



Title:	FDA-Regulated Research		
SOP Number:	1301	Effective Date:	June 2, 2017
Previous Version Dates:			

1 Purpose

FDA regulations apply to research that involves a FDA-regulated test article in a clinical investigation involving human subjects as defined by the FDA regulations. For FDA-regulated research, the IRB must apply the FDA regulations at 21 CFR 50 and 21 CFR 56. If required by organizational policy or a FWA, 45 CFR 46 must also be applied.

Clinical trials with investigational drugs must be conducted according to FDA's IND regulations, 21 CFR Part 312, and other applicable FDA regulations. Use of an investigational device in a clinical trial to obtain safety and effectiveness data must be conducted according to FDA's IDE regulations, 21 CFR Part 812, and other applicable FDA regulations.

The following procedures describe the review of FDA-regulated research conducted under the auspices of the University of North Carolina at Chapel Hill (UNC-Chapel Hill).

2 Procedure

2.1 FDA Review Procedures

- A. At initial submission, the investigator must indicate whether the research involves a test article and is a clinical investigation involving human subjects on the application form. The investigator may use the IND Exemption Checklist to assist in making this determination.
- B. During the pre-review process, the IRB Analyst will confirm whether FDA regulations are applicable using the IND Exemption Checklist. If FDA regulations apply and the research is not exempt, the IRB Analyst add the study to the next available full board agenda.
- C. UNC-Chapel Hill follows ICH-GCP E6 to the extent it is consistent with FDA regulations.

2.2 FDA Exemptions

The following categories of clinical investigations are exempt from the requirements of FDA regulations for IRB review:

1. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review. [21 CFR §56.104(c)]
2. Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient

at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. [21 CFR §56.104(d)]

2.3 Investigator Responsibilities

The investigator holds additional responsibilities when conducting a clinical trial evaluating FDA-regulated drugs, devices, and other articles. These responsibilities include, but are not limited to, the following:

1. The investigator is responsible for ensuring that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs (including biological products) or agreement for clinical investigations of medical devices, the investigational plan and other applicable regulations, and any requirements imposed by the IRB or FDA.
2. The investigator is responsible for personally conducting or supervising the investigation. When certain study-related tasks are delegated by an investigator, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.
3. The investigator must maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated. This list should also describe the delegated tasks, identify the training that individuals have received that qualifies them to perform delegated tasks (e.g., it can refer to an individual's CV on file and/or training conducted by the investigator/sponsor), and identify the dates of involvement in the study. An investigator should maintain separate lists for each study conducted by the investigator.
4. The investigator is responsible for protecting the rights, safety, and welfare of subjects under their care during a clinical trial. This responsibility includes:
 - Informing subjects that the test articles is being used for investigational purposes and ensuring that the requirements relating to obtaining informed consent are met
 - Providing reasonable medical care for study subjects for medical problems arising during participation in the trial that are, or could be, related to the study intervention
 - Providing reasonable access to needed medical care, either by the investigator or by another identified, qualified individual (e.g., when the investigator is unavailable, or when specialized care is needed)
 - Adhering to the protocol/research plan so that study subjects are not exposed to unreasonable risks

- As appropriate, informing the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and the subject agrees to the primary physician being informed
5. The investigator is responsible for reading and understanding the information in the investigator brochure or device risk information, including the potential risks and side effects of the drug or device.
 6. The investigator is responsible for maintaining adequate and accurate records in accordance with FDA regulations and to making those records available for inspection by the FDA. These records include: correspondence with other investigators, the IRB, the sponsor, monitors, or the FDA; drug and device accountability records; case histories; consent forms; and documentation that consent was obtained prior to any participation in the study. Records must be obtained for a minimum of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such. Other regulations, such as HIPAA, organizational policies, or contractual agreements with sponsors may necessitate retention for a longer period of time.
 7. The investigator is responsible for controlling drugs, biological products, and devices according to FDA regulations and the Controlled Substances Act, if applicable.
 8. The investigator proposing the clinical investigation will be required to provide a plan that includes storage, security, and dispensing of the test article. This information may be documented in the IRB application or Master Protocol.
 - a. If the test article is an investigational drug, according to the Joint Commission standards, Investigational Drug Services (IDS) must be used for storage, security, dispensing, administration, return, disposition, and records of accountability, unless there is an exception granted by IDS pharmacy, in which case, researchers must provide a written plan that describes the proper and safe handling of the investigational product to IDS.
 - b. All devices received for a study must be stored in a locked environment under secure control with limited access. Proper instructions on the use of the device must be provided to the subjects. A log must be kept regarding the receipt, use, and/or dispensing of the device and the disposition of remaining devices at the conclusion of the investigation.
 9. The investigator shall furnish, upon request, all reports required by the sponsor of the research including adverse events, progress reports, safety reports, final reports, and financial disclosure reports.
 10. The investigator will permit inspection of research records by the sponsor, sponsor representatives, HRPP and IRB representatives, the FDA, accrediting bodies, and any other agencies or individuals entitled to inspect such records under regulation, organizational policy, or contractual agreement.

2.4 Dietary Supplements

Research involving dietary supplements may or may not fall under FDA regulations. Under the Dietary Supplement Health and Education Act (DSHEA) of 1994, a dietary supplement is not considered a drug and is not subject to the premarket approval requirements for drugs if the intended use for which it is marketed is only to affect the structure or any function of the body (i.e., not intended to be used for a therapeutic purpose). Whether a study falls under FDA oversight is determined by the intent of the clinical investigation. If the clinical investigation is intended only to evaluate the dietary supplement's effect on the structure or function of the body, FDA research regulations do not apply. However, if the study is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, then FDA regulations do apply. Studies involving the ingestion of dietary supplements that are not subject to FDA oversight are still research, and therefore must be reviewed by the IRB.

Similarly, whether an IND is needed for a study evaluating a dietary supplement is determined by the intent of the study. If the study is intended only to evaluate the dietary supplement's effect on the structure or function of the body, an IND is not required. However, if the study is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, an IND is required under part 312.

As with any research involving a test article, the investigator must supply the IRB with sufficient information to determine that the criteria for approval are satisfied and to determine or verify whether or not the research requires an IND. Applications should provide detail consistent with that expected on a drug protocol/research plan and consistent with the level of risk associated or anticipated with the research. At a minimum, the research plan should provide the following information regarding the supplement: Name, Manufacturer, Formulation, Dosage, Method/Route of Administration, Mechanism of Action, Known Drug Interactions, Risk Profile, IND number (or justification for why an IND is unnecessary), documentation of approval for use in humans, documentation or certification of Quality or Purity. As with drugs and devices there should be an accountability plan for the product describing where the product will be stored and how it will be dispensed, usage tracked, and disposal or return. If the study entails greater than minimal risk, a plan for Data and Safety Monitoring must be included.

2.5 Clinical Investigations of Drugs and Devices

2.5.1 IND/IDE Requirements

For studies evaluating the safety or effectiveness of medical devices or experiments using drugs, biologics, dietary supplements, and other compounds that may be considered a drug under FDA regulations, the investigator must indicate on the IRB application whether or not an IDE or IND is in place, and, if not, the basis for why an IDE or IND is not needed.

Documentation must be provided by the sponsor or the sponsor-investigator. Documentation of the IND/IDE could be a:

1. Industry-sponsored study with IND/IDE number indicated on the protocol/research plan.

2. Letter/communication from FDA.
3. Letter/communication from industry sponsor.
4. Other document and/or communication verifying the IND/IDE.

For investigational devices, the study may be exempt from IDE requirements or, in the case of Non-significant Risk (NSR) device studies, follow abbreviated IDE requirements which do not require formal approval by the FDA. If a sponsor has identified a device study as exempt or NSR, then the investigator should include documentation with the submission providing the basis for exempt or NSR categorization. If the FDA has determined that the study is exempt or NSR, documentation of that determination must be provided.

The IRB will review the application and, based upon the documentation provided, determine: (1) that there is an approved IND/IDE in place, (2) that the FDA has determined that an IND is not required or that a device study is exempt or NSR, or, (3) if neither of the above, whether or not an IND is necessary, or that a device study is exempt or NSR, using the criteria below. The IRB cannot grant approval and research cannot begin, including recruiting, obtaining consent, and screening participants, until the IND/IDE status is determined, and, if necessary, an approved IND or IDE is in place. . Please Note: An IND goes into effect 30 days after the FDA receives the IND, unless the sponsor receives earlier notice from the FDA.

2.5.1.1 IND Exemptions

For drugs, an IND is not necessary if the research falls in one of the following seven (7) categories:

1. The drug being used in the research is lawfully marketed in the United States and all of the following requirements are met:
 - a. The research 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
 - b. In the case of a prescription drug, the research is not intended to support a significant change in the advertising for the product;
 - c. The research does not involve a route of administration, dose, subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
 - d. The research is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];
 - e. The research is conducted in compliance with the requirements of 21 CFR 312.7 (i.e., the research is not intended to promote or commercialize the drug product); and
 - f. The research does not intend to invoke FDA regulations for planned emergency research [21 CFR 50.24].

2. The research only involves one or more of the following: (a) Blood grouping serum, (b) Reagent red blood cells or (c) Anti-human globulin;
3. For clinical investigations involving an in vitro diagnostic biological product, an IND is not necessary if a) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and b) it is shipped in compliance with 312.160
4. A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.
5. Bioavailability or Bioequivalence (BA/BE) studies if all of the following conditions are met:
 - a. The drug product does not contain a new chemical entity [21 CFR 314.108], is not radioactively labeled, and is not cytotoxic;
 - b. The dose (single dose or total daily dose) does not exceed the dose specified in the labeling of the approved version of the drug product;
 - c. The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively]; and
 - d. The sponsor meets the requirements for retention of test article samples [21 CFR 320.31(d)(1)] and safety reporting [21 CFR 320.31(d)(3)].
6. Research using a radioactive drug or biological product if all of the following conditions are met:
 - a. It involves basic research not intended for immediate therapeutic, diagnostic, or similar purposes, or otherwise to determine the safety and efficacy of the product;
 - b. The use in humans is approved by a Radioactive Drug Research Committee (RDRC) that is composed and approved by FDA;
 - c. The dose to be administered is known not to cause any clinically detectable pharmacological effect in humans, and
 - d. The total amount of radiation to be administered as part of the study is the smallest radiation dose practical to perform the study without jeopardizing the benefits of the study and is within specified limits.
7. FDA practices enforcement discretion for research using cold isotopes of unapproved drugs if all of the following conditions are met:
 - a. The research is intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a drug labeled with a cold isotope or regarding human physiology, pathophysiology, or biochemistry;
 - b. The research is not intended for immediate therapeutic, diagnostic, or preventive benefit to the study subject;

- c. The dose to be administered is known not to cause any clinically detectable pharmacologic effect in humans based on clinical data from published literature or other valid human studies;
- d. The quality of the cold isotope meets relevant quality standards; and
- e. The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively].

2.5.1.2 IDE Exemptions

For clinical investigations of devices, an IDE is not necessary if:

1. The research involves a device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time;
2. The research involves a device other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of 21 CFR 807 in determining substantial equivalence (a “501k” device);
3. The research involves a diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing:
 - a. Is noninvasive,
 - b. Does not require an invasive sampling procedure that presents significant risk,
 - c. Does not by design or intention introduce energy into a subject, and
 - d. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure;
4. The research involves a device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk;
5. The research involves a device intended solely for veterinary use;
6. The research involves a device shipped solely for research on or with laboratory animals and labeled in accordance with 21 CFR 812.5(c);
7. The research involves 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.

2.5.1.3 Significant and Non-Significant Risk Device Studies

A device study is a Non-Significant Risk (NSR) Device study if it is not IDE exempt and does not meet the definition of a Significant Risk (SR) Device study.

Under 21 CFR 812.3(m), an SR device means 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 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;
- 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.

If the FDA has already determined a study to be SR or NSR, documentation evidencing such should be provided to the IRB. The FDA's determination is final and the IRB does not have to make the device risk determination.

Unless the FDA has already made a device risk determination for the study, the IRB will review studies that the sponsor or investigator have put forth as NSR at a convened meeting to determine if the device represents SR or NSR.

The sponsor or sponsor-investigator is responsible for providing the IRB with an explanation describing the basis for their initial determination of NSR and any other information that may help the IRB in evaluating the risk of the study (e.g., reports of prior investigations of the device).

The IRB will review the information provided by the sponsor and investigator including, but not limited to: the sponsor or investigator's NSR assessment, the description of the device, reports of prior investigations of the device (if applicable), the proposed investigational plan, and subject selection criteria.

The NSR/SR determination made by the IRB will be based on the proposed use of the device in the investigation, not on the device alone. The IRB will consider the nature of any harms that may result from use of the device, including potential harms from additional procedures subjects would need to undergo as part of the investigation (e.g., procedures for inserting, implanting, or deploying the device). The IRB may consult with the FDA or require the sponsor or investigator to obtain a determination from the FDA. The IRB will document the SR or NSR determination and the basis for it in the meeting minutes and provide the investigator, and sponsor when applicable, with the determination in writing.

Non-significant risk device studies do not require submission of an IDE application to the FDA but must be conducted in accordance with the abbreviated requirements of IDE regulations (21 CFR 812.2(b)). Under the abbreviated requirements, the following categories of investigations are considered to have approved applications for IDE's, unless FDA has notified a sponsor under 812.20(a) that approval of an application is required:

(1) An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor (or sponsor-investigator):

- (i) Labels the device in accordance with 812.5;
- (ii) Obtains IRB approval of the investigation after presenting the reviewing IRB with an explanation of why the device is not a significant risk device, and maintains such approval;
- (iii) Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under part 50 and documents it, unless documentation is waived by an IRB under 56.109(c).
- (iv) Complies with the requirements of 812.46 with respect to monitoring investigations;
- (v) Maintains the records required under 812.140(b) (4) and (5) and makes the reports required under 812.150(b) (1) through (3) and (5) through (10);
- (vi) Ensures that participating investigators maintain the records required by 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7); and
- (vii) Complies with the prohibitions in 812.7 against promotion and other practices.

When the FDA or IRB determines that a study is SR, the IRB may approve the study, but the study cannot begin until an IDE is obtained.

2.6 Humanitarian Use Devices

A Humanitarian Use Device (HUD) is an approved (marketed) medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year [21 CFR 814.3(n)]. Federal law requires that IRBs approve the use of an HUD at a facility. Once approved, the clinical use of the HUD may be considered as any other approved device, with the caution that effectiveness has not been shown in clinical trials.

2.6.1 Definitions

Humanitarian Device Exemption. A Humanitarian Device Exemption (HDE) is a “premarket approval application” submitted to FDA pursuant to Subpart A, 21 CFR Part 814 “seeking a humanitarian device exemption from the effectiveness requirements of sections 514 and 515 of the [FD&C Act] as authorized by section 520(m)(2) of the [FD&C Act].” HDE approval is based upon, among other criteria, a determination by FDA that the HUD will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from use of the device outweighs the risk of injury or illness from its use while taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

HDE Holder. An HDE Holder is a person who or entity that obtains to approval of an HDE from the FDA.

2.6.2 IRB Review Requirements

A Humanitarian Use Device (HUD) may only be used in a facility after an IRB has approved its use, except in certain emergencies. The HDE holder is responsible for ensuring that a HUD is provided only to facilities having an IRB constituted and acting in accordance with the FDA's regulations governing IRBs (21 CFR Part 56), including continuing review of use of the device.

When a HUD is used in a clinical investigation (i.e., research involving one or more subjects to determine the safety or effectiveness of the HUD), the full requirements for IRB review and informed consent apply (21 CFR 50 and 56) as well as other applicable regulations. It is essential to differentiate whether the HUD is being studied for the indication(s) in its approved labeling or for different indication(s). When the HUD is being studied for the indication(s) in its approved labeling, the IDE regulations at 21 CFR 812 do not apply. However, when the HUD is being studied for a different indication(s), 21 CFR 812 does apply, including the requirement for a FDA-approved IDE before starting the clinical investigation of a Significant Risk device.

2.6.3 Procedures

The relevant requirements and procedures for investigators and for IRB review described elsewhere in this manual apply to clinical investigations of HUDs. The material within this section applies to diagnostic or treatment uses of HUDs.

The health care provider seeking approval for diagnostic or treatment use of a HUD at the UNC-Chapel Hill is responsible for obtaining IRB approval prior to use of the HUD at the facility and for complying with the applicable regulations, including those for medical device reporting, institutional policies, and the requirements of the IRB.

Health care providers seeking initial IRB approval for diagnostic or treatment use of a HUD for the indication(s) in the HUDs approved labeling should submit the following materials to the IRB:

1. Humanitarian Use Device (HUD) Application Addendum
2. A copy of the HDE approval letter from the FDA
3. A description of the device, such as a device brochure
4. The patient information packet for the HUD
5. The proposed clinical consent process
6. Other relevant materials (e.g., training certificates) as identified in the Application Form

The IRB will review the proposal at a convened meeting ensuring that appropriate expertise is available either within the membership in attendance or via the use of consultants. The IRB will review the risks to patients that are described in the product labeling and other materials, the proposed procedures to ensure that risks are minimized, and will evaluate whether the risks are reasonable in relation to the potential benefits to patients at the facility. The IRB will evaluate

the patient information packet and proposed consent process and will determine if the materials are adequate and appropriate for the patient population.

The IRB may specify limitations on the use of the device, require additional screening and follow up procedures, require interim reports to the IRB, require continuing review more often than annually, or set other conditions or requirements as appropriate to minimize risks to patients and ensure the safe use of the device in the facility.

Once use of the HUD is approved, the health care provider is responsible for submitting any proposed changes to the IRB-approved plan or patient materials and obtaining approval for those changes prior to implementation, unless the change is necessary to avoid or mediate an apparent immediate risk to a patient. Proposed changes may be submitted by submitting a modification to the approved application and should be accompanied by any revised materials or supporting documentation. The IRB may review these changes using expedited review procedures or refer the changes for review by the convened IRB.

The health care provider is responsible for submitting reports to the FDA, the IRB, and the manufacturer/HDE Holder whenever a HUD may have caused or contributed to a death, and must submit reports to the manufacturer (or to FDA and the IRB if the manufacturer is unknown) whenever a HUD may have caused or contributed to a serious injury (21 CFR 803.30 and 814.126(a)). Serious injury means an injury or illness that (1) is life-threatening, (2) results in permanent impairment of a bodily function or permanent damage to a body structure, or (3) necessitates medical or surgical intervention to preclude permanent impairment of a bodily function or permanent damage to a body structure (21 CFR 803.3). The specific requirements for this reporting are in the Medical Device Reporting (MDR) Regulation, at 21 CFR Part 803. The IRB will review these reports via either expedited or convened review, as appropriate, and will consider whether any changes are needed to the IRB-approved plan or patient materials.

The health care provider is responsible for submitting continuing review materials to the IRB sufficiently in advance of the expiration date to ensure IRB review and re-approval prior to expiration. Materials to be submitted include:

1. The Continuing Review Report – Humanitarian Use Devices (non-research uses)
2. Any safety reports or summaries provided by the HDE holder that had not previously been submitted
3. The current patient information packet, if applicable
4. The current consent, if applicable
5. Other materials as identified on the Continuing Review Report
6. Any other new relevant information or materials

The IRB may conduct continuing review using expedited review procedures or review by the convened IRB.

2.6.4 Compassionate Use of off-label HUD

The IRB may approve, on a case-by-case basis, applications for the off-label emergency or compassionate use of a Humanitarian Use Device (HUD) based on a physician/principal investigator (PI) request that meets the following IRB criteria.

- The treating physician/investigator (PI) has determined that there is no alternative device for the patient's condition and there is no emergency.
- The PI has provided the HDE holder and the Medical IRB with the following:
 - A description of the patient's condition and the circumstances necessitating treatment with the device;
 - A discussion of why alternative treatments are unsatisfactory; and
 - Assurances and information about patient protection measures.
- In addition, the PI shall request that the HDE holder submit an HDE amendment for FDA approval prior to the use of the device. If the FDA grants approval, the PI shall report the use of the HUD to the IRB and the HDE holder for subsequent submission to the FDA database.

Compassionate use shall be reviewed by the full IRB in a convened meeting using all standard full review criteria. In addition, the PI shall provide the HDE holder and the IRB with information addressing the criteria listed above. The approval applies to the single case requested and does not apply to a class of patients.

2.6.5 Emergency Uses of HUDs

If an appropriately trained and licensed health care provider in an emergency situation determines that IRB approval for the use of the HUD at the facility cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be used without prior IRB approval. The health care provider must, within 5 days after the emergency use of the device, provide written notification of the use to the IRB including the identification of the patient involved, the date of the use, and the reason for the use.

If a HUD is approved for use in a facility, but an appropriately trained and licensed health care provider wants to use the HUD outside its approved indication(s) in an emergency or determines that there is no alternative device for a patient's condition, the physician should consult with the HDE holder and IRB in advance if possible, obtain informed consent if possible, and ensure that reasonable measures are taken to protect the well-being of the patient such as a schedule and plan for follow up examinations and procedures to monitor the patient, taking into consideration the patient's specific needs and what is known about the risks and benefits of the device. The provider should submit a follow up report to the HDE holder and the IRB and must comply with medical device reporting requirements.

The IRB may require additional reports, patient protection measures, or other requirement, as appropriate given the specifics of the situation.

2.7 Expanded Access to Investigational Drugs, Biologics, and Devices

Expanded access pathways, also referred to as “compassionate use”, are designed to make investigational medical products available as early in the drug and device evaluation process as possible to patients without therapeutic options, because they have exhausted or are not a good candidate for approved therapies and cannot enter a clinical trial. Expanded access refers to access to investigational medical products outside of a clinical trial, where the intent is treatment, rather than research. Because the investigational products have not yet been approved by FDA as safe and effective, it is important to remember that the product may not be effective and there may be unexpected serious adverse effects and to take appropriate measures to ensure that this is understood by the patient or their representative and to monitor for safety.

2.7.1 Expanded Access to Investigational Drugs and Biologics

The FDA’s expanded access rule for investigational drugs, including biologics classified as drugs, is intended to improve access to investigational drugs, and approved drugs with limited availability under a risk evaluation and mitigation strategy (REMS), for patients with serious or immediately life-threatening diseases or conditions who lack other therapeutic options and may benefit from the investigational diagnostic or therapy.

Under the FDA’s expanded access rule, access to investigational drugs for treatment purposes will be available to:

- Individual patients, including in emergencies [21 CFR 312.310]
- Intermediate-size patient populations [21 CFR 312.315]
- Larger populations under a treatment protocol or treatment IND [21 CFR 312.320]

Expanded access submissions are categorized by FDA as either “Access Protocols”, which involve a protocol amendment to an existing IND, or “Access INDs”, which are managed separately from any existing INDs.

The FDA has also established a rule, “Charging for Investigational Drugs Under an Investigational New Drug Application”, to:

- Provide general criteria for authorizing charging for an investigational drug [21 CFR 312.8(a)]
- Provide criteria for charging for an investigational drug in a clinical trial [21 CFR 312.8(b)]
- Set forth criteria for charging for an investigational drug under the expanded access for treatment use
- Clarify what costs can be recovered

At UNC health care system, Investigational Drug Services (IDS) will be utilized for storage, security, dispensing, administration, return, disposition, and accountability of expanded access

investigational drugs. The investigator (or the holder of the IND) is responsible for drug procurement under the IND and will supply IDS with the investigational drug as necessary.

Investigators, when seeking access to drugs under the expanded access provisions, should work closely with the sponsor or manufacturer, the FDA, and the UNC-Chapel Hill OHRE, to determine the appropriate access mechanism and ensure that proper regulatory procedures are followed.

Unless the conditions that permit an emergency use exemption (see Section 13.9) are satisfied, prospective IRB review and approval is required for all expanded access uses, including clinical patient use. This requires, among other things, that the IRB review the expanded access use at a convened meeting at which a majority of IRB members are present.

2.7.2 Expanded Access to Investigational and Unapproved Medical Devices

As with investigational drugs, unapproved medical devices may normally only be used in humans in an approved clinical trial under the supervision of a participating clinical investigator. However, there may be circumstances under which a health care provider may wish to use an unapproved device when a patient is facing life-threatening circumstances or suffering from a serious disease or condition for which no other alternative therapy or diagnostic exists or is a satisfactory option for the patient.

FDA has made the following mechanisms available for these circumstances:

- Emergency Use
- Planned Emergency Research (See Section 11.11.1)
- Compassionate Use (or Single Patient/Small Group Access)
- Treatment Use
- Continued Access

Investigators, when seeking access to investigational or unapproved devices under one of the above provisions, should work closely with the sponsor or manufacturer, the FDA, and the UNC-Chapel Hill OHRE to ensure that proper regulatory procedures are followed.

Unless the conditions that permit an emergency use exemption are satisfied (see Section 13.9), prospective IRB review and approval is required. This requires, among other things, that the IRB review the proposed use at a convened meeting at which a majority of IRB members are present.

2.7.2.1 Emergency Use

If an appropriately trained and licensed health care provider in an emergency situation determines that IRB approval for the use of an investigational drug/device at the facility cannot be obtained in time to prevent serious harm or death to a patient, the drug or device may be used without prior IRB approval. If the research involves an investigational drug, the FDA has issued an IND. The health care provider must, within 5 days after the emergency use of the

drug or device, provide written notification of the use to the IRB including information about the patient involved (e.g., age, diagnosis, health status), the date of the use, and the reason for the use.

Informed consent is not required when all of the following are true:

- Before the use of the test article both the investigator and a physician who is not otherwise participating in the clinical investigation certified the specific conditions in writing.
- The above written certification is submitted to the IRB within five working days after the use of the test article.
- Informed consent is not required because all of the following are true:
 - Immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject.
 - Time is not sufficient to obtain the independent determination a physician who is not otherwise participating in the clinical investigation.
 - Before the use of the test article, the investigator will certify the specific conditions in writing.

Note: DHHS regulations do not permit research activities to be started, even in an emergency, without prior IRB approval. When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject under 45 CFR Part 46. However, nothing in the DHHS regulations at 45 CFR Part 46 is 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.

2.7.2.1.1 Emergency Exemption from Prospective IRB Approval

Under FDA regulations [21 CFR 56.104(c)], FDA exempts the emergency use of a test article from the requirement for prospective IRB approval, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article in the facility requires IRB review. However, 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 issue.

FDA defines emergency use as the use of a test article 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)]. If all conditions described in 21 CFR 56.102(d) exist then the emergency exemption from prospective IRB approval found at 21 CFR 56.104(c) may be used. The emergency use of a test article, other than a medical device, is a clinical investigation, the patient is a participant, and the FDA may require data from an emergency use to be reported in a marketing application.

Life-threatening, for the purposes of 21 CFR 56.102(d), includes both life-threatening and severely debilitating.

Unless the provisions for an emergency exception from the informed consent requirement are satisfied (see Section 13.9.2), informed consent must be obtained in accordance with 21 CFR 50 and documented in writing in accordance with 21 CFR 50.27.

The IRB must be notified within 5 working days when an emergency exemption is used via the submission of a “Report of Emergency Use of a Test Article” form. The IRB Chair or designated member will review the report to verify that circumstances of the emergency use conformed to FDA regulations. This must not be construed as an approval for the emergency use by the IRB, as an exemption from the requirement for prospective IRB approval has been invoked. When appropriate, in the event a manufacturer requires documentation from the IRB, the IRB will provide a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c). Reports of emergency uses will be brought to the convened IRB for their information. Investigators are reminded that they must comply with all other organizational policies and requirements applicable to the use of the investigational or unapproved article.

2.7.2.1.2 Emergency Exception from the Informed Consent Requirement

An exception under FDA regulations at 21 CFR 50.23(a-c) permits the emergency use of an investigational or unapproved test article without informed consent where the investigator and an independent physician who is not otherwise participating in the clinical investigation certify in writing all four of the following specific conditions:

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

If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent physician determination in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

The IRB must be notified within 5 working days when an emergency exception is used via the submission of a “Report of Emergency Use of a Test Article” form. Documentation of the independent physician evaluation must be provided. The IRB Chair or designated member will review the report to verify that circumstances of the emergency exception conformed to FDA regulations.

2.7.2.1.3 Waiver of Informed Consent for Planned Emergency Research

The UNC-Chapel Hill IRB follows FDA regulations, 21 CFR 50.24, and any applicable state requirements which permit waiver of informed consent requirements for emergency research when human subjects in need of emergency medical intervention cannot provide legally effective informed consent and **their** legally authorized representatives (LARs) are also unable or unavailable to give informed consent on their behalf.

See SOP 1101.2.1 for additional detail on Planned Emergency Research.

2.8 Use of test articles in research: INDs or IDEs Investigational New Drug and Investigational Device Exemption studies

An Investigational New Drug (IND) Application or Investigational Device Exemption (IDE) are exemptions from the law that otherwise requires that a drug, biologic, or device must be approved before it can be transported across state lines. Generally, one of these exemptions is required whenever a research study uses a drug, biologic or significant risk device that has not received FDA marketing approval. An IND may also be required for a drug that does have FDA marketing approval if the research study proposes a use of the drug that was not included in the existing FDA approval. (See the FDA Information Sheets on "Off-Label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices" for additional requirements.) IND and IDE research studies are subject to the same new and continuing review requirements as for human subjects research in general, but they also require FDA approval for the proposed research use.

Most IND and IDE studies at the University are research protocols developed and sponsored by the commercial entity that is developing a drug or device pursuant to FDA regulations and is itself responsible for obtaining the IND or IDE approvals and for fulfilling all other FDA requirements for such a study. There are some IND or IDE studies for which the study protocol has been developed independently by a university investigator and for which that investigator is responsible for obtaining the IND or IDE and for fulfilling all FDA required filings and other documentation. Investigators should contact the Office of Clinical Trials for guidance and support regarding IND and IDE studies.

Investigators will provide the IND or IDE number as a part of the IRB application; the IRB primary reviewer should verify that the IND or IDE number is valid by assuring consistency across documents (e.g., FDA letters, sponsor protocol).

The IRB is not required to monitor the investigator's performance of required FDA paperwork. However, in reviewing the study, the IRB should be mindful that in this context, the IRB review should include a determination of whether an IND or IDE is required and may also require more intense IRB scrutiny of the protocol and related risks as well as more guidance to the investigator regarding the scientific design, subject safety parameters, informed consent process and other human subjects protection factors.

For non-emergency situations, prospective IRB approval is required. Single patient use allows a physician to obtain access to an investigational drug upon receiving approval from the IRB. This

approval is granted for the treatment of a single patient. The treatment use may occur only after IRB approval is obtained.

2.8.1 Compliance with IND regulations

When research involves the use of a drug other than the use of a marketed drug in the course of normal medical practice, the University will confirm that:

- The drug has an IND; or
- The protocol meets one of the FDA exemptions from the requirement to have an IND:

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.
- If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product.
- The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
- The investigation will be conducted in compliance with 21 CFR 50 and 56.
- The investigation will be conducted in compliance with the requirements of 21 CFR 312.7.

Exemption 2

- A clinical investigation is for an in vitro diagnostic biological product that involves one or more of the following:
 - Blood grouping serum.
 - Reagent red blood cells.
 - Anti-human globulin.
- The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure.
- The diagnostic test will be shipped in compliance with 21 CFR 312.160.

Exemption 3

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

Exemption 4

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

2.8.2 Compliance with IDE regulations

When research is conducted to determine the safety or effectiveness of a device, the University will confirm that:

- The device has an IDE issued by the FDA; or
- The device fulfilled the requirements for an abbreviated IDE:
 - The device is not a banned device.
 - The sponsor labels the device in accordance with 21 CFR 812.5.
 - The sponsor will obtain IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval.
 - The sponsor will ensure that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, consent under 21 CFR 50 and documents it, unless documentation is waived.
 - The sponsor will comply with the requirements of 21 CFR 812.46 with respect to monitoring investigations;
 - The sponsor will maintain the records required under 21 CFR 812.140(b) (4) and (5) and report as required under 21 CFR 812.150(b) (1) through (3) and (5) through (10);
 - The sponsor will ensure that participating investigators maintain the records required by 21 CFR 812.140(a)(3)(i) and report as required under 812.150(a) (1), (2), (5), and (7); and
 - The sponsor will comply with the prohibitions in 21 CFR 812.7 against promotion and other practices; or
- The device fulfills one of the IDE exemption categories:
 - A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
 - A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that the FDA had determined to be substantially equivalent to a device in commercial distribution immediately

before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.

- A diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 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 participant.
 - Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
 - A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put participants at risk.
 - A custom device as defined in 21 CFR 812.3(b), unless the device was being used to determine safety or effectiveness for commercial distribution.

2.8.3 Humanitarian Use Device

FDA regulations define a “humanitarian use device” (“HUD”) as a device that is intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect fewer than 4,000 individuals in the United States per year. Because of the extremely limited market for such devices, they do not receive full FDA review and approval. For this reason FDA requires prospective IRB approval (except in exceptional emergency situations for any use of the HUD with human research subjects or with patients. The investigator or health care provider is required to submit an application for IRB review of the proposed HUD use. Included in the application must be evidence that the investigator/sponsor has obtained a Humanitarian Device Exemption (HDE) from the FDA in accordance with 21 CFR 814.100-126.

While the effectiveness of the device does not have to be demonstrated, the IRB will verify that the device does not pose an unreasonable risk of illness or injury to the recipient, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. The IRB approval must verify that the use of the HUD, as proposed, is consistent with current labeling of the device and does not exceed the scope of the FDA approved indication. The device’s labeling must state that the device is a humanitarian use device and that, although the device is authorized by Federal Law, the effectiveness of the device for the specific indication has not been proven or demonstrated. The initial review of a HUD is to be completed by a convened IRB. The IRB may approve use of the HUD without any further restrictions, or under a protocol, or on a case-by-case basis. The convened Board may make the

determination at initial review that continuing review may occur using the expedited procedure if the HUD is not being used in the course of a research study. Criteria the IRB may use to grant continuing review using the expedited procedure include: initial use of the HUD was approved without any further restrictions, and the continuing review period was not less than 1 year. Criteria for subsequent continuing review using the expedited procedure may include: there have been no subject complaints, and no additional risks have been identified.

FDA regulations do not require informed consent for patient care uses of a HUD; in these cases there will be no “research consent form” and consent should be obtained in accordance with UNC Healthcare policies and practices. When the HUD is being used in a research study, consent should be obtained in accordance with research policies and practices.

2.8.4 Investigational Drug Service (IDS)

An agent/drug (including supplements) will be considered investigational if both the following two criteria are met: 1) administration of the agent is part of a protocol that requires IRB approval, and 2) a subject is required to sign an Informed Consent Form before receiving the agent. Researchers using investigational drugs in studies must register all studies with and, if appropriate, use the services of, the IDS Pharmacy.

(See <http://pharmacy.intranet.unhealthcare.org/services/investdrugs>)

The IDS pharmacists coordinate the preparation and dispensing of clinical trial medications, to the extent possible, within the framework of existing policies and procedures of the Department of Pharmacy. In addition, IDS pharmacists assist investigators in the design of clinical trials, which include the blinding and randomization of drug therapies. IDS pharmacists maintain inventory and dispensing records, ensure compliance with State laws and federal regulations for the handling of investigational drugs, and provide drug information to medical and nursing personnel.

2.8.4.1 Storage and control of investigational devices

Investigational devices will be stored, controlled and dispensed in accordance with UNC Health Care System policy, once enacted. Pursuant to this policy, the investigator will describe the plan for storage, control, and dispensing of the device. The department of the investigator will be responsible for reviewing the plan and evaluating whether it is adequate to ensure that only authorized investigators will use the device and they will use the device only in participants who have provided consent.

Definitions

Biologic. Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other technologies. In general, the term "drugs" includes therapeutic biological products.

Dietary Supplement. A dietary supplement is a product taken by mouth that is intended to supplement the diet and that contains a dietary ingredient. The dietary ingredients in these products can include vitamins, minerals, herbs and other botanicals, amino acids, other dietary substances intended to supplement the diet, and concentrates, metabolites, constituents, extracts, or combinations of the preceding types of ingredients. See section 201(ff) of the FD&C Act [21 U.S.C. 321(ff)].

Investigational Drug. Investigational or experimental drugs are new drugs that have not yet been approved by the FDA or approved drugs that are being studied in a clinical investigation.

Investigational Device. Investigational device means a device (including a transitional device) that is the object of an investigation. Investigation, as it pertains to devices, means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.

IND. IND means an investigational new drug application in accordance with 21 CFR Part 312.

IDE. IDE means an investigational device exemption in accordance with 21 CFR 812.

In Vitro Diagnostic Product (IVD). In vitro diagnostic products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the 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. [21 CFR 809.3(a)]

Emergency Use. Emergency use is defined as the use of an investigational product with 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. [21CFR 56.102(d)]

Significant Risk (SR) Device. Significant risk device means an investigational device that:

- (1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- (2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- (3) 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
- (4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Non-Significant Risk (NSR) Device. A non-significant risk device is an investigational device that does not meet the definition of a significant risk device.

Humanitarian Use Device (HUD). A Humanitarian Use Device is a device intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year.