Institutional Review Board Policies and Procedure Manual

SECTION 8: INVESTIGATIONAL AND EMERGENCY USE OF A TEST ARTICLE

8.1 RESPONSIBILITIES FOR BIOMEDICAL RESEARCH

Biomedical research involving the investigational use of test articles is subject to FDA regulations. A test article is any food additive, color additive, drug, biological product, electronic product, medical device for human use, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act. FDA regulations also describe additional requirements for investigations involving the use of approved drugs, biologics, or devices in a manner that differs from the specifications under which the article was originally approved.

Clinical investigations involving test articles must comply with the FDA regulations outlined in 21 CFR 50 and reviewed in concordance with 21 CFR 56. A clinical investigation is an experiment that involves a test article and one or more human subjects. The terms research, clinical research, clinical trial, clinical study, study, and clinical investigation are deemed synonymous for the purposes of this chapter.

In addition, the FDA has issued numerous information sheets that provide further guidance on FDA requirements for conducting clinical trials and provide answers to frequently asked questions. The FDA information sheets can be accessed on the FDA website - Guidance Documents (Including Information Sheets) and Notices.

i. Investigators

An Investigator is an individual who conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals; the investigator is the responsible leader of the team.

Investigators have responsibilities that include:

- Conducting the study in accordance with Good Clinical Practice, the protocol as outlined and approved by the IRB, and all applicable FDA regulations; and follow Institutional responsibilities outlined in Section 5: Investigator Responsibilities of this Policies and Procedures Manual;
- Ensuring that the informed consent of each subject is obtained (and retained in study files);
- Personally conducting or supervising the investigation;
- Protecting the rights, safety, and welfare of subjects;
- Ensuring adequate medical care for the study subjects;
- Obtaining necessary approvals from the IRB;
- Maintaining and retaining drug disposition and subject case history records
- Providing written reports to the IRB as required (e.g. reports of unanticipated problems that place subjects or others and risk of harm);
- Ensuring changes are not implemented without prospective IRB/FDA approval (unless the change is required to prevent immediate harm);
- Furnishing Progress Reports and Safety Reports; and
- Ensuring all study personnel are informed of their obligations.

ii. Sponsors

Sponsor is a person or other entity that initiates a clinical investigation, but that does not actually conduct the investigation (i.e., the test article is administered or dispensed to, or used involving, a subject under the immediate direction of another individual). A person other than an individual (e.g., a corporation or agency) that uses one or more of its own employees to conduct an investigation that it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained within the FDA application, including maintenance of the an effective applications with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug.

The full responsibilities of Sponsors of clinical investigations involving test articles can be found at 21 CFR 312 (drugs/biologics) and 21 CFR 812 (devices).

iii. Sponsor-Investigators

Sponsor-Investigator is an individual who both initiates and conducts a clinical investigation, and under whose immediate direction the test article is administered or dispensed. Similarly, if the investigator initiates a study to test a commercially available drug for a new indication, the investigator is generally considered a Sponsor-Investigator.

Responsibilities of Sponsor-Investigators (in addition to the general responsibilities of investigators above) include:

- Filing and updating the test article paperwork with the FDA;
- Selecting participating sites and investigators;
- Ensuring proper manufacture, labeling and control of the test article and disposition of unused supply of investigational drug;
- Developing and implementing plans for monitoring study conduct;
- Reporting of adverse events and adverse device effects in accordance with FDA regulations;
- Keeping participating investigators, reviewing IRBs, and the FDA informed of new findings, reports of problems related to the research, new information affecting risks to subjects, and other relevant information related to the conduct of the ongoing research;
- Filing reports of study progress with the FDA at least annually and upon study closure; and
- Determining whether the study needs to be registered on the clinicaltrials.gov website.

8.2 INVESTIGATIONAL USE OF DRUGS OR BIOLOGICS

A. Investigational New Drug (IND)

Federal law prohibits the distribution of a new drug or biological product until the FDA has reviewed clinical data and determined that the agent is safe and effective for a specific indication in humans. Investigational New Drug (IND) means a new drug or biological product that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. A biological product is a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings. An IND application must be submitted by the sponsor of a new drug or biological product to the FDA before tests on human subjects can begin. All information related to the IND must be provided at the time a sponsor applies for IRB approval to conduct the research.

In accordance with 21 CFR 312.40, 30 days after the FDA receives the IND application the sponsor may begin clinical investigations, unless the FDA notifies the sponsor that the clinical investigation described in the IND application are subject to a clinical hold.

B. Exemptions from IND Requirement

Investigations involving drugs/biologic that are considered exempt from IND regulations must still be reviewed by the IRB. The Sponsor must provide the IRB with documentation that the investigation with the drug/biologic meets one of the FDA exemptions from the requirement to have an IND.

i. Exemption 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/biologic;
- If the drug/biologic that is undergoing investigation is lawfully marketed as a prescription 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/biologic product;
- The investigation is conducted in compliance with the requirements for IRB review and obtaining informed consent; and
- The investigation is conducted in compliance with the requirements of 21 CFR 312.7 (waiver of informed consent requirements for emergency research).

ii. Exemption 2

- A clinical investigation involving one of the following in vitro diagnostic biological product: (a) blood grouping serum; (b) reagent red blood cells; and (c)

anti-human globulin is exempt 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 21 CFR 312.160.

iii. Exemption 3

- A drug intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.160.

iv. Exemption 4

- A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

The IRB can request that the investigator contact the FDA for review of the proposed clinical investigation to determine whether the use qualifies for an exemption from the IND requirements.

8.3 EMERGENCY USE OF AN INVESTIGATIONAL DRUG OR BIOLOGIC

The emergency use provision in the FDA regulations (21 CFR 56.104(c)) is an exemption from prior review and approval by the IRB if time does not allow. The exemption, allows for one emergency use of a drug/biologic for the treatment of a single patient only. Any subsequent use of the test article at the institution is subject to IRB review.

FDA regulations are not intended to "limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law" (21 CFR 50.25(d)).

Emergency use of an investigational drug/biologic for a patient may be appropriate if the FDA determines that the following criteria are met:

1. The patient, or patients, to be treated have a serious **or** immediately life-threatening disease or condition, **and** there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition (21 CFR 312.305(a));

    - *Serious disease or condition* means 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.

    - *Immediately life-threatening* disease or condition means 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.

2. The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; *and*

3. Providing the investigational drug/biologic for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use (21 CFR 312.310(a)).
4. The physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition; *and*
5. FDA must determine that the patient cannot obtain the drug under another IND or protocol.

The emergency use of an unapproved investigational drug/biologic requires an IND. The FDA may authorize expanded access for an individual patient without a written submission and by telephone if there is "an emergency that requires the patient to be treated before a written submission can be made." The licensed physician or sponsor, however, must agree to submit an expanded access IND or protocol within 15 working days of FDA's authorization of the use (312.310(d)(2)).

The contact information for the FDA review division and required forms can be found at: http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm

If there is sufficient time, the following is to be submitted via Cayuse IRB for acknowledgment of the use:

a. Initial Application in Cayuse IRB, which includes: A description of the patient's disease including recent medical history and previous treatments; a summary outlining the rationale for the use, including an explanation of why there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition; and the rationale for why this investigational drug/biologic is preferable. The submission is also to include the method of administration and duration of therapy, and a description of the clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the drug/biologic and minimize its risks. This summary information must support the criteria for emergency use as described above.
b. A copy of the informed consent that will be used. The consent form must explain the purpose of the use of drug/biologic, and must not include references to a research investigation. It must include an explanation of what data will be collected and the reporting requirements to the FDA and/or sponsor. If the physician is unable to obtain consent, the submission must meet the criteria for exception to obtaining informed consent as described below.
c. The emergency expanded access IND letter from the FDA, or, documentation that verbal authorization was obtained from the FDA due to time constraints.
d. The statement from the supplier of the drug/biologic that they will ship the product and authorize its use under the emergency IND or verbal FDA authorization.
e. A letter of support from the Research Pharmacy if it will dispense the drug/biologic.

The IRB Chair will confirm that the necessary requirements for an emergency use are met. Once the review is completed, an Acknowledgement letter will be forwarded to the treating physician, along with a stamped version of the consent document (as applicable).

Within five-working days after administration, whether the drug/biologic was administered with prior IRB acknowledgement or not, the treating physician must submit to the IRB the following:

a. A summary of the administration of the test article and outcome.

b. A summary of any unexpected fatal or life-threatening suspected adverse reactions because of the administration of the drug/biologic.

c. If IRB acknowledgement was not obtained prior to administration, the treating physician is required to submit all the elements listed above for prior IRB notification.

If the treating physician determines that there is a likelihood of treating additional patients with the drug/biologic, the treating physician should consider submitting an expanded access IND or protocol to the FDA and submit an Initial Application via Cayuse IRB to obtain IRB review approval for the prospective use.

A. Exception from the Informed Consent Requirement for Emergency Use

An exception from the requirement to obtain informed consent for the emergency use of a drug/biologic is permissible if both the physician and a physician who is not otherwise participating in the patient's treatment certify in writing that the emergency meets each of the following (21 CFR 50.23(a)):

1. The subject is confronted by a life-threatening situation necessitating the use of the drug/biologic;
2. Informed consent cannot be obtained because of an inability to communicate with or obtain legally effective consent from the patient;
3. Time is not sufficient to obtain consent from the patient's legally authorized representative; and
4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the patient's life.

If the investigator cannot obtain the independent assessment of a physician to certify the above, then within five days after the use of the drug/biologic a physician who is not otherwise participating in the clinical investigation must document in writing that the above criteria were satisfied. This determination is to be included in the five working day report to the IRB.

B. Reporting Responsibilities

The treating physician is responsible for reporting the use of the drug/biologic to the FDA:

a. If an expanded access IND for emergency use was obtained by the treating physician prior to the administration of the drug/biologic, the treating physician is responsible to submit the following (using Form 3926):

- Submit written progress reports required at intervals not exceeding one year and are due within 60 days of the application anniversary date (i.e., the date granted the IND).
- Report any unexpected fatal or life-threatening suspected adverse reactions to no later than 7 calendar days after initial receipt of the information.

- Report any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to the FDA and to all investigators (as applicable) no later than 15 calendar days after determining that the information qualifies for reporting .
- When the treating physician has completed treatment of the patient with the drug/biologic or if it has been decided not to treat the patient, the FDA must be notified so that the IND may be withdrawn. The final report to the FDA should include a summary of the results of treatment, including adverse effects, and information concerning the disposition of any unused supplies of the test article.

b. If no prior expanded access IND was obtained (only verbal FDA approval), the following reporting actions are required:

- Submit an expanded access IND application **within 15 working days** of FDA's initial authorization of the expanded access use (21 CFR 312.310(d)(2)).

8.4 EXPANDED ACCESS USE OF INVESTIGATIONAL DRUGS/BIOLOGICS

Expanded access refers to the use of an investigational drug/biologic when the primary purpose is to diagnose, monitor, or treat a patient rather than to obtain the kind of information about the drug/biologic (i.e., safety and efficacy data) that is generally derived from clinical trials. Expanded access to an investigational drug/biologic can only be provided under an expanded access IND or protocol if the sponsor is actively pursuing marketing approval of the drug/biologic for the expanded access use.

Expanded access, access, and treatment use may also refer to (1) use in situations when a drug/biologic has been withdrawn for safety reasons, but there exists a patient population for whom the benefits of the withdrawn drug continue to outweigh the risks; (2) use of a similar, but unapproved drug/biologic (e.g., foreign-approved product) to provide treatment during a shortage of the approved drug/biologic; (3) use of an approved drug/biologic where availability is limited by a risk evaluation and mitigation strategy (REMS) for diagnostic, monitoring, or treatment purposes, by patients who cannot obtain the drug/biologic under the REMS; or (4) use for other reasons.

There are three categories of expanded access to an investigational drug/biologic:

- Expanded access for individual patients, including for emergency use.
- Expanded access for intermediate-size patient populations (generally smaller than those typical of a treatment IND or treatment protocol — a treatment protocol is submitted as a protocol to an existing IND by the sponsor)
- Expanded access for widespread treatment use through a treatment IND or treatment protocol (designed for use in larger patient populations)

For each category of expanded access, there are two types of regulatory submissions that can be made:

1. Expanded access ***protocol*** submitted as a protocol amendment to an existing IND (i.e., an expanded access protocol). An expanded access protocol submission for expanded access should be used only if the sponsor has an existing IND — typically under which

the sponsor is developing the drug/biologic for marketing. When there is an existing IND in effect, the FDA encourages the submission of an expanded access protocol, rather than a new expanded access IND; having all expanded access and clinical trial use consolidated under a single IND may facilitate identification of safety concerns, may make the administrative process less burdensome for sponsors and FDA, and may help in product review.

2. ***New*** expanded access IND submission, which is separate and distinct from any existing INDs and is intended only to make an investigational drug/biologic available for treatment. A new expanded access IND submission generally should be used when (1) there is no existing IND in effect for the drug/biologic or, more commonly, (2) when the sponsor of an existing IND declines to be the sponsor of the expanded access use (e.g., for an individual patient use, the sponsor of the existing IND may prefer that a patient's physician take on the role of sponsor-investigator and submit a separate individual patient IND).

When proposing an expanded access application for treatment of groups (or populations) of patients, an applicant should ensure that their proposal satisfy all of the following criteria:

1. Patient(s) have a serious or immediately life-threatening disease **or** condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;
2. The potential patient benefit justifies the potential risks of the treatment and the potential risks are not unreasonable in the context of the disease or condition to be treated; and
3. The expanded use of the investigational drug for the requested treatment will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the product.

The party who (1) submits a request to open an expanded access application and (2) receives FDA's authorization to use the investigational product is considered the sponsor of the application. In the absence of any other sponsor (e.g. pharmaceutical company), the treating physician is the sponsor of the expanded access.

Sponsors of expanded access applications have the same Investigators' Responsibilities as sponsors of IND applications intended for clinical investigations. The procedures for safety, annual, and other IND Application Reporting for expanded access applications are like those for investigational IND applications. The requirements for mandatory IND Application Safety Reporting are the same as for all other IND applications.

Submission of an expanded access application for a group of patients would be appropriate in any of the following situations:

i. The intended investigational drug/biologic is not being developed, for example, because the disease or condition is so rare that the sponsor is unable to recruit patients for a clinical trial.

ii. The intended investigational drug/biologic is being developed and studied in a clinical trial, but patients requesting the expanded access use are unable to participate in the trial. For example, patients may not be able to participate in the trial because they have a different disease or stage of disease than the one being studied or otherwise do not

meet the enrollment criteria, because enrollment in the trial is closed, or because the trial site is not geographically accessible.

iii. The intended investigational drug/biologic is an approved drug product that is no longer marketed for safety reasons or is unavailable through marketing due to failure to meet the conditions of the approved application.

iv. The intended investigational drug contains the same active moiety as an approved drug product that is unavailable through marketing due to failure to meet the conditions of the approved application or a drug shortage.

When the expanded access IND or protocol has been procured from the FDA the following must be submitted to the IRB:

a. Initial Application in Cayuse IRB: an outline of the rationale for the use, including a description of available therapeutic options, an explanation of why use of this test article is preferable, description of the disease, the method of administration of the drug, dose, and duration of therapy. A description of the clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the drug and minimize its risks

b. A copy of the written consent form that will be used to obtained informed consent. The consent form must contain all the elements of consent per FDA regulations, and must explain the purpose of the use of this investigational drug. The consent document must include an explanation of what data will be collected regarding the administration, to whom it will be shared and for what purpose(s), and the reporting requirements to the FDA and/or sponsor. Investigators treating a patient(s) with an investigational drug under expanded access are responsible for ensuring that the informed consent requirements are met.

c. The Approval/Acknowledgment IND or protocol letter from the FDA.

d. A copy of the current Investigational Brochure for the investigational drug.

Individual expanded access INDs, including emergency use, may be reviewed by the IRB Chair or other designated IRB member for concurrence before treatment use begins, if authorization for the waiver of convened IRB review has been obtained from the FDA (via FDA Form 3926). This is only applicable for protocols intended to treat one patient. Expanded access INDs for intermediate-size patient populations or widespread treatment use through a treatment IND or treatment protocol will be reviewed at a convened IRB meeting, following standard IRB procedures.

8.5 GROUP C TREATMENT IND

The Group C Treatment IND was established to provide a means for the distribution of investigational agents to oncologists for the treatment of cancer under protocols outside the controlled clinical trial. Group C drugs are generally drugs that have completed Phase III trials and have shown evidence of reproducible efficacy in a specific tumor type. They are distributed only by the NIH under NCI protocols.

Although treatment is the primary objective in these cases, efficacy and safety data are also collected. However, since administration of Group C drugs is not done with research intent, the FDA usually grants a waiver of IRB requirements (21 CFR 105). If an investigator plans to treat cancer patients with Group C drugs, he or she is required to submit a copy to the IRB of the following documentation: (a) FDA letter waiving the requirement for IRB review, (b) the treatment

protocol, and (c) the FDA-approved informed consent document. An IRB Chair will review the document and decide whether a local IRB review is needed, then the IRB Chair's decision will be communicated to the investigator in writing.

8.6 INVESTIGATIONAL USE OF MEDICAL DEVICES

All clinical investigation of medical devices must comply with FDA regulations for investigational device exemptions (21 CFR 812).

Medical Device: an instrument, apparatus, implement, contrivance, implant, in vitro reagent, or other similar or related article, including component, part, or accessory, which is: (a) recognized in the official national Formulary, or the United States Pharmacopoeia, or any supplement to them; (b) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in humans; or (c) intended to affect the structure or any function of the human body; and does not achieve any of its principal intended purposes through chemical action within or on the human body and is not dependent upon being metabolized for the achievement of its principal intended purposes.

Investigational Device: a device that is the object of an investigation. Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices.

Investigation: a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.

Medical Device Labeling: any label or written material on the device or material that accompanies the device. This can include instructions for use, advertising and promotional material. This information must be provided to the FDA during the Premarket Approval (PMA) process. Labeling must provide adequate directions for use, unless it is exempt; it cannot be false or misleading.

In Vitro Diagnostics (IVDs): Reagents, instruments and systems intended for use in the diagnosis of disease or other conditions, including a determination of state of health, in order to cure, mitigate, treat or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. IVDs are medical devices as defined in section 210(h) of the Federal Food, Drug, and Cosmetic Act, and may also be biological products subject to section 351 of the Public Health Service Act. Like other medical devices, IVDs are subject to premarket and postmarket controls. IVDs are also subject to the Clinical Laboratory Improvement Amendments (CLIA '88) of 1988. Under FDA's regulations governing the conduct of IVD device studies, the definition of "subject" includes individuals on whose specimens an investigational device is used (21 CFR 812.3(p)). As a result, an IVD study using human specimens involves human subjects. IVDs require an IDE if the proposed IVD study does not meet an exemption in 21 CFR 812.2. The requirements for an IDE depend on the level of risk that the study.

A. Investigational Device Exemption (IDE)

An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data. Clinical studies are most often conducted to support a PMA. Only a small percentage of 510(k)s require clinical data to support the application. Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices. All clinical evaluations of

investigational devices, unless exempt, must have an approved IDE before the study is initiated.

Clinical evaluation of devices that have not been cleared for marketing requires:

1. an investigational plan;
2. informed consent from all patients;
3. labeling stating that the device is for investigational use only;
4. monitoring of the study; and
5. required records and reports.

An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device without complying with other requirements of the Food, Drug, and Cosmetic Act (FD&C Act) that would apply to devices in commercial distribution.

B. Exemption from IDE Requirements

The device fulfills one of the IDE exemption categories (21 CFR 812.2) (and thus, does not require an IDE application to be filed with the FDA) when it is:

i. Exemption 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.

ii. Exemption 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 in determining substantial equivalence

iii. Exemption 3

- A diagnostic device (e.g., an *in vitro* diagnostic device) 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.

iv. Exemption 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.

v. Exemption 7

- 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

Clinical investigations that are exempt from IDE regulations still require IRB review and approval.

C. Determination of Significant Risk and Non-Significant Risk

Sponsors are responsible for making the initial risk determination and presenting it to the IRB with sufficient evidence for the determination. Unless the FDA has already made a risk determination for the study, the IRB must review the sponsor's significant risk (SR) or non-significant risk (NSR) determination for every investigational device study and review and modify the determination if the IRB disagrees with the sponsor's assessment. If the FDA has already made the SR or NSR determination for the study, the agency's determination is final, and the IRB need not duplicate the assessment. If the IRB assigns a device NSR status but the FDA does not agree, the FDA may overrule the IRB's decision and require that the sponsor submit an IDE application. If a sponsor has filed an IDE but the FDA then classifies the device study as NSR, the FDA will return the IDE application to the sponsor and the IRB should be informed of the FDA's determination. If necessary, the IRB may consult with the FDA before making a determination of SR/NSR.

For studies that are exempt from the IDE regulations, the IRB does not need to make an SR or NSR determination. However, the IRB must still review the study in accordance with the IRB regulations before the investigation may begin.

Under 21 CFR 812.3(m), a SR device means an investigational device that:

i. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

ii. Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;

iii. 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

iv. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

If the device presents a significant risk to subjects, the sponsor must apply for an IDE from the FDA. If the device does not pose significant risks to subjects, justification for the NSR determination must be indicated on the IRB application in Cayuse IRB. NSR is an investigational device that does not meet the definition for a SR device.

Sponsors must provide the IRB with sufficient technical information about the device, reports of prior investigations conducted with the device, documentation of other IRBs' determinations about the study, and an indication of whether the FDA has determined the risk category on the device to facilitate the IRBs decision about its risk status.

The IRB makes the risk determination by reviewing relevant information at a convened meeting, including the following:

- The description of the device;

- Prior investigations conducted with the device;
- The proposed use and investigational plan;
- The subject selection criteria;
- The nature of any harm that may result from the use of the device;
- The potential harm of any additional procedures needed as part of the investigational study.

The IRB meeting minutes will document the rationale for SR/NSR assignment in addition to subsequent approval or disapproval decisions for the clinical investigation. If the IRB determines the study is an NSR device study, the study may begin without submission of an IDE application to the FDA. If the IRB disagrees with the sponsor's NSR assessment and decides the study is an SR device study, the sponsor must obtain an IDE from the FDA. The IRB considers investigation of any SR device to present greater than minimal risk; thus, full IRB review is required for all studies involving SR devices.

D. 510(k) Device

A 510(k) device refers to a new device that the FDA determines to be substantially equivalent to a device that was marketed prior to passage of the Medical Device Amendments of 1976 [510(k) refers to the section of the Food, Drug and Cosmetic Act that describes pre-market notification]. Devices that qualify as 510(k) devices may be marketed immediately without additional investigation of safety and efficacy. Research activities involving a 510(k) device do not require an FDA Investigational Device Exemption (IDE) prior to approval by the IRB; however, the IRB should be provided with documentation of the FDA's determination that the device qualifies as a 510(k) device.

E. Reporting Requirements for Investigational Device Studies

i. Investigators must submit to the sponsor and to the IRB a report of any unanticipated adverse device effect or problem that places subjects or others at a greater risk of harm occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

ii. Investigators must report to the sponsor, within 5-working days, a withdrawal of approval by the IRB of the investigator's part of an investigation.

iii. Investigators must notify the sponsor and the IRB of any deviation from the investigational plan to protect the life or physical well-being of a research subject in an emergency. Such notice must be given as soon as possible, but in no event later than 72 hours to the IRB and 5-working days to the sponsor after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human participants, FDA and IRB in accordance with 21 CFR 812.35(a) also is required.

iv. If an investigator uses a device without obtaining informed consent, the investigator must report such use to the sponsor and the IRB within 5-working days after the use occurs.

v. Investigator must, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the IRB.

F. Continued Access

FDA may allow continued enrollment of subjects after the controlled clinical trial under an IDE has been completed in order to allow access to the investigational device while the marketing application is being prepared by the sponsor or reviewed by FDA.

The sponsor of a clinical investigation is permitted to continue to enroll subjects if there is:

- A public health need for the device; or
- Preliminary evidence that the device is likely to be effective and no significant safety concerns have been identified for the proposed indication.

Extended investigations permit patients and/or physicians continued access to the devices while also allowing the collection of additional safety and effectiveness data to support the marketing application or to address new questions regarding the investigational device. A sponsor's request for Continued Access should be submitted as an IDE supplement.

If the IDE application for the Continued Access of the device is approved by the FDA, the physician should submit the following in an Initial Application in Cayuse IRB:

- The current, written original clinical trial protocol for reference.
- A written summary describing the device use; including the rationale for the use, an explanation of why the use of the investigational device is preferable to the use of available marketed treatments; and a description of the clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the device and minimize its risks.
- Information that is relevant to the safety and effectiveness of the device for the intended continued use. A description of the data to be collected for support of the marketing application.
- A copy of the written consent form that will be used to obtained informed consent. The consent form must contain all the elements of consent per FDA regulations, and must explain the purpose of the use of this device, and the description of the data that will be collected to report safety and effectiveness data to the FDA and sponsor or collected in support of the device approval.
- The approval from the FDA of the IDE supplement for the Continued Access.
- A statement from the sponsor of the IDE supplement that they will provide the device; including a description of what costs the patients will incur, if any, from the use of the device.

Once the review is submitted to the IRB, the Continued Access documents will be reviewed at a convened IRB meeting, following standard IRB procedures. All Continued Access IDEs do not meet the criteria for expedited review and it must go to the full IRB for review. Since it involves the use of an investigational device, it does not qualify as minimal risk.

8.7 HUMANITARIAN USE DEVICES

A humanitarian use device (HUD) is a device intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year. A HUD must receive approval for use through the receipt of a humanitarian device exemption (HDE), which exempts it from the standard requirements for clinical investigation of effectiveness.

A HUD may be administered only in facilities having oversight by an IRB, including continuing review of use of the device. In addition, a HUD may be administered only if such use has been approved by an IRB. The Lurie Children's IRB will review the use of a HUD at the Institution or it may agree to rely on an external IRB to oversee such use and an Institutional Authorization Agreement will be executed.

When applying for IRB approval to use an HUD, an investigator must submit an Initial application in Cayuse IRB. The IRB will only consider use of an HUD for the indication identified in the HDE.

While administration of an HUD in accordance with its indication as approved by the FDA does not constitute research and may not meet the FDA requirements for informed consent, the Lurie Children's IRB requires informed consent to protect the rights and welfare of the patients. If the holder of the HDE wishes to collect safety and effectiveness data in a clinical investigation for the HDE-approved indication(s) the HUD is not subject to IDE requirements. However, other clinical investigation requirements still apply, including IRB approval.

Clinical investigations of a HUD for a different indication other than the HDE-approved indication must be conducted in compliance with the IDE regulations at 21 CFR Part 812, subject to IRB approval, and in compliance with protection of human subjects, including informed consent and, if applicable, additional safeguards for children

Investigators will be asked to provide periodic reviews to the IRB no less than once year, and may be required to implement special precautions or follow-up evaluations. The FDA considers expedited review procedures to be appropriate for continuing review when the use of a HUD within its approved labeling does not constitute research.

i. Determination of a significant risk (SR) or non-significant risk (NSR) device for HUD

   When the IRB is deciding whether to approve the use of a HUD according to its approved indications, its review does not include an SR/NSR determination. In addition, the IRB does not have to make a SR/NSR determination when it receives a request to review a clinical investigation of a HUD (e.g., collection of safety and effectiveness data) when that clinical investigation concerns the HDE-approved indication(s) only. The FDA considers such investigations exempt from the IDE requirements in 21 CFR Part 812.

   If the IRB receives a request to review an application for an investigational study of the HUD for a different indication than the HDE-approved indication, then the clinical investigation is subject to the IDE regulations at 21 CFR Part 812 and a SR/NSR determination must be made.

ii. Emergency Use of an HUD without Prior IRB Approval

An HUD may be administered a single time without prior approval by the IRB in an emergent situation in which a physician determines that approval from the IRB cannot be obtained in time to prevent serious harm or patient death.

The FDA recommends that the physician obtain informed consent from the patient and ensure that reasonable patient protection measures are followed, such as devising schedules to monitor the patient, taking into consideration the patient's specific needs and the limited information available about the risks and benefits of the device.

The FDA further recommends that the physician submit a follow-up report on the patient's condition to the HDE holder and first check with the IRB before such use to review any Institutional policy.

In such an emergency situation, the physician shall, within 5 days after the use of the device, provide written notification to the IRB of such use.

Note: user facilities must submit reports to FDA, the IRB of record, and the manufacturer whenever a HUD may have caused or contributed to a death, and must submit reports to the manufacturer (or to FDA and the IRB of record if the manufacturer is unknown) whenever a HUD may have caused or contributed to a serious injury.

8.8 EMERGENCY USE AND EXPANDED ACCESS FOR MEDICAL DEVICES

An unapproved device usually may only be used on human subjects through an approved clinical study in which the subjects meet certain criteria and the device is only used in accordance with the approved protocol. Circumstances under which a health care provider may wish to use an unapproved device to save the life of a patient or to help a patient suffering from a serious disease or condition for which there no other alternative therapy exists. The use of an investigational device outside of a clinical trial for treatment of a patient is called "expanded access."

If enrollment in an existing clinical trial protocol is not possible (e.g., a patient is not eligible for any ongoing clinical trials, or there are no ongoing clinical trials to address the patient's condition), patients/physicians have the potential to receive expanded access to investigational devices under one of three alternative mechanisms:

- Emergency Use
- Compassionate Use (or Single Patient/Small Group Access)
- Treatment Use

A. Emergency Use

Emergency use is the use of an investigational device in an emergency situation. It is intended to provide patients and physicians with access to devices intended to treat life-threatening or serious diseases or conditions when there is no available alternative and no time to obtain FDA approval. Emergency use may apply even if the investigational device is being studied in a clinical trial under an IDE: if a physician needs to use the device in a manner inconsistent with the approved investigational plan; or a physician who is not part of the clinical study, wishes to use the device to treat a patient with a life-threatening or serious disease or condition. Emergency use of an investigational device may occur before an IDE is approved and when a device is not being studied under an IDE.

A physician may treat a patient with an unapproved device in an emergency situation if he/she concludes that:

a. The patient has a life-threatening condition that needs immediate treatment;

b. No generally acceptable alternative treatment for the condition exists; *and*

c. Because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

If all of the above criteria are met, an unapproved device may be used in an emergency situation without prior approval by FDA. FDA expects the physician to make the determination that the patient's circumstances meet the above criteria, to assess the potential for benefit from the use of the unapproved device, and to have substantial reason to believe that benefits will exist.

If a device is used in circumstances meeting the criteria listed above, the physician should follow as many of the patient protection procedures listed below as possible:

a. Informed consent from the patient or a legal representative;

b. Clearance from the Institution;

c. Concurrence of the IRB chair;

d. An independent assessment from an uninvolved physician; and

e. Authorization from the device manufacturer.

Prior approval from the FDA for shipment or emergency use of the investigational device is not required.

When the physician determines that the use of the unapproved device in the patient meets the criteria for emergency use and there is sufficient time to obtain IRB Chair review, the following is to be submitted via Cayuse IRB for concurrence of the emergency use:

a. Initial Application in Cayuse IRB: A description of the patient's disease, including recent medical history and previous treatments outlining the rationale for the use, an explanation of that there is no generally acceptable alternative treatment for the condition that exists and there is no time to use existing procedures to get an IDE for the use. The submission is also to include the method of administration, and duration of therapy, a description of the clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the device and minimize its risks. This summary information must support the criteria for emergency use above.

b. A copy of the written informed consent that will be used to obtain informed consent. The consent form must explain the purpose of the use of this device. The consent document must not include references to a research investigation, however, it must include an explanation of what data will be collected regarding the administration and the reporting requirements to the FDA and IDE sponsor (if applicable). If the physician is unable to obtain consent, the submission must include a justification for an exception and must meet the criteria for exception to obtaining informed consent.

c. Any relevant safety information from the device manufacturer or patient information materials.

d. Documentation of communication with the FDA, if applicable.

e. Documentation that the physician has access to the device or documentation of the decision from the supplier of the device that they will ship the product and authorize its use.

If the test article is a device with an FDA-approved IDE, the treating physician is responsible to notify the device sponsor of the emergency use.

The emergency use of the device should be reported to FDA by the IDE sponsor via a supplement within 5-working days from the time the sponsor learns of the use. The supplement submitted to the FDA should contain a summary of the following:

a. Conditions constituting the emergency

b. The patient protection measures that were followed such as:

- Informed consent from the patient or a legal representative;
- Clearance from the Institution;
- Concurrence of the IRB Chair or his/her designee;
- An independent assessment from an uninvolved physician; and
- Authorization from the IDE sponsor, if an approved IDE exists for the device.

c. Patient outcome information

If an FDA-approved IDE does not exist for the device, the information above should be submitted by the treating physician directly to the FDA.

B. Compassionate Use (or Single Patient/Small Group Access)

The compassionate use of an IDE provides a mechanism for patients with serious disease or condition, for which there is no alternative treatment available and who do not qualify for inclusion in a clinical investigation, access to an investigational device which the treating physician believes may provide a benefit in treating and/or diagnosing. It can also be used for devices that are not being studied in a clinical investigation (i.e., an IDE for the device does not exist). This provision is typically approved for individual patients but may be approved to treat a small group.

The criteria for compassionate use of an investigational device are:

- The patient has a life-threatening or serious disease or condition; and
- No generally acceptable alternative treatment for the condition exists.

FDA approval is required before compassionate use occurs. Physicians (if there is no current IDE for the device), or sponsors (who has submitted the IDE to conduct the clinical study for the device), are required to submit an IDE Supplement containing the following to the FDA when requesting a compassionate use of an investigational device:

a. A description of the patient's condition and the circumstances necessitating treatment;

b. A discussion of why alternatives therapies are unsatisfactory and why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition;

c. An identification of any deviations in the approved clinical protocol (if applicable) that may be needed in order to treat the patient

d. The patient protection measures that will be followed:
   - A draft of the informed consent document that will be used;
   - Concurrence of IRB chairperson;
   - Clearance from the Institution;
   - Independent assessment from an uninvolved physician; and
   - Authorization from the device manufacturer on the use of the device.

The above compassionate use criteria and procedures can also be applied when a physician wishes to treat a small group of patients. In this case, the physician should request access to the device through the IDE sponsor. The sponsor should submit an IDE supplement that includes the information identified above and indicates the number of patients to be treated. Such a supplement should include the protocol to be followed or identify deviations from the approved clinical protocol.

A monitoring schedule should be designed to meet the needs of the patients while recognizing the investigational nature of the device. Follow-up information on the use of the device should be submitted in an IDE supplement after all patients have been treated.

The treating physician is to submit the following documents to the IRB for review of the compassionate use:

a. Initial Application in Cayuse IRB: an outline of the rationale for the use, an explanation of why use of this device is preferable to the use of available therapeutic options, description of the patient's (or patients') disease, the method of administration of the device, and duration of therapy, description of the clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the device and minimize its risks.

b. A copy of the written consent form that will be used to obtained informed consent. The consent form must contain all the elements of consent per FDA regulations, and must explain the purpose of the use of this investigational device. The consent document must reference the investigation as a treatment and it must include an explanation of what data will be collected regarding the administration, to whom it will be shared and for what purpose(s), and the reporting requirements to the FDA and/or sponsor

c. The approval from the FDA of the compassionate use of the device.

d. Documentation of an independent assessment from an uninvolved physician.

e. A statement from the sponsor of the IDE that they will provide the device; including a description of what costs the patients will incur, if any, from the use of the device.

Once the review is submitted to the IRB, the Compassionate use IDE documents will be reviewed by the IRB Chair for concurrence.

C. Treatment Use

If data from a clinical trial suggests that an investigational device is effective, the trial may be expanded to include additional patients with life-threatening or serious diseases for whom no comparable alternatives are available. During the clinical trial, or prior to final action on the

marketing application, it may be appropriate to use the device in the treatment of patients not in the trial under the provisions of the Treatment IDE regulation (21 CFR 812.36).

The FDA would consider the use of an investigational device under a Treatment IDE if:

- The device is intended to treat or diagnose a serious or immediately life-threatening disease or condition;
- There is no comparable or satisfactory alternative device or other therapy available to treat or diagnose that stage of the disease or condition in the intended patient population;
- The device is under investigation in a controlled clinical trial for the same use under an approved IDE, or such clinical trials have been completed; and
- The sponsor of the investigation is pursuing marketing approval/clearance of the investigational device.

The use of an investigational device for Treatment Use requires an IDE application submitted to the FDA for approval.

If the IDE application for the treatment use of the device is approved by the FDA, the physician should submit the following documents to the IRB for review and approval by the IRB:

a. Initial Application in Cayuse IRB: the rationale for the use, including, as appropriate, either a list of the available regimens that ordinarily should be tried before using the investigational device or an explanation of why the use of the investigational device is preferable to the use of available marketed treatments; and a description of the clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the device and minimize its risks.

b. Information that is relevant to the safety and effectiveness of the device for the intended treatment use. Information from other IDE's may be incorporated by reference to support the treatment use.

c. A copy of the written consent form that will be used to obtained informed consent. The consent form must contain all the elements of consent per FDA regulations, and must explain the purpose of the use of this device, and the description of the data that will be collected to report safety and effectiveness data to the FDA and sponsor or collected in support of the device approval.

d. The approval from the FDA of the treatment use of the device.

e. A statement from the sponsor of the IDE that they will provide the device; including a description of what costs the patients will incur, if any, from the use of the device.

Once the review is submitted to the IRB, the Treatment IDE documents will be reviewed at a convened IRB meeting, following standard IRB procedures. All Treatment IDEs do not meet the criteria for expedited review and it must go to the full IRB for review. Since it involves the use of an investigational device, it does not qualify as minimal risk.

The sponsor of a Treatment IDE must submit progress reports on a semi-annual basis to the FDA until the filing of a marketing application. After filing of a marketing application,

progress reports must be submitted annually in accordance with applicable IDE regulations. The sponsor of a Treatment IDE is responsible for submitting all other reports required under 21 CFR 812.150; such as unanticipated adverse device effects and final reports. The reports are submitted as supplements to the original IDE application.

8.9 OFF-LABEL USE OF MARKETED DRUGS, BIOLOGICS, AND DEVICES

At the time that the FDA approves a new drug, biologic, or device for marketing, it also specifies the indications, patient groups, and formulation under which the drug, biologic, or device may be used. Any variance from these approved specifications constitutes "off-label" usage.

If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgement. Use of a marketed product in this manner when the intent is the "practice of medicine" does not require the submission of an IND or IDE to the FDA or review by the IRB.

8.10 FDA CONTACTS

- For drug products: Drug Information Branch at (301) 796-3400; druginfo@fda.hhs.gov; Questions about whether a product is subject to IND regulations: call (301)796-3400
- For biological products: (301) 827-2000; Questions about whether a product is subject to IND regulations: call 301-827-2000
- For device products: visit the webpage: Division of Industry and Consumer Education (DICE); DICE@fda.hhs.gov
- For physicians seeking information on Expanded Access/ Emergency Use visit this FDA webpage.
- FDA Emergency Call Center, telephone: 866-300-4374 after 4:30 pm EST weekdays and all day on weekends.