the expedited procedure may include:

- there have been no subject complaints, and
- no additional risks have been identified.

The MU IRB requires that documented informed consent will be obtained from a patient prior to the use of an HUD, regardless of whether the HUD is being used in the course of a research study, or in non-research clinical care.

The IRB may impose more stringent restrictions for use of the HUD as a means of ensuring additional protection, as deemed necessary. For example, the IRB may require re-review at an interval of time more frequent than annually, or may want to conduct re-review after a specified number of patients have been accrued.

Physician/Investigator Responsibilities

The Physician/Investigator will provide all applicable information regarding the use of the HUD in his/her application materials submitted to the IRB.

The Physician/Investigator will provide the IRB with a copy of the FDA HUD application which will contain the following supplemental information:

1. The generic and trade name of the device;
2. The FDA HDE number;
3. The date of HUD designation;
4. The indication(s) for use of the device;
5. A description of the device;
6. Contraindications, warnings, and precautions for use of the device;
7. Adverse effects of the device on health;
8. Alternative practices and procedures;
9. The HUD brochure;
10. Marketing history; and
11. A summary of studies using the device.

The Physician/Investigator will obtain informed consent from each patient prior to use of the HUD, whether the HUD will be used as part of a treatment plan or as part of a research

protocol. The consent document must state that effectiveness for the labeled indication has not been demonstrated. A discussion of the potential risks and benefits of the HUD, and any procedures associated with use of the device, must be included in the consent document. If the document is not for a research study of the HUD, the document must not use the term “research” to refer to the activities associated with this use of the device.

The Physician/Investigator will provide the HUD brochure (prepared by the manufacturer) to the patient, and review it with the patient prior to use.

The Physician/Investigator will fulfill continuing review requirements at the designated IRB intervals. At each continuing review, the Physician/Investigator will provide the following information to the IRB:

1. The clinical indications for the use of the HUD in each patient;
2. Adverse events or unanticipated problems involving risk to participants or others that are possibly related (more likely related than unrelated) to the use of the HUD; and
3. Clinical outcomes of each participant, if known.

The Physician/Investigator utilizing the HUD for treatment, diagnosis, or research without an IDE must use the HUD only in accordance with the labeling of the device, intended purpose, and in the designated population for which the FDA approved its use. (See [Off- Label Use](#) below).

Using an HUD for Research Purposes

When an Investigator seeks to collect safety and effectiveness data about the device, if the use is within the approved labeling, no IDE is needed, but IRB approval is required with the submission of the IRB Medical Application, and informed consent must be obtained, since [this constitutes research](#).

If the Investigator plans to collect data for a new use of the device, then the IDE regulations must be followed, and as described previously, IRB approval is required with the submission of the IRB Medical Application, and informed consent must be obtained, and continuing review must occur using the convened IRB.

When the use of an HUD is for diagnosis or treatment, and not associated with research or data collection, HIPAA regulations for research are not applicable. However, HIPAA regulations for hospital medical records per HSIRB institutional policy are applicable.

Considerations for Prompt Reporting

Whenever a physician or health care provider receives or otherwise becomes aware of information from any source that reasonably suggests that an HUD has or may have caused or contributed to the death or serious injury of a patient, the physician or health care provider must report such findings to the FDA and the IRB as soon as possible, in keeping with the

MU IRB's policy on Unanticipated Problems. This reporting is in addition to, not a substitute for, FDA and/or manufacturer reporting requirements in accordance with 21 CFR 803.30.

The physician or health care provider shall promptly report any FDA action(s) regarding the HUD to the IRB. Modifications to the HUD or the clinical use of the HUD are to be promptly reported to the IRB in accordance with the IRB policy for amendments.

Off-Label Use of an HUD

An HUD may be used off-label for clinical care with the approval of the manufacturer of the device. The documentation of approval must be provided to the IRB. (see [FDA Frequently Asked Questions About Medical Devices](#))

Emergency Use of an HUD

If there is no time to obtain FDA approval, FDA recommends that the emergency use procedures described for unapproved devices be followed (see [FDA Frequently Asked Questions regarding HDE Regulation](#))

If a physician in an emergency situation determines that FDA approval of the HUD's use cannot be obtained in time to prevent serious harm or death to a patient, the HUD may be used without prior FDA approval. The following conditions must be present:

- Patient's life is threatened and patient needs immediate care.
- No generally accepted alternative exists.
- There is no time to obtain FDA approval.
 - In such emergency circumstances, the physician should follow as many patient protection procedures as possible. These include:
 - o Independent assessment of an uninvolved physician
 - o Concurrence of the IRB Chair
 - o Clearance by the institution
 - o Informed consent from the patient or legal representative
 - o Authorization from the IDE sponsor, if an IDE exists for the device.

The HUD may also be used without prior patient consent if a life-threatening emergency exists, the patient lacks the capacity to consent, and a legally authorized representative is unavailable. The term "life-threatening" is meant to include the presence of a serious disease or condition that involves risk of irreversible morbidity, such as loss of eyesight.

Within 5 working days of the emergency use, the physician needs to provide written notification to the Chair of the IRB of such use. Email notification is acceptable for this purpose. The notification must include:

- the identification of the patient involved;

- the date on which the device was used; and
- the reason for the use.

Data Retention When Participants Withdraw From a Clinical Trial

- When a participant withdraws from a study, the data collected on the participant to the point of withdrawal remains part of the study database and may not be removed. The consent document cannot give the participant the option of having data removed.

- A researcher may ask a participant who is withdrawing whether the participant wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the participant would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through noninvasive chart review, and address the maintenance of privacy and confidentiality of the participant's information.

- The researcher must obtain the participant's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). The IRB must approve the consent document.

- If a participant withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the researcher must not access for purposes related to the study the participant's medical record or other confidential records requiring the participant's consent. However, a researcher may review study data related to the participant collected prior to the participant's withdrawal from the study, and may consult public records, such as those establishing survival status.

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