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This chapter outlines policy for:

- research using investigational drugs, devices, or biologics (in this chapter, the term investigational means unapproved drugs, unapproved devices or devices not cleared to market, or unlicensed biologics)
- research with FDA-approved drugs, approved/cleared devices, or licensed biologics (sometimes called “commercially available”)
- sponsor-investigator research
- radiation devices and radioactive materials
- handling (inventory control and storage) of investigational drugs, devices, or biologics
- emergency, humanitarian, or compassionate use of investigational drugs, devices, or biologics

FDA regulates clinical investigations (research) “that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including foods, dietary supplements that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products.” (See 21 CFR 56.101)
All such investigations must be conducted in accordance with FDA requirements for informed consent and IRB review, regardless of funding source or sponsor.

Required Study Registration

**ClinicalTrials.gov:** Applicable clinical trials, as defined in 42 U.S.C. 282(j)(1)(A), must be registered on ClinicalTrials.gov; clinical trial information must be submitted for inclusion in the clinical trial registry databank (Public Health Service Act, section 402(j) and a corresponding statement added to the consent form.

Applicable clinical trials are:

- Drug or biologic studies, with or without IND (except Phase 1, expanded access/compassionate use, or drug being used as part of routine care and not under study)
- Device studies, with or without IDE (except small feasibility studies, expanded access/compassionate use, or device being used as part of routine care and not under study)

Comparison of FDA and HHS Regulations

The FDA web page Comparison of FDA and HHS Human Subject Protection Regulations outlines differences between FDA regulations and OHRP 45 CFR 46 regulations for the protection of human subjects. Where regulations differ, the IRB applies the stricter one.

### 5.1 Research with Test Articles

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Research with FDA-regulated test articles may commence only after the IRB has approved the protocol and:

- receives documentation that the research will be conducted under an applicable Investigational New Drug Application (IND) or Investigational Device Exemption (IDE); The IND goes into effect generally 30 days after the FDA assigns the IND, unless the sponsor receives earlier notice from the FDA; or
- formally determines and documents that the proposed use of any investigational device satisfies the FDA criteria for non-significant risk devices; or
- formally determines that satisfactory justification has been provided by the investigator as to why an IND or IDE is not required.

For research requiring an IND, the IRB will not issue final approval of the study until the valid IND is in place. The researcher must not begin recruiting, obtaining consent, and/or screening participants for the study until the valid IND is in effect and final IRB approval letter has been received.

**Definitions**

**Biologic:** A biological or related product, regulated by the FDA, including blood, vaccines, allergens, tissues, and cellular and gene therapies. Biologics, in contrast to drugs that are chemically synthesized, are derived from living sources (such as humans, animals, and microorganisms). Studies of unlicensed biologics are regulated according to the IND regulations, except in some cases when the biologic is in a combination product with a
medical device. FDA regulates biologics general use and licensing under 21 CFR 600 and 601. (42 U.S.C 262 of the Public Health Service Act.

**Clinical investigation:** 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 Federal Food, Drug and Cosmetic Act (FD&C 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. (See 21 CFR 56.102)

**Combination product:** A product containing a combination of a drug, a device, or a biological product. Studies of combination products are regulated according to the IND or IDE regulations, depending on the components of the product. The FDA determines which of its organizational components has primary jurisdiction for the premarket review and regulation of products that are comprised of any combination of a drug, device, and/or biological. (See 21 CFR 3.2(e))

**Human subject:** An individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient. (See 21 CFR 56.102)

**Off-Label:** Use of an approved drug, an approved or cleared device, or a licensed biologic for an indication not in the approved labeling. Most research involving off-label uses requires IND or IDE applications. See FDA "Off-Label" and Investigational Use of Marketed Drugs, Biologics and Medical Devices.

**Test article:** 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 subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act. (See 21 CFR 56.102)

### 5.2 Research with Drugs

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Clinical investigations of drugs are subject to the Investigational New Drug Application (IND) regulations, 21 CFR 312. An investigational new drug application (IND) is synonymous with “Notice of Claimed Investigational Exemption for a New Drug.” 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.

Applications for research on the use of a drug, unless that research is exempt from the IND regulations, must be accompanied by documentation from the FDA that includes a valid IND number. The IND number must either match the number on the sponsor protocol with the same title as the proposed research, or be listed on communication from the sponsor specific to the proposed research, or on communication with the FDA. IND numbers may not be validated with an Investigator Brochure (which may serve multiple INDs).
As stated in 21 CFR 312.2(b), clinical investigation of a drug is exempt from the IND regulations if the drug is lawfully marketed in the United States and all of the following are true:

(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 312.8 (Promotion and charging for investigational drugs).

Additionally, a clinical investigation involving use of a placebo is exempt from the requirements of 21 CFR 312 if the investigation does not otherwise require submission of an IND. Clinical investigations that are exempt from IND regulations still require IRB review and approval.

Even when there is no immediate intent to change product labeling or advertising, investigators who are planning rigorous, carefully controlled clinical investigations of off-label uses of approved drugs or biologics should contact the FDA regarding obtaining an IND before submitting a protocol to the IRB.

See the FDA guidance for FDA’s current thinking on exemptions from IND regulations for oncology combination protocols. See the FDA guidance IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products.

5.3 Research with Devices

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Clinical investigations of devices are subject to the Investigational Device Exemptions (IDE) regulations, 21 CFR 812. An approved investigational device exemption (IDE) permits a device that is not approved (via premarket authorization, PMA) or cleared to market (via 510(k)) by the FDA to be shipped to conduct clinical investigations of that device. Significant risk investigational devices must have an IDE issued by FDA before they can be shipped. Non-significant risk devices are considered to have an approved IDE when the IRB agrees with the sponsor that the device meets the criteria for a non-significant risk device.

Research with devices falls into three categories:

- Investigations of significant risk devices to determine safety and effectiveness of the device
- Investigations of non-significant risk devices to determine safety and effectiveness of the device
- Investigations exempted from the IDE regulations
See:
- Guide-028 - Significant Risk (SR) and Non-significant Risk (NSR) Medical Device Studies
- Frequently Asked Questions Medical Devices [FDA],
- Significant Risk and Non-significant Risk Medical Device Studies [FDA]

Studies that include medical device use in an incidental way, where the device or the use of the device is not the focus of the research, are generally not considered to be FDA-regulated research or subject to 21 CFR 812, and in some instances are eligible for IRB review according to the expedited procedure.

Initial review by the expedited procedure might also be designated for certain NSR device studies involving no more than minimal risk and satisfying criteria for expedited review categories 1 or 4.

**Significant Risk Device Research**

Applications for research on the use of a significant risk device must be accompanied by documentation from the FDA that includes a valid IDE number. The IDE number must either match the number on the sponsor protocol with the same title as the proposed research, or be listed on communication from the sponsor specific to the proposed research, or on communication with the FDA. IDE numbers may not be validated with a device manual (which may serve multiple IDEs).

**Non-significant Risk Device Research**

When research is conducted to determine the safety or effectiveness of a device, the organization confirms that the device fulfills the requirements for an abbreviated IDE (21 CFR 812.2(b)(1)):

- The device is not a banned device;
- The sponsor labels the device in accordance with 21 CFR 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, consent under 21 CFR 50 and documents it, unless documentation is waived;
- The sponsor complies with the requirements of 21 CFR 812.46 with respect to monitoring investigations;
- The sponsor maintains the records required under 21 CFR 812.140(b) (4) and (5) and makes the reports required under 21 CFR 812.150(b) (1) through (3) and (5) through (10);
- The sponsor ensures that participating investigators maintain the records required by 21 CFR 812.140(a)(3)(i) and make the reports required under 21 CFR 812.150(a) (1), (2), (5), and (7); and
- The sponsor complies with the prohibitions in 21 CFR 812.7 against promotion and other practices.

If the investigator applies to the IRB for a non-significant risk determination for a device study, but the IRB determines that the device is significant risk, the IRB shall notify the investigator and the sponsor, if appropriate.

**Exempt Device Research**

Clinical investigations that are exempt from IDE regulations still require IRB review and approval. An investigation of a medical device in human subjects research that is exempt from the IDE regulations must fall into one of the following categories (Criteria in 21 CFR 812.2(c)):

- A device legally marketed in the US that is used or investigated in accordance with the indications in the FDA-approved labeling.
- A diagnostic device (that is, an in vitro diagnostic device) if the testing:
o Is noninvasive
o Does not require an invasive sampling procedure that presents significant risk,
o Does not by design or intention introduce energy into a subject, and
o Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

- 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.
- 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.
- 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.
- 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.

A clinical investigation involving an in vitro diagnostic biological product (i.e., blood grouping serum, reagent red blood cells, or anti-human globulin) is exempt from IND requirements 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 21CFR312.160.

In Vitro Diagnostic Device Research
In vitro diagnostic (IVD) device investigations may be exempt from the IDE requirements of 21 CFR 812 if the devices are properly labeled and meet the criteria set forth in 21 CFR 812.2(c)(3). However, such studies are still subject to the FDA regulations and IRB review requirements if the research is to support an application for research or marketing of the device (see 21 CFR 50.1). This is true regardless of whether the samples to be used are individually identifiable or not. The FDA regulations define a subject to include a human on whose specimens an investigational device is used (21 CFR 812.3(p)). Thus, an IVD study to support a premarket submission to the FDA is considered a human subject investigation and is subject to IRB review under 21 CFR parts 50 and 56. IVD research may be eligible for expedited review and without informed consent if the study involves leftover human specimens and as long as subject privacy is protected by using only specimens that are not individually identifiable, when appropriate.

In addition to the above, FDA Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable makes clear that IRB review is one of several criteria for IVD studies using leftover specimens that are not individually identifiable.

5.4 Radiology Devices and Radioactive Materials

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The FDA regulates radiology devices and radioactive materials used in research. Oversight for issues of radiation safety at the University of Louisville is handled by the Radiation Safety Committee (RSC). RSC membership includes representatives of both the faculty and administration. The RSC sets University policies and oversees the
implementation of all aspects of the safe use of radioisotopes and radiation on the Belknap campus, the Health Sciences
Campus, the Shelby Campus and the U of L Hospital.

5.5 Research with Biologics

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Clinical investigations of biologics are regulated in the same way as clinical investigations for drugs, and require an IND, unless the biologic is part of a combination product that the FDA has assigned for premarket approval to the Center for Devices and Radiological Health (CDRH). In such cases, the biologic/device combination product would require an IDE prior to research approval by the IRB.

Generally, protocols using biological agents or recombinant DNA vectors are reviewed by IRB A (biomedical) and the Institutional Biosafety Committee (IBC).

5.6 Sponsor-Investigator Research

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In reviewing research involving test articles, the IRB determines if a University of Louisville investigator holds his or her own IND or IDE. If so, the IRB confirms that the investigator understands his or her additional responsibilities as the sponsor of the research, including reporting requirements to the FDA. See Guide-013 - FDA-IND Application Guidance and Guide 12 - Special Considerations for Oversight of Research of FDA Regulated Drugs and Devices.

**Sponsor-investigators** who submit protocols to the IRB involving FDA test articles must include all supporting FDA documentation for their IND or IDE and any University of Louisville required approvals for applying for an IND or IDE. Prior to approving a protocol that involves a sponsor-investigator, the IRB must be satisfied that the sponsor-investigator is knowledgeable about his/her responsibilities and has adequate policies and procedures in place to comply with the FDA regulatory requirements.

**Investigator-held INDs**
A sponsor-investigator for an IND protocol must follow the FDA regulations in 21 CFR 312 applicable to sponsor responsibilities. Check with the Office of University Counsel for any University guidance that may be required.

**Investigator-held IDEs - Significant Risk Devices**
A sponsor-investigator for an IDE protocol must follow the FDA regulations in 21 CFR 812. Check with the Office of University Counsel for any University guidance that may be required.
Non-significant Risk Device Studies when Investigator Acts as Sponsor

Investigators studying non-significant devices, regulated by the abbreviated IDE regulations, have abbreviated sponsor responsibilities when there is no industry sponsor.

5.7 Internal Handling of Test Articles

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For clinical investigations, University of Louisville University promotes researchers’ adherence to ICH guidelines as presented by the FDA in the form of the Consolidated Guidance for Good Clinical Practice (GCP).

All studies submitted to the University of Louisville IRB that involve an investigational drug or device must have a dispensing plan in place. Those studies that are not utilizing pharmacy oversight must submit their dispensing plan to the IRB prior to receiving approval.

5.8 Expanded Access to Investigational Drugs and Devices for Treatment Use

Expanded access to investigational drugs and devices requires prior IRB review and approval (with the exception of Emergency Use).

5.8.1 Drugs

*Expanded access*: Use of investigational new drugs and approved drugs where availability is limited by a risk evaluation and mitigation strategy (REMS) when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition. The aim of this subpart is to facilitate the availability of such drugs to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition. [21 CFR 312.300 (Subpart I)]

*Expanded Access Programs (EAPs)*: The FDA uses this term to refer to the various types of allowable expanded access use.

*Immediately life-threatening disease or condition*: A stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

*Serious disease or condition*: A disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

There are 3 categories of expanded access program (EAP) for investigational drugs:

I. Single patients, including for emergency use(21 CFR 312.310).
II. Intermediate-size patient populations (21 CFR 312.315)
III. Treatment IND or “treatment protocol” for widespread treatment use (21 CFR 312.320)

5.8.2 Devices

The FDA may make an unapproved device available under several mechanisms:
- Emergency Use
- Compassionate Use (or Single Patient/Small Group Access)
- Treatment Use (Larger Group/More Widespread Use)
- Continued Access

5.9 Emergency Use of a Test Article

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Emergency Use: Use of a test article on a human participant in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval (21 CFR 56.102(d)). Specific additional requirements apply; see Emergency Use of a Test Article.

5.10 Humanitarian Use Device (HUD); Orphan Drugs

Humanitarian Use Device (HUD)

A Humanitarian Use Device (HUD) is a device intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year. The regulations under 21 CFR 814 (Subpart H) were designed to promote the development of devices for diseases affecting these populations.

Orphan Drugs

The Orphan Drug Designation program provides orphan status to drugs and biologics which are defined as those intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the U.S. These drugs are not expected to recover the costs of developing and marketing as treatment drugs.

5.11 Planned Emergency Research

Planned emergency research: Planned research in life-threatening emergent situations where obtaining prospective informed consent has been waived (21 CFR 50.24).

The research plan must be approved in advance by the FDA and IRB. The research plan must also be disclosed to the communities where the research will be conducted and from where participants will be drawn, including presentation of the risks and expected benefits of the research. An independent data monitoring committee (DMC) must be established to exercise oversight of the research. Advance notice of these protocols will be provided to the Office for Human Research Protections pursuant to federal regulation 45 CFR 46.101(i).

- PIs who wish to conduct planned emergency research should consult with IRB staff prior to submission of the protocol to the IRB.
- Planned emergency research is usually not eligible for emergency use approvals. See Exception from Informed Consent Requirements for Emergency Research [FDA].

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