Chapter 18
FDA-Regulated Research

This chapter covers research involving products regulated by the Food and Drug Administration (FDA), including investigational and approved drugs, biologics, and devices. This chapter also describes procedures for emergency use of investigational drugs, biologics, and devices, and other regulations unique to FDA-regulated products. Research involving FDA-regulated products may also be subject to 45 CFR 46, California regulations, and institutional policies.

18.1 FDA-Regulated Research

The FDA regulations for drugs are outlined in 21 CFR 312, devices are in 21 CFR 812, and biologics are in 21 CFR 600. FDA regulations for informed consent (21 CFR 50) and Institutional Review Boards (21 CFR 56) also apply. For a comparison of FDA and HHS regulations on human subject protection, click here. Reporting of adverse events and unanticipated problems related to research on FDA-regulated products is covered in Chapter 20 - Reportable Events, Noncompliance, Suspensions, and Terminations.

The USC IRBs are registered with both the Office for Human Research Protections (OHRP) and FDA in the OHRP database.

Definitions for FDA Regulated Research

Biological Product	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.
Clinical Investigation	Any experiment that involves a test article and one or more human subjects.

Device	An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease; or intended to affect the structure or any function of the body; AND which does not achieve its primary intended purposes through chemical action within or on the body and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.
Drug	Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and articles (other than food) intended to affect the structure or any function of the body.
Test Article	Any drug, biological product, medical device, electronic product, or other product regulated by the FDA.

18.2 Investigational Drugs

An Investigational New Drug (IND) application is the FDA regulatory mechanism by which a sponsor can ship an unapproved drug or biologic to study sites and initiate clinical research on the drug. The FDA assigns an IND number and allows the investigation to begin after it determines that research participants will not be exposed to unreasonable risk. An IND application is required for:

- Testing of unapproved drugs
- Testing of approved drugs that involves new indications or significant labeling changes

IND regulations are found at 21 CFR 312.

Investigators must describe the regulatory status of each study drug in the iStar application as well as rationale for determining whether or not an IND is required for the study. If a drug is covered by an IND, the IND number and documentation of the IND number must be provided. Documentation may include FDA correspondence to the sponsor that provides the IND number, or a clinical protocol or investigator's brochure that identifies the IND number. The IRB staff verifies that there is an IND number and

that the number provided in the iStar application is correct. The study will not be approved until the IND number is verified.

Certain drug investigations may be exempt from the requirement for an IND. A clinical investigation of a ***marketed*** drug is exempt from the IND requirements if ***all*** of the criteria are met:

- 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 and there is no intent to use it to support any other significant change in the labeling of the drug
- In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug
- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product
- The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR 56) and with the requirements for informed consent (21 CFR 50)
- The investigation is conducted in compliance with the requirements of 21 CFR 312.7 (the investigation is not intended to promote or commercialize the drug product)

Investigations of marketed drugs or biologics must have an IND if none of the exemptions described above apply. When the principal intent of the investigation is to develop information about an approved product's safety or efficacy, IRB approval and an IND are required.

Additional information about exemptions from IND requirements is found in the FDA guidance document "Investigational New Drug Applications (INDs) - Determining Whether Human Research Studies Can Be Conducted Without an IND."

The IRB will determine if the IND exemption proposed in the iStar application is consistent with FDA regulations and guidance. The committee determination will be recorded in the meeting minutes. If there is no IND and the study does not meet any of the FDA exemption categories, the IRB will not approve the study. The investigator may

re-submit the iStar application after obtaining an IND number from the FDA or obtaining a written determination from the FDA that no IND is needed.

When there is a question as to whether the use of a marketed drug or biologic for an unapproved indication requires an IND, the investigator should contact the FDA directly for a determination. The IRB may require that an investigator contact the FDA if this has not been done at the time of IRB review. If the FDA indicates that an IND is not required, documentation of contact with the FDA is required. This may be either a written notification from the FDA, or documentation of contact with the FDA, including who was contacted, the phone number, the time of the call, and a summary of the information provided by the FDA.

Off-Label Use

An IND is not required when a health care provider prescribes a marketed drug to treat an individual patient for an unlabeled indication. This is referred to as "off-label use." An IND is not required because this use falls within the scope of medical practice and it is not research.

Expanded Access of Investigational Drugs

The use of investigational drugs and biologics is usually limited to subjects enrolled in clinical trials under an IND. However, investigational products may show some promise before the trials are completed. When there is no satisfactory standard treatment for a serious, life-threatening, or debilitating condition, the FDA has a mechanism that allows expanded access to investigational drugs before the clinical trials are complete. When no satisfactory alternative treatment exists, subjects are generally willing to accept greater risks from investigational drugs that have potential benefits.

Expanded access to investigational drugs requires an IND and prospective IRB approval. In some cases, the sponsor will have an expanded access protocol under an existing IND. In other cases, an investigator may have to obtain a new IND for expanded access to an investigational drug. A new IND is needed if there is no existing IND or if the sponsor does not want to amend an existing IND to include expanded access. The following mechanisms expand access to promising therapeutic agents without compromising the protection afforded to human subjects or the thoroughness and scientific integrity of product development and marketing approval.

Treatment IND

A treatment protocol added to an existing IND is called a "treatment IND." The treatment IND 21 CFR 312.34 and 312.35 is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND may be granted after sufficient data have been collected to show that the drug may be effective and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment INDs also serve to expand the body of knowledge about the drug.

There are four requirements that must be met before a treatment IND can be issued:

- The drug is intended to treat a serious or immediately life-threatening disease
- There is no satisfactory alternative treatment available
- The drug is already under investigation, or trials have been completed
- The trial sponsor is actively pursuing marketing approval

Treatment IND studies require prospective IRB review and informed consent.

Open Label Protocol or Open Protocol IND

These protocols are usually uncontrolled studies, carried out to obtain additional safety data (Phase 3 studies). They are typically used when the controlled trial has ended and treatment is continued to enable the subjects and the controls to continue to receive the benefits of the investigational drug until marketing approval is obtained. These studies require prospective IRB review of the protocol and informed consent.

Parallel Track

The FDA's Parallel Track policy 57 FR 13250 permits wider access to promising new drugs for AIDS/HIV-related diseases under a separate "expanded access" protocol that "parallels" the controlled clinical trials that are essential to establishing the safety and effectiveness of new drugs. It does so by providing an administrative system that expands the availability of drugs for treating AIDS/HIV. These studies require prospective IRB review and informed consent.

18.3 Investigational Medical Devices

Definitions Related to Investigational Medical Devices

Medical Device	A medical device is any health care product that does not achieve its primary intended purposes by chemical action or by being metabolized. Medical devices also include reagents and test kits for in vitro diagnosis of disease and other medical conditions such as pregnancy.
Significant Risk Device	A device that presents a potential for serious risk to the health, safety, or welfare of a subject, and 1) Is intended as an implant; 2) Is used in supporting or sustaining human life; 3) Is of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise prevents impairment of human health; or 4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
Non-Significant Risk Device	A device that does not meet the definition of a significant risk study. (A nonsignificant device should not be confused with the concept of "minimal risk" used in IRB regulations under 45 CFR 46.)
510(k) Device	A new device determined by the FDA to be substantially equivalent to an approved device. 510(k) devices are “cleared” by the FDA and may be marketed immediately.
Investigational Device Exemption (IDE)	An approved IDE permits an investigational device to be shipped lawfully for the purpose of conducting investigations of that device.

Medical devices range from simple products such as bandages and tongue depressors to complex products such as cardiac pacemakers, surgical lasers, orthopedic implants, and imaging systems and software. Medical devices also include diagnostic products such as pregnancy test kits. When medical device research involves in vitro diagnostics and unidentified tissue specimens, the FDA defines the unidentified tissue specimens as human subjects.

The FDA has several regulatory mechanisms for studying and approving new devices and modifications to existing devices. These regulatory mechanisms are based on the level of risk to participants. Investigators who are studying devices must provide the IRB with

complete and accurate information about the regulatory status and risk level of each device.

An Investigational Device Exemption (IDE) permits an investigational device to be shipped lawfully for the purpose of conducting investigations of that device. Investigational use also includes clinical evaluation of new intended uses of legally marketed devices. The IDE regulations found at 21 CFR 812 describe three types of device studies:

Significant Risk Device Studies

A significant risk device is an investigational device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject
- Is for use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject
- 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
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject

Significant risk device studies must follow all the IDE regulations. An IDE application must be approved by the FDA and the IRB before the study can begin.

Nonsignificant Risk Device Studies

A nonsignificant risk device is one that does not meet the definition of a significant risk device. Studies of nonsignificant risk devices must follow the abbreviated IDE requirements at 21 CFR 812.2(b). An IDE application is not required.

IDE Exempt Studies

Certain device studies are exempt from IDE requirements, including studies using:

- A legally marketed device when used in accordance with its labeling (including 510(k) devices)

- A diagnostic device if it complies with the labeling requirements in §809.10(c) and, if the testing is noninvasive, does not require an invasive sampling procedure that presents significant risk; does not by design or intention introduce energy into a subject; and is not used as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure
- A device used for consumer preference testing, testing of a modification, or testing of a combination of devices if the device(s) are legally marketed device(s) AND if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk
- The device is 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

Determination of Risk Level

The study sponsor is responsible for the initial determination that a device poses significant or nonsignificant risk to subjects. If there is no industry sponsor, the Principal Investigator is considered to be the sponsor and must make the initial risk determination. The IRB must review the initial determination for each device study and make an independent risk determination. The FDA guidance document Significant Risk and Nonsignificant Risk Medical Device Studies is available to help distinguish significant from nonsignificant risk studies. This guidance document provides many examples of significant and nonsignificant risk devices. Sponsors, investigators, and IRBs may need to request additional assistance from the FDA to make the risk determination.

Significant Risk Devices

The sponsor makes the initial determination that a device presents significant risk to subjects. If the sponsor determines it to be a significant risk device, the sponsor must submit an IDE application to the FDA. The study cannot begin until the FDA approves the IDE application. When the FDA receives an IDE application, FDA notifies the sponsor in writing that the application was received and that an IDE number was assigned. The IDE application is considered approved 30 days after it was received by FDA, unless the FDA informs the sponsor within 30 days that the IDE application was not approved or that it must be modified.

The IRB must make an independent determination of device risk when reviewing the study. Because significant risk devices present more than minimal risk to subjects, all significant risk device studies will be reviewed by the full committee. In deciding if a study poses a significant risk, the committee will consider the nature of the harm that may result from use of the device in the investigation, and not the risks of the device alone. For example, if subjects must undergo a surgical procedure as part of the study, the IRB will consider the potential risks of the surgery in addition to the potential risks of the device.

The investigator cannot begin a significant risk device study until the IDE is approved and the USC IRB approves the study. The sponsor and investigators must comply with IDE regulations in conducting the study.

Nonsignificant Risk Devices

The sponsor makes the initial determination that the device presents nonsignificant risks to subjects. The proposed study can then be submitted directly to the IRB for review, without an IDE application and without FDA notification or approval. The IRB reviews the study and makes an independent determination about the risk level.

The IRB determination is based on information provided by the sponsor. In deciding if a device presents nonsignificant risks, the committee will consider the nature of the harm that may result from use of the device in the investigation, and not the risks of the device alone. The sponsor must provide a statement that the study involves nonsignificant risk to subjects and an explanation why the study does not involve significant risks to subjects. The IRB may require additional information from the sponsor or investigator, including: a description of the device, reports of prior investigations with the device, the proposed investigational plan, a description of subject selection criteria and monitoring procedures, any other information the IRB finds necessary to make a risk determination, whether other IRBs have reviewed the study and the determinations that were made, and the FDA's assessment of the device's risk (if the FDA has made such an assessment).

If the IRB agrees with the nonsignificant risk determination, the study can begin after the investigator receives IRB approval. The FDA does not have to be notified of IRB approval of a nonsignificant risk device study.

If the IRB does not agree with the sponsor’s nonsignificant risk determination and instead finds that the study involves significant risk, the IRB will notify the investigator, and where appropriate, notify the sponsor. The sponsor must notify the FDA in writing (21

CFR 812.150(b)(9)) of the IRB determination. The IRB can review the study as a significant risk device study, but the study may not begin until FDA approves an IDE application or makes its own nonsignificant risk determination.

Abbreviated IDE Requirements

Nonsignificant risk device studies must follow the abbreviated IDE requirements under 21 CFR 812.2(b). These requirements address labeling of the device, IRB approval, informed consent, monitoring, and records and reports.

IRB Responsibilities

The IRB must review the initial risk determination for each device study and make an independent determination of the risk. The determination is based on information provided in the device section of the iStar application. If the device information is incomplete or inaccurate, the IRB will not approve the study until the investigator provides additional information.

Investigators must describe the regulatory status of each study device in the iStar application as well as rationale for determining whether or not an IDE is required for the study. If the study requires an IDE, the IRB staff will verify that the IDE number provided in the iStar application matches the number provided in the sponsor's protocol or in FDA correspondence. The committee will discuss the study risks and make a determination about the device. This determination will be recorded in the meeting minutes. If an IDE number is not provided, the study will not be approved. The investigator will be asked to re-submit the application after obtaining the IDE number.

If the study is proposed as a nonsignificant risk device study, the committee will discuss the study risks and make a determination about the device. This determination will be recorded in the meeting minutes. The minutes will instruct the investigator to comply with the abbreviated IDE requirements.

If the study is proposed to be exempt from IDE requirements, the committee or expedited reviewer will confirm the exemption type proposed by the investigator. The IRB determination will be recorded in the meeting minutes or expedited review correspondence. For studies involving 510(k) devices, the IRB staff will check the FDA database to verify the regulatory status of the device. The IRB may require that the investigator obtain written documentation of 510(k) clearance and attach this

documentation in the iStar application. A device with 510(k) clearance is a legally marketed device when used in accordance with its labeling.

Off-Label Use of Devices (Treatment)

An IDE is not required when a health care provider uses an approved device to treat an individual patient for an unlabeled indication. This is referred to as "off-label use." An IDE is not required because this use falls within the scope of medical practice and it is not research.

18.4 Sponsor-Investigators

USC investigators who initiate and submit IND or IDE applications to the FDA assume the responsibilities of both the investigator and the sponsor. Sponsor-Investigators must provide FDA documentation of their IND or IDE in the iStar application.

Sponsor-Investigators are required to complete and sign the USC Sponsor-Investigator Agreement form (found in the Forms pages of the HSIRB and UPIRB websites) and attach it in the iStar application. This agreement serves as an assurance that the investigator will review, be cognizant of, and comply with regulatory requirements of sponsor-investigators. The IRB may require the PI to receive training / education from the HSIRB Chair, an experienced HSIRB member, or other designee before beginning the research.

A sponsor-investigator for an IDE protocol must follow the FDA regulations in 21 CFR 812 applicable to sponsor responsibilities. This includes:

- The record keeping requirements of 21 CFR 812.140(b)
- The reporting requirements of 21 CFR 812.150(b) including annual IDE progress report to the IRB (and annual progress report to FDA if the IDE is for a significant risk device)

- The required notification under 21 CFR 812.150(b)(1) to the FDA and all participating investigators of any evaluation of an unanticipated adverse device effect within 10 working days of first receiving notice of the effect. Unanticipated adverse device effects are described in Section 7.13 Reportable Events.

A sponsor-investigator for an IND protocol must follow the FDA regulations in 21 CFR 312 applicable to sponsor responsibilities, particularly Subpart D. This includes:

- The recordkeeping and record retention requirements of 21 CFR 312.57
- The annual report requirements of 21 CFR 312.33 and safety reporting of 312.32 and
- Prompt reporting as required in 21 CFR 312.55(b) to the FDA and all participating investigators of significant new adverse effects or risks with respect to the drug or biologic

The IND or IDE product must be stored, secured, dispensed, and documented in accordance with policies of the Institution where the test article will be used, such as Keck Hospital of USC, USC Norris Comprehensive Cancer Center and Hospital, Keck Medicine clinics, LAC+USC Medical Center, and other USC locations.

If the sponsor-investigator holding the IND or IDE leaves USC or transfers to USC, the sponsor-investigator is responsible for notifying FDA about the change in Institution and address.

For additional information, refer to Section 13.2 – Investigator-Initiated Research and Sponsor-Investigators. Additionally, refer to the OPRS booklet "Are You the Holder of an IND or IDE?"

18.5 Compassionate Use of Medical Device

The FDA compassionate use provision allows patients who do not meet eligibility criteria for a clinical trial to have access to an investigational device. This provision applies to an individual patient or a small number of patients for whom the treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition. Patients must have a serious disease or condition and have no acceptable alternatives for treatment.

This provision is unlike those that provide for Emergency Use of Test Article or Humanitarian Use Devises (HUD). Prior FDA approval and IRB approval are needed before compassionate use occurs. The sponsor must submit an IDE supplement and request approval for a compassionate use under section §812.35(a) in order to treat the patient(s). The IDE supplement should include:

- A description of the patient's condition and the circumstances requiring treatment
- 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
- An identification of any deviations in the approved clinical protocol that may be needed in order to treat the patient
- The patient protection measures that will be followed (including informed consent, concurrence of IRB Chair, clearance from the Institution, independent assessment from uninvolved physician, and authorization from IDE sponsor)

Physicians Responsibilities

The physician should not treat the patient until FDA and the manufacturer approves the specific compassionate use of the device under the proposed circumstances. If the request is approved, the physician should submit an Emergency Use/Compassionate Use application in iStar to obtain concurrence of the IRB Chair. The physician must devise an appropriate schedule for monitoring the patient, taking into consideration the investigational nature of the device and the specific needs of the patient. The patient should be monitored to detect any possible problems arising from the use of the device.

Following the compassionate use of the device, a follow-up report should be submitted to FDA as an IDE Report in which summary information regarding patient outcome is presented. If any problems occurred as a result of device use, these should be discussed in the IDE Report and reported to the reviewing IRB as soon as possible.

IRB Responsibilities

The IRB will acknowledge and evaluate the submission to determine whether the compassionate use met the eligibility criteria and complied with the regulatory requirements. Compassionate use is a clinical care activity, not research. Data obtained from compassionate use cannot be used for research purposes.

Compassionate Use for Multiple Patients

Compassionate use is typically approved by the FDA for individual patients but may be approved to treat a small group. Clinician may treat multiple patients rather than an individual patient suffering from a serious disease or condition for which no adequate alternative therapy meets the medical need. In this case, the clinician should request access to the investigational device through the IDE sponsor. The sponsor should submit to the FDA 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. As with single patient compassionate use, 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 to the FDA in an IDE supplement after all compassionate use patients have been treated.

More information can be found on the FDA website:

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051345.htm#compassionateuse

18.6 Humanitarian Use Devices (HUD)

Definitions Related to Humanitarian Use Devices (21 CFR 814)

Humanitarian Use Device (HUD)	A device that is 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.
Humanitarian Device Exemption (HDE)	An authorization from the FDA to market an HUD; indicates the device does not pose unreasonable risk of injury to patient. The probable benefit outweighs risk of injury from use. Exempt from "effectiveness" requirements.

A special type of medical device, the Humanitarian Use Device (HUD), is intended to benefit patients with rare conditions or diseases (affecting fewer than 4,000 people in the United States per year) and that is exempt from the effectiveness requirements. The Office of Orphan Products Development determines if a device can be designated as an HUD. The FDA must approve a Humanitarian Device Exemption (HDE) application

before the device can be marketed. The HDE authorization clears the HUD for marketing.

The use of the device does NOT constitute research; however, federal regulations require the local IRB approve the use of an HUD before it is administered to local patients. USC clinicians who wish to use an HUD must submit an iStar application and select "Use of Humanitarian Use Device (Not Research)" as the submission type. Initial IRB review is conducted at a Full Board meeting, but annual continuing review is conducted by an expedited reviewer.

The clinician submitting the IRB application must provide documentation to the IRB that the device's sponsor has obtained an HDE. The device's sponsor must document the following information in writing:

- The generic and trade name of the device
- The FDA HDE number (a six-digit number preceded by the letter H)
- The date of the HUD designation
- Indications for use of the device
- A description of the device
- Contraindications, warnings, and precautions for use of the device
- Adverse effects of the device on health
- Alternative practices and procedures
- Marketing history
- Summary of studies using the device

FDA regulations do not require an informed consent form for clinical use of an HUD (i.e., 21 CFR 50: see reference 7.5). However, sponsors often provide a sample consent form and the IRB or the Institution may require the investigator to use the template informed consent form specific for HUDs with all references to research eliminated.

The USC clinician must verify in the iStar application that the HUD is not being tested as part of a research study. The IRB is not required to determine whether the device is "significant risk" or "non-significant risk". Investigators who intend to study the efficacy

and safety of an HUD in research require an IDE. Clinicians will also be asked about intended off-label use of the HUD.

18.7 Emergency Use of a Test Article (Investigational Drug, Biologic or Device)

Emergency use is defined as the use of a test article in a human subject 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)). The emergency use provision in the FDA regulations 21 CFR 56.104(c) provides an exemption from prior review and approval by the IRB. The exemption allows for one emergency use of a test article without prospective IRB review for a subject in a life-threatening or severely debilitating situation in which no standard treatment is available.

- Life-threatening means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.

- Severely debilitating means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

FDA regulations require that any subsequent use of the test article at the Institution must have prospective IRB review and approval. Subsequent use includes a second use in the first subject or the use in another subject. An IRB application must be submitted immediately after the first emergency use if additional uses of the test article are anticipated. However, the FDA acknowledges that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the proposed use.

When there is time for prospective IRB approval before the test article is used, the investigator must complete an IRB application. The proposal will be scheduled for review at the next convened meeting. FDA regulations do not provide for expedited IRB

approval by an expedited reviewer. Treatment cannot be initiated until IRB approval is obtained.

Procedures for IRB Notification of Emergency Use

The treating physician must notify the IRB of any intended emergency use of a test article before the use occurs. This is done through the "New Emergency Use Application" activity in iStar. The physician must provide assurances that the proposed use of the test article meets the emergency use criteria and that an IND, IDE, or HDE will be obtained. The physician must submit the first part of the application to the IRB as notification of the intended use. If the physician proceeds with emergency use of the test article, the physician is required to notify the IRB within 5 working days of the use. This is done by completing and submitting the second part of the Emergency Use Application to the IRB. The IRB will acknowledge the emergency use at the next convened meeting. In the acknowledgment letter, the physician is reminded that subsequent uses of the test article require prior IRB approval.

Some manufacturers will not ship the test article to the physician without written agreement from the IRB. The physician will receive an acknowledgement notice from the IRB when the emergency use application is submitted. If this acknowledgement notice is not sufficient documentation for the sponsor to ship the test article, the physician should contact the IRB immediately for additional documentation.

Emergency Use of an Investigational Drug or Biologic

The emergency use of an unapproved investigational drug or biologic requires an IND. The treating physician must contact the manufacturer to find out if the manufacturer will ship the drug or biologic for emergency use under the manufacturer's IND.

The need for an investigational drug or biologic may arise in an emergency situation that does not allow time for submission of an IND. In such a case, FDA may authorize shipment of the test article in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means.

Informed Consent

The treating physician is required to obtain informed consent of the subject or the subject's legally authorized representative for emergency use of a drug or biologic, unless

both the treating physician and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

- The subject is confronted by a life-threatening situation necessitating the use of the test article
- Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from the subject
- Time is not sufficient to obtain consent from the subject's legal representative
- No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life

If the treating physician believes that immediate use of the test article is required to preserve the subject's life and if time is not sufficient to obtain an independent physician's assessment, the treating physician should make the determination and, within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

Emergency Use of an Investigational Device

Unapproved devices are normally used only in approved clinical studies conducted under an IDE. Emergency situations may arise in which there is a need to use an investigational device in a manner inconsistent with the clinical study or by a treating physician who is not part of the clinical study.

Emergency use of an unapproved device may occur before an IDE is approved if all the following criteria are met:

- The subject has a life-threatening disease or serious condition requiring immediate use
- There are no generally accepted alternative treatments
- There is no time to obtain FDA approval of an IDE

If an IDE exists, authorization from the IDE sponsor should be obtained. The sponsor is responsible for reporting the emergency use to the FDA within 5 working days. If no IDE exists, the treating physician is responsible for reporting the emergency use to the FDA.

The treating physician has the following responsibilities:

- Obtain an independent assessment by a physician who is not participating in the investigation
- Obtain institutional clearance according to institutional policy (if required by the healthcare facility)
- Obtain concurrence from the IRB Chair
- Obtain authorization from the sponsor if an IDE exists
- Obtain informed consent for the emergency use

Informed Consent

The treating physician is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the treating physician and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following (21 CFR 50.23):

- The subject is confronted by a life-threatening situation necessitating the use of the device
- Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject
- Time is not sufficient to obtain consent from the subject's legal representative
- No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life

Independent Physician Assessment

If the treating physician believes immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's assessment, the treating physician should make the determination. Within 5 working days after the use of the article, the treating physician must have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the IRB within 5 working days after the use of the test article (21 CFR 50.23).

18.8 Planned Emergency Research with Exception from Informed Consent

Planned emergency research is a rare type of research that allows participants to be enrolled without prior informed consent. It differs from emergency use of a test article described above. Investigators who wish to conduct planned emergency research should consult with IRB staff prior to submission of the protocol to the IRB. All of the following conditions must be present for emergency research with an exception from informed consent requirements, as described in 21 CFR 50.24:

- The human subjects are in a life-threatening situation that necessitates urgent intervention
- Available treatments are unproven or unsatisfactory
- Collection of valid scientific evidence is necessary to determine the safety and effectiveness of the intervention
- Obtaining informed consent is not feasible because the subjects are not able to give their informed consent as a result of their medical condition
- The intervention must be administered before consent can be obtained from the subject’s legally authorized representative
- There is no reasonable way to identify prospectively individuals likely to become eligible for participation
- Participation in the research holds out the prospect of direct benefit to the subjects

- The clinical investigation could not practicably be carried out without the waiver

Planned emergency research refers to research planned to occur in emergency settings, and it requires prospective IRB approval. Studies meeting the criteria for an exception from informed consent for emergency research must be approved by the FDA and have a separate IND or IDE.

Before the research is approved, investigators must consult with representatives of the communities where the research will be conducted and from which participants will be drawn and publicly disclose the research plan and potential risks and benefits to the communities. Investigators must also publicly disclose the results of the trial to the community after the trial is completed. An independent data monitoring committee must be established to exercise oversight of the research.

The IRB must ensure that there are appropriate procedures in place to inform subjects, their legally authorized representative, or their family members of their inclusion in the study, details about the study, the subject's right to discontinue participation, and other information contained in the informed consent form. This must be done at the earliest feasible opportunity.

The IRB and/or the investigator will only provide advance notice of these protocols to the Office for Human Research Protections (OHRP) when the research is not subject to FDA regulations.

Additional responsibilities of investigators, the IRBs, and the sponsors are described in the FDA's Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors – Exception from Informed Consent Requirements for Emergency Research.

Research Supported by the Department of Defense (DOD)

Research supported by or in collaboration with the Department of Defense (DOD) is subject to additional regulations. The USC IRBs do not approve exceptions from consent in emergency medicine research funded by DOD unless a waiver is approved by the Secretary of Defense.

18.9 Dietary Supplements

Dietary supplements are regulated by the FDA under the Dietary Supplement Health and Education Act of 1994 (DSHEA). Dietary supplements include vitamins, minerals, herbs, botanicals, amino acids, and other dietary substances intended to supplement the diet.

Investigators who wish to use dietary supplements in clinical studies will be asked to add information about each dietary supplement product to the iStar application. This should include the composition of the product and whenever possible, information about previous human use, testing, and safety.

Although dietary supplements are not subject to the same FDA regulations as drugs, clinical testing of a dietary supplement may still require an Investigational New Drug (IND) application. If the intent of the study is to evaluate a dietary supplement's effects on the normal structure or function of the body, no IND is required. If the intent of the study is to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, an IND is required before the IRB will approve the study. Investigators should review the FDA guidance document "Investigational New Drug Applications (INDs) – Determining Whether Human Research Studies Can Be Conducted Without an IND" when planning a clinical study using a dietary supplement. The IRB may ask investigators to contact the FDA for a written opinion about the need for an IND for clinical studies of dietary supplements. Additional information is available in the FDA guidance document "Botanical Drug Products."

18.10 Screening Procedures and Consent for FDA Research

The following is excerpted from the FDA Information Sheet "Screening Tests Prior to Study Enrollment": http://www.fda.gov/RegulatoryInformation/Guidances/ucm126430.htm

In general, for some studies, the use of screening tests to assess whether prospective subjects are appropriate candidates for inclusion in studies is an appropriate pre-entry activity. While an investigator may discuss availability of studies and the possibility of entry into a study with a prospective subject without first obtaining consent, **informed consent must be obtained prior to initiation of any screening procedures that are performed solely for the purpose of determining eligibility for research.**

Screening may qualify as a minimal risk procedure [21 CFR 56.102(i)] and the IRB may choose to use expedited review procedures [21 CFR 56.110] to approve such screening. The IRB should receive a written outline of the screening procedure to be followed and how consent for screening will be obtained. The IRB may find it appropriate to limit the scope of the screening consent to a description of the screening tests and to the reasons for performing the tests including a brief summary description of the study in which they may be asked to participate.

Unless the screening tests involve more than minimal risk or involve a procedure for which written consent is normally required outside the research context, the IRB may decide that prospective study subjects need not sign a screening consent document [21 CFR 56.109(c)]. If the screening indicates that the prospective subject is eligible, the informed consent procedures for the study, as approved by the IRB, would be followed.

HIPAA Waiver for Screening Medical Records

HIPAA regulations apply to the screening process if it involves review of medical records. Investigators must obtain prospective HIPAA authorization from participants or apply for a partial waiver of HIPAA authorization for recruitment and screening. Refer to Section 11.5 – Health Insurance Portability and Accountability Act (HIPAA) for additional information.

18.11 Data Retention Requirements Related to Subject Withdrawal from FDA-Regulated Research

In FDA-regulated research, specific data retention requirements and disclosure to subjects apply, as described below:

- When a participant withdraws from a study, the data collected on the participant to the point of withdrawal remains part of the study database and may not be removed. The consent document cannot give the participant the option of having data removed.
- A researcher may ask a participant who is withdrawing whether the participant wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this

circumstance, the discussion with the participant distinguishes between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and address the maintenance of privacy and confidentiality of the participant's information.

- The researcher must obtain the participant's consent for this limited participation in the study (assuming such a situation was not described in the original consent document). The IRB must approve the consent document.
- If a participant withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the researcher must not access for purposes related to the study the participant's medical record or other confidential records requiring the participant's consent. However, a researcher may review study data related to the participant collected prior to the participant's withdrawal from the study, and may consult public records, such as those establishing survival status.

18.12 Registration of Clinical Trials and Other Types of Research

FDA regulations under section 801 of the Food and Drug Administration Amendments Act (FDAAA 801) require that all "applicable clinical trials" be registered in the ClinicalTrials.gov clinical trials data bank. ClinicalTrials.gov was developed by NIH in collaboration with the FDA. It is a public registry and results database of clinical trials supported by public or private funds. The "Responsible Party" (the sponsor or the principal investigator designated by the sponsor) must register and report results of applicable clinical trials involving:

- Drugs and Biologics: controlled, clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation or
- Devices: controlled trials with health outcomes, other than small feasibility studies, and pediatric post market surveillance

"*Applicable clinical trials*" generally include interventional studies (with one or more arms) of FDA-regulated drugs, biological products, or devices that meet one of the following conditions:

- Have one or more sites in the U.S
- Involve a drug, biologic, or device that is manufactured in the US (or its territories) and is exported for research
- Be conducted under an investigational new drug application (IND) or investigational device exemption (IDE).

For more information on definitions of terms, refer to FDA's draft guidance document "Elaboration of Definitions of Responsible Party and Applicable Clinical Trial." It is important to note that FDA and HHS regulations are inconsistent in the use of the terms "clinical trials" and "clinical investigation". For more information, refer to 21 CFR 50, 56, 312 and 812.

Registration and results reporting are required for applicable clinical trials; however, ClinicalTrials.gov allows voluntary reporting of other studies that:

- Are in conformance with any applicable human subject or ethics review regulations (or equivalent) and
- Are in conformance with any applicable regulations of the national (or regional) health authority (or equivalent)

Investigators may choose to register a study that is not an applicable clinical trial as a condition to publish study results in a journal.

FDA regulations require reporting of results from registered trials. The Responsible Party must generally report results no later than 12 months after the trial completion date. Results must include participant baseline characteristics, participant flow diagram, outcomes, and adverse events. Instructions for submitting results are available at ClinicalTrials.gov. FDA also requires sponsors or investigators to certify compliance with ClinicalTrials.gov registration when submitting certain applications to the FDA. Form FDA 3674 is used to certify compliance.

Mandatory Informed Consent Language

FDA regulations require that informed consent forms contain specific language about clinical trial registration. Informed consent documents for applicable clinical trials or any study that will be registered in Clinicaltrials.gov must contain the following language in the Confidentiality section:

"A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time."

Federal Enforcement

Investigators who fail to comply with registration or reporting of results on ClinicalTrials.gov can be penalized. Penalties include civil monetary fines and withholding of grant funds if the study is federally funded.

Other Registration Requirements

National Institutes of Health

NIH requires all grantees, regardless of whether or not they are the Responsible Party, to certify that they are complying with FDAAA 801 in grant applications and progress reports. Grantees must certify that the responsible party has made all required submissions to ClinicalTrials.gov for applicable clinical trials funded in whole or in part by the NIH. Click here for more details about *Certifying Compliance with FDAAA in NIH Applications and Progress Reports*. NIH certification is different from the FDA certification described above.

Centers for Medicare & Medicaid Services (CMS)

CMS now requires providers and suppliers to report an 8-digit clinical trial number (NCT number) assigned by ClinicalTrials.gov on claims for items/services furnished pursuant to clinical trials that qualify for coverage as set forth in the Medicare National Coverage Determination Manual. This requirement became effective 1/1/2014. Any qualifying clinical trial that bills tests and procedures to Medicare must be registered to receive payments from CMS. Claims submitted without the NCT number will be returned to providers for reprocessing and addition of the NCT trial number.

Journals

Journals may require registration of clinical trials and other types of health-related interventions in order to publish manuscripts. The International Committee of Medical Journal Editors (ICMJE) policy requires, and recommends that all medical journal editors

require, registration of clinical trials in a public trials registry prior to enrollment of the first subject. Investigators should carefully review registration requirements at ICMJE Clinical Trials Registration.

How to Register a USC Study

For industry-sponsored research:

The industry sponsor is responsible for registration of the research on ClinicalTrials.gov. USC Clinical Trials Office (CTO) will verify that the sponsor has registered the trial and provided the NCT number.

For investigator-initiated research:

Investigators in the Cancer Center should contact the Clinical Investigations Support Office (CISO) for assistance in registering their research on ClinicalTrials.gov.

Investigators who are not in the Cancer Center should contact the Associate Director of HSC Department of Contracts and Grants to request a user account for ClinicalTrials.gov:

Email: jeanbcha@usc.edu

Telephone: 323-442-2825

Webpage: https://research.usc.edu/clinical-trials-at-usc/9309-2/

For more information on registration of research on ClinicalTrials.gov, see the links below.

Helpful Links

- FDA "Guidance for Industry: Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions" http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126838.pdf

- Clinicaltrials.Gov Protocol Registration System http://prsinfo.clinicaltrials.gov/index.html

- USC Vice President of Research Memorandum "ICMJE Journals Require Advanced Registration of Human Studies"
  https://oprs.usc.edu/files/2014/04/Registration-of-Human-Studies_4-7-14.pdf

- ICMJE List of Journals Following the ICMJE Recommendations
  http://www.icmje.org/journals-following-the-icmje-recommendations/

- OPRS "Intend to Publish Your Human Subjects Research Findings?"
  http://oprs.usc.edu/review/publication/

Chapter 19:

Continuous Quality Improvement (CQI)

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