Investigational or Unlicensed Test Articles – Research with Drugs, Devices or Biologics

The FDA regulates clinical investigations (research) “that support applications for research or marketing permits for projects 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, biological projects for human use, and electronic products.”

Therefore, such research must be conducted in accordance with FDA requirements for informed consent and IRB review, regardless of funding source or sponsor.

The following GPM focuses on:
- Research using investigational (unapproved) drugs, devices, or biologics
- Research with FDA-approved drugs, approved/cleared devices, or licensed biologics (aka “commercially available”)
- Sponsor-Investigator research
- Handling of investigational drugs, devices or biologics
- Emergency, humanitarian, or compassionate use of investigational drugs, devices, or biologics

Registration Requirements

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 (see GUIDE 606: Consent Form Guidance). The following are considered applicable clinical trials:

- 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)

---

88 21 C.F.R. § 56.101
213.1 Research with Test Articles

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

- Received documentation that the research will be conducted under an applicable Investigational New Drug Application (IND) or Investigational Device Exemption (IDE); or
  - The IND goes into effect generally thirty (30) days after the FDA assigns the FDA, unless the sponsor receives earlier notice from the FDA
- 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.

The IRB collaborates with local research hospitals and regulatory offices such as The Queen’s Medical Center, Hawaii Pacific Health Research Institute, and the UH Cancer Center Regulatory Office to support UH clinical Investigators who conduct FDA-regulated research.

213.2 Research Involving Drugs

Clinical investigations of drugs are subject to the Investigational New Drug Application (IND) regulations, 21 C.F.R. Part 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 transported, unless one of the exemptions listed in 21 C.F.R. § 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 because it may cover multiple INDs.

Investigators who are planning ANY rigorous, carefully controlled clinical investigations of off-label uses of approved drugs or biologics shall contact the FDA regarding obtaining an IND before submitting a protocol to the IRB. For any FDA-regulated research involving an investigational drug where the FDA required, a valid IND must be obtained before the research can commence.

For FDA-regulated research involving an investigational drug conducted outside the U.S., an IND is not required provided the protocol is conducted in accordance with the Good Clinical Practice guidelines and FDA is able to validate the data from the protocol through an onsite inspection if FDA requires it.

Exempt Drug Research

Per 21 C.F.R. § 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:
1. 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;

2. 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;

3. 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 project;

4. 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

5. The investigation is conducted in compliance with the requirements of 21 C.F.R. § 312.8 (Promotion and charging for investigational drugs).

A clinical investigation involving the use of a placebo is also exempt from the requirements of 21 C.F.R. Part 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.

213.3 Research with Devices

Clinical investigations of devices are subject to the IDE regulations, 21 C.F.R. Part 812.

An approved investigational device exemption (IDE) permits a device that is not approved (via premarket authorization (PMA)) or cleared to market (pursuant to § 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 concurs with the sponsor that the device meets the criteria for non-significant risk device.

Research with devices falls into three categories:

1. Investigations of significant risk devices to determine safety and effectiveness of the device
2. Investigations of non-significant risk devices to determine safety and effectiveness of the device
3. Investigations exempted from the IDE regulations

See:

- Significant Risk and Non-significant Risk Medical Device Studies [FDA]
- Frequently Asked Questions Medical Devices [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 C.F.R. Part 812, and in some instances are eligible for IRB review according to the 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 protocol 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 because it may cover 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 (per 21 C.F.R. § 812.2(b)(1)):

- The device is not a banned device;
- The sponsor labels the device in accordance with 21 C.F.R. § 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 C.F.R. 50 and documents it, unless documentation is waived;
- The sponsor complies with the requirements of 21 C.F.R. § 812.46 with respect to monitoring investigations;
- The sponsor maintains the records required under 21 C.F.R. §§ 812140(b)(4) and (5) and makes the reports required under 21 C.F.R. §§ 812.150(b)(1) through (3) and (5) through (10);
- The sponsor ensures that participating Investigators maintain the records required by 21 C.F.R. § 812.140(a)(3)(i) and make the reports required under 21 C.F.R. 812.150(a)(1), (2), (5), and (7); and
- The sponsor complies with the prohibitions in 21 C.F.R. § 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 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 participant research that is exempt from the IDE regulations must fall into one of the following categories (per criteria under 21 C.F.R. § 812.2(c)):

- A device legally marketed in the U.S. that is used or investigated in accordance with the indications in the FDA-approved labeling.
- A diagnostic device (i.e., an in vitro diagnostic device) if the testing:
  - Is noninvasive.
  - Does not require an invasive sampling procedure that presents significant risk.
o Does not by design or intention introduce energy into a subject.
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 C.F.R. § 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.

### 213.4 Research with Biologics

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 Device and Radiological Health (CDRH). In such cases, the biologic/device combination product would require an IDE prior to research approved by the IRB.

Usually, protocols using biological agents or recombinant DNA vectors are reviewed by Biosafety Committee. The Biosafety Program provides more information about research with biohazardous agents and human participants.

### 213.5 Handling of Test Articles

The University does not have medical facilities (e.g., clinics, hospitals) that physically hold test articles. Research that requires the internal handling of test articles are kept in medical facilities stated in the protocol, and as such follow the policies and procedures of the involved facilities.

Most clinical investigations involve local hospitals such as The Queen’s Medical Center (QMC), Hawaii Pacific Health (HPH) facilities, and Castle Medical Center (Castle). The policies for QMC, HPH, and Castle outline the standards related to drugs and devices for pharmacy practices, inventory control and documentation.

### 213.6 Emergency Use of a Test Article

An Emergency Use is defined as the use of a test article on a human patient 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.\textsuperscript{89}

Under the HHS regulations, emergency use of a test article does not constitute research; the patient may not be considered as a research subject/participant; and any data derived from the use may not be included in any report of research activities. This is because HHS regulations do not permit research activities to be initiated without prior IRB review and approval, even in emergency.\textsuperscript{90}

FDA regulations allow emergency use of a test article when the human subject have been 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.\textsuperscript{91} A clinical investigation involving emergency use is still a clinical investigation under the FDA regulations. FDA may require data from emergency use to be included in marketing applications.\textsuperscript{92}

Emergency use involves four (4) major issues:
(1) approval by or notification to FDA;
(2) exemption from prospective IRB approval;
(3) waiver or alteration of informed consent requirements in emergency research; and
(4) emergency exception from informed consent requirements.

Specific additional requirements apply. See:
• SOP 121: Emergency Use of a Test Article
• Section 209.5 for information on consent and approval for emergency use

213.7 Planned Emergency Research

\textbf{Planned Emergency Research} applies to a narrow exception to the FDA requirement to obtain and document informed consent; applies to a limited class of research activities involving human participants who are in need of emergency medical intervention, but cannot provide legally effective informed consent (See 21 C.F.R. § 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 provide oversight of the research. Advance notice of these protocols will be provided to the OHRP pursuant to federal regulations 45 C.F.R. § 46.101(i).

• PIs who wish to conduct planned emergency research shall consult with HSP staff prior to submission of the protocol to the IRB.
• Planned emergency research is usually not eligible for emergency use approvals.

See \textbf{Exception from Informed Consent Requirements for Emergency Research} [FDA].

\textsuperscript{89} 21 C.F.R. § 56.102(d).
\textsuperscript{90} 45 C.F.R. § 46.103(b) (2014); HHS on Emergency Care.
\textsuperscript{91} 21 C.F.R. § 56.102(d).
\textsuperscript{92} 21 C.F.R. §§ 314.50, 814.20(b)(2) (2014).