

Policy I7 Investigational Drugs and Devices: Research, Treatment and Emergency Use

Scope

This policy applies to all University of Nevada, Reno (the University) and affiliate investigators conducting human research under an investigational new drug application (IND), an investigational device exemption (IDE) or treatment IND; and for emergency or compassionate (devices only) use of investigational drugs and devices by investigators and clinicians.

Policy Statement

Investigators who conduct human research regulated by the Food and Drug Administration (FDA) are required to know and comply with all relevant FDA regulations governing the use of investigational drugs, devices or other test articles. Under FDA regulations (21 CFR 312), research that involves the use of a drug other than the use of a marketed drug in the course of medical practice must be conducted under an IND application, unless the protocol meets one of the five exemptions from the requirement for an IND. Research that is conducted to determine the safety or effectiveness of a device must have an Investigational Device Exemption (IDE) (21 CFR 812) issued by the FDA, unless the device meets the requirements for an abbreviated IDE or the protocol meets one of the five exemptions from the requirement for an IDE.

FDA also recognizes that circumstances may exist in which individuals may benefit from the use of investigational articles outside of a clinical investigation.

Reason for the Policy

The University supports and encourages the discovery and development of efficacious drugs and devices for human use as long as such efforts include safeguards ensuring the protection of research subjects, and public health and safety; and are consistent with ethical standards. For conducting such investigations, an accepted IND application or approved IDE allows the lawful shipment of a drug or device that otherwise would be required to comply with a performance standard or to have pre-market approval by FDA. This policy helps to ensure that when the University and affiliate investigators conduct human subjects research under an IND or IDE, or abbreviated IDE or IDE Exemption, they know and comply with the regulatory requirements for the safe conduct of clinical investigations of drugs and devices. This policy also describes the use of investigational articles outside of the research setting.

Definitions

Clinical Investigation

Any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the FDA under section 312 (new drug applications) of the Federal Food, Drug, and Cosmetic Act (Act), or is not subject to requirements for prior submission to the FDA under these sections of the Act, but the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit.

Compassionate Use

For purposes of this policy, compassionate use refers to the use of an investigational device as the only option available for a patient faced with a serious, albeit not life-threatening condition. (The term “compassionate use” is not recognized by the FDA when referring to investigational drugs.)

Device Categories

FDA will place all IDEs it approves into one of two categories:

Category A - Experimental

The IDE involves innovative devices in which "absolute risk" has not been established (i.e., initial questions of safety and effectiveness have not been resolved, thus FDA is unsure whether the device type can be safe and effective).

Category B - Investigational; Non-experimental

The clinical investigation involves device types believed to be in FDA classes I or II or device types believed to be in FDA class III where incremental risk is the primary risk in question (i.e., underlying questions of safety and effectiveness of that device type have been resolved). This category includes device types that can be safe and effective because, for example, other manufacturers have obtained FDA approval for that device type. Nonsignificant risk studies may also be included in this category. (Investigators who are uncertain of the classification of a medical device may wish to review the Device Classification pages of the FDA website.)

Human Subject

DHHS

A living individual about whom an investigator (whether professional or student) conducting research obtains either (a) data through intervention or interaction with the individual; or (b) identifiable private information.

FDA

A living individual who is or becomes a participant in research involving drugs or devices, either as a recipient of a test article or as a control.

Note that the Office of Human Research (OHRP) policies and procedures use both human “subject” and human “participant” are. While the term participant conveys the voluntary nature of an individual’s

agreement to participate in the research, it may convey a sense of partnership that is not reflected in all types of research. In some research, the volunteer is the recipient of specific acts and any sense of partnership is absent, in which case the term subject may be more appropriate.

A subject may be either a healthy human or a patient. Specifically in regard to investigational device studies, subject means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used, or as a control. A subject may be in normal health or may have a medical condition or disease.

Experimental Subject and Research Involving a Human Being as an Experimental Subject (Department of Defense-sponsored Research)

An activity, for research purposes, where there is an intervention or interaction with a human being for the primary purpose of obtaining data regarding the effect of the intervention or interaction (32 CFR 219.102(f), reference(c)). Examples of interventions or interactions include, but are not limited to, a physical procedure, a drug, a manipulation of the subject or subject's environment, and the withholding of an intervention that would have been undertaken if not for the research purpose.

Immediately Life-Threatening Disease

A stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

Investigational New Drug

A new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms "investigational drug" and "investigational new drug" are deemed to be synonymous.

Investigational New Drug Application

Exempts an investigational new drug from FDA premarketing approval requirements that are otherwise applicable thus allowing the drug to be shipped lawfully for the purpose of conducting clinical investigations of that drug. Because a sponsor will usually ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND refers to the application and is the means through which the sponsor obtains this exemption from the FDA.

Three additional IND types and two IND categories are defined below.

IND Types

Investigator IND (Sponsor-Investigator)

An Investigator IND is submitted to the FDA by an investigator who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. An investigator might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.

Treatment IND

A treatment IND is submitted to the FDA to make promising new drugs available to desperately ill patients as early in the drug development process as possible. FDA will permit an investigational drug to be used under a treatment IND if there is preliminary evidence of drug efficacy and the drug is intended to treat a serious or life-threatening disease in its later stage of development or if there is no alternative drug or therapy available to treat that stage of the disease in the intended individuals.

Emergency Use IND

The Emergency Use IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with the regulations. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist. Emergency and Treatment INDs are sometimes referred to as "Compassionate Use" INDs, but the term "Compassionate Use" is not in the IND regulations.

IND categories

Commercial

Applications submitted primarily by companies whose ultimate goal is to obtain marketing approval for a new product.

Research

Applications submitted for non-commercial use.

Significant Risk (SR) 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, or 2) is used in supporting or sustaining human life, or 3) is of substantial importance in diagnosing, curing, mitigating or treating a 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.

Sponsor-Investigator

Sponsor-investigator is an individual who both initiates and actually conducts, alone or with others, a clinical investigation: in individual under whose immediate direction the investigational drug or device is administered, dispensed or used. The term does not include a corporation or agency. The obligations of a sponsor-investigator include those of an investigator and those of a sponsor.

Test Article

Any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the Act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).

I7-IND Investigational New Drug

An IND is required for investigational or experimental drugs if the drugs are being used for developing information about their safety or efficacy (i.e., clinical investigations).

Approved, marketed drugs may also require an IND if the proposed use in research differs from the previously FDA-approved use, including administration by an unapproved route or delivery method or in an altered dosage. The intended use of an approved drug may be exempt from IND requirements under certain conditions (itemized immediately below).

I7-IND1 Exemption from IND Requirements

If the clinical investigation of a marketed drug or biologic meets all six of the conditions itemized below, and IND is not required.

- (1) it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
- (2) it is not intended to support a significant change in the advertising for the product;
- (3) it does not involve a route of administration or dosage level, use in a 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;
- (4) it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];
- (5) it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]; and
- (6) it does not intend to invoke 21 CFR 50.24 for the exception from informed consent requirements for emergency research.

Two other situations allow clinical investigations to be exempt from IND requirements:

1. The clinical investigation is for an in vitro diagnostic test that
 - a. involves one or more of these biological products
 - Blood grouping serum,
 - Reagent red blood cells or
 - Anti-human globulin;
 - b. is intended for use in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and
 - c. the diagnostic test is shipped in compliance with 21 CFR 312.160.

2. The clinical investigation involves use of a placebo if the investigation does not otherwise require submission of an IND.

I7-IND2 IND Requirements for IRB Review and Approval

For a new human research protocol conducted under an IND, during the preliminary regulatory review an IRB Program Manager or the IRB Chair will verify that regulatory approval for the test article has been obtained and confirm the validity of the IND number noted in the application materials. She or he will make this determination by comparing the IND number in the IRB submission with the IND number in the sponsor protocol, or through communication with the sponsor or FDA.

The fully convened Institutional Review Board (IRB) reviews all new human research protocols conducted under an IND in accordance with IRB review requirements for new protocols, protocol amendments and continuing reviews with three exceptions for renewals: Requests for re-approval of protocols conducted under an IND may be reviewed under expedited procedures for if the remaining research meets the criteria for expedited review under Categories 8(a), 8(b) or 8(c). The option for expedited continuing review will be made on a case-by-case basis by the IRB Chair, designated IRB member, or senior OHRP staff. IRB meetings for human research protocols conducted under an IND will include at least one licensed physician.

Under University policy, IRB reviews of clinical investigations require both a primary and secondary reviewer. The IRB member designated as the primary reviewer will complete the reviewer checklists for new protocols and for drugs and biologics checklists and the secondary reviewer will complete the informed consent checklist for their reviews and reporting to the IRB.

IRB Review of Protocols for Investigational Drugs without an IND

In the case of studies involving investigational drugs for which an IND has not been obtained, investigators must justify to the IRB why exemption is appropriate. The IRB will review the proposed use of the drug with consideration for the exemption criteria, the investigator's statements, and members' knowledge of relevant scientific information (see I7-IND1 above IND exemption criteria).

The IRB may determine that indeed an IND is not required, or the IRB may require the investigator to file an IND with the FDA or to obtain an exemption determination from the FDA. The IRB's determination is generally driven by consideration of item I7-IND1 Exemption from IND Requirements above. If the IRB determines that the research involves some new aspect that may significantly increase risks over what is already known about the use of the drug, it is likely that an IND will be required.

I7-IND3 Investigator Responsibilities

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

An investigator shall obtain the informed consent of each human subject to whom the drug is administered, except when an exception to the requirements for informed consent is met.

Regulatory and Reporting Requirements for Investigators

The principal investigator (PI)

1. will conduct the study in accordance with the relevant, current protocol and will only make changes in a protocol after securing IRB approval and notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects;
2. will comply with all requirements regarding the obligations of clinical investigators and all other pertinent regulatory requirements;
3. will personally conduct or supervise the described investigation;
4. will inform any potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent and IRB review and approval are met;
5. will report to the IRB and the sponsor adverse experiences that occur in the course of the investigation in accordance with policy on adverse event reporting, and 21 CFR 312.64;
6. has read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug;
7. will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments; and
8. will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to the human subjects.

Drug Handling and Documentation Requirements for Investigators

Pursuant to (21 CFR 312 Subchapter D)

Investigators are responsible for

1. administering the drug only to subjects under the investigator's personal supervision or under the supervision of a co-investigator responsible to the investigator;
2. supplying the drug only to persons authorized to receive it;
3. maintaining adequate records for the disposition of the drug (dates, quantity, and use by subjects);
4. returning unused supplies to the sponsor (agency, industry or investigator) or otherwise providing for the disposition in accordance with the direction of the sponsor;

5. maintaining adequate and accurate case histories on each individual receiving the drug or employed as a control (all observations and other data pertinent to the investigation including case report forms and supporting data (source documents, e.g., signed and dated consent forms, medical records including progress notes, hospital charts and nurses notes);
6. retaining records for 2 years after either the date a marketing application is approved for the drug for the indication under investigation, or, if no application is to be filed or if the application is not approved, until 2 years after the investigation is discontinued and FDA is notified;
7. submitting progress reports and safety reports to the sponsor and IRB;
8. providing financial disclosures to the sponsor and the IRB;
9. storing drugs properly and securely;
10. obtaining IRB and FDA review and approval prior to initiating the research (including the consent process) and prior to initiating any changes to the approved research; and
11. permitting authorized individuals (e.g., IRB personnel, University auditing personnel, FDA personnel, federal Drug Enforcement Agency (DEA) personnel) to have access to and to copy relevant records.

In the event that a PI is also the sponsor of the IND, the PI must comply with requirements of sponsor-investigators as described in section I7-INV Investigator-held IND or IDE below.

Additional Investigator Requirements for Research Involving Controlled Substances

If the investigational drug is subject to the Controlled Substances Act (<http://www.deadiversion.usdoj.gov/21cfr/21usc/index.html>), the investigator shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

I7-IDE Investigational Devices

Research that is conducted to determine the safety or effectiveness of a device must have an IDE (21 CFR 812) issued by the FDA, unless the device meets the requirements for an abbreviated IDE or the protocol meets one of the five exemptions from the requirement for an IDE. The clinical study of a new indication for an already marketed, FDA-approved device also falls under the IDE regulations.

I7-IDE1 IRB Review and Approval of Investigational Devices

Initial Determination of Requirements for Review

Upon receipt of a protocol application for human subjects research to determine the safety or effectiveness of a device, the Chair of the Biomedical IRB (or Vice Chair in the Chair's absence) will confirm one of the following:

1. the device has an IDE issued by the FDA;
2. the device fulfills the requirements for an abbreviated IDE (itemized below); or
3. the device fulfills one of the IDE exemption categories (itemized below).

Human subject research conducted under an IDE will undergo initial and continuing review at convened meetings, unless the protocol meets the criteria for expedited continuing review under Categories 8(a), 8(b), or 8(c). The option for expedited continuing review will be made on a case-by-case basis by the IRB Chair or other qualified IRB member or senior OHRP staff.

Under University policy, IRB reviews of clinical investigations require both a primary and secondary reviewer. The IRB member designated as the primary reviewer will complete the reviewer checklists for new protocols and the secondary reviewer will complete the informed consent checklist for their reviews and reports to the IRB. IRB meetings with IDE determinations will include at least one licensed physician.

IRB Review of Significant Risk and Non-Significant Risk Devices

The FDA established three regulatory classes for medical devices based upon the degree of control necessary to assure that the various types of devices are safe and effective. Devices are classified depending upon their intended use as well as the risk the device presents to humans. FDA guidance for determination of classification of devices and regulatory control is located at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/default.htm#introduction>.

The sponsor of the device will make the initial determination of whether the device presents a significant risk (SR) or non-significant risk (NSR).

For SR device studies, the sponsor must submit an IDE application to the FDA for approval and the IRB must approve the study before it may commence. SR device studies must be reviewed at a convened IRB meeting. In the event that a University PI is also the sponsor of the IDE, the PI must comply with requirements of sponsor-investigators as described below in section I7-INV.

A NSR device study is one that does not meet the definition of a SR study. However NSR device studies are not necessarily minimal risk studies. For a list of NSR devices, [see http://www.fda.gov/oc/ohrt/irbs/devices.html#risk](http://www.fda.gov/oc/ohrt/irbs/devices.html#risk)

NSR device studies do not require submission to the FDA but these studies must comply with the abbreviated regulations set forth in 21 CFR 812.2(b). Unless otherwise notified these NSR devices are considered to have an approved IDE if the sponsor fulfills the regulatory requirements of 21 CFR 812.2(b). While exempt from FDA approval, NSR studies must receive IRB approval prior to commencing. NSR studies generally require review at a convened IRB meeting but may be approved through the expedited review procedure if the study falls within a designated approvable category and is minimal risk.

The IRB will make the final determination for NSR devices. If the IRB disagrees with the sponsor and designates the device as SR, the IRB will require that the sponsor submit to the FDA for an IDE. The study will not be approved by the IRB until the IDE is obtained or official communication from the FDA indicating its determination of NSR is obtained. The investigator will be informed of the IRB's determination in writing and the investigator must inform the sponsor.

In assessing the risk level of a device, the IRB will consider the following:

1. information contained within the protocol application or investigator's brochure including
 - a. descriptions of the device and its proposed use
 - b. the nature and seriousness of the harm that may result from the use of the device or from procedures required for use of the device (e.g., surgical implants);
2. reports of prior investigations conducted with the device;
3. the proposed investigational plan; and
4. descriptions of subject selection criteria and safety monitoring procedures.

The investigator must provide the following additional materials for the IRB to consider:

- the sponsor's risk assessment and rationale for its determination as NSR and
- the FDA's assessment of the device's risk if such an assessment has been made.

The IRB may choose to consult directly with the FDA.

Requirements for an Abbreviated IDE

When making the determination that a NSR medical device meets the requirements of an abbreviated IDE, the Biomedical IRB Chair or Vice Chair will confirm that all of the following are true:

- The device is not a banned device.
- The sponsor labels the device in accordance with 21 CFR 812.5.
- The sponsor obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval.
- The sponsor ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, consent under 21 CFR 50 and documents it, unless documentation is waived.
- The sponsor complies with the requirements of 21 CFR 812.46 with respect to monitoring investigations.

- The sponsor maintains the records required under 21 CFR 812.140(b) (4) and (5) and makes the reports required under 21 CFR 812.150(b) (1) through (3) and (5) through (10).
- The sponsor ensures that participating investigators maintain the records required by 21 CFR 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7).
- The sponsor complies with the prohibitions in 21 CFR 812.7 against promotion and other practices.

The Chair or Vice Chair may require documentation from the investigator or FDA to confirm that the above criteria have all been satisfied before finalizing her or his determination that a medical device fulfills the requirements for an abbreviated IDE.

Criteria for a Medical Device Exemption

The Chair or Vice Chair of the Biomedical IRB may determine that a medical device fulfills one of five IDE exemption categories.

1. A medical device other than a transitional device, may be considered exempt from §812 if it was in commercial distribution immediately before May 28, 1976 when the device is used or investigated in accordance with the indications in labeling in effect at that time.
2. A medical device other than a transitional device, may be considered exempt from §812 if it was introduced into commercial distribution on or after May 28, 1976 and FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.
3. A diagnostic device may be considered exempt from § 812 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 subject; and
 - is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
4. A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, may be exempt from § 812 if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.
5. A custom device as defined in 21 CFR 812.3(b) may be exempt from § 812 unless the device is being used to determine safety or effectiveness for commercial distribution.

Investigational Device Categories

To assist Medicare (CMS) in determining coverage for such devices, and thereby assisting IRBs in understanding subject economic responsibilities for such devices, the FDA further assigns each device with an FDA-approved IDE into one of two categories:

Category A – Experimental (safety and efficacy not yet established), and

Category B – Investigational; Non-experimental (underlying questions on safety and efficacy have been resolved).

See *Definitions* for complete descriptions of device categories.

I7-IDE4 IDE Research: Investigator Responsibilities

The PI of a device study is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of devices under investigation. An investigator also is responsible for ensuring that informed consent is obtained in accordance with regulatory requirements.

IDE Research: Additional Investigator Responsibilities

Pursuant to 21 CFR 812.110, Subparts E and G

Principal investigators conducting human subjects research involving investigational devices must

1. obtain appropriate approvals (IRB, YNHH, FDA) prior to obtaining consent and enrolling any subjects;
2. make financial disclosures to the sponsor and the IRB;
3. supervise the device use, and ensure that the device is used only with subjects under the investigator's supervision;
4. supply the device to only individuals authorized under the regulations;
5. upon completion or termination of a clinical investigation, or the investigator's part of an investigation, or at the sponsor's request, return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs;
6. permit authorized persons (e.g., IRB staff, FDA staff) to inspect and copy records relating to the investigation;
7. if authorized, permit authorized persons (e.g., IRB staff, FDA staff) to enter and inspect any establishment where devices are held (manufactured, processed, packed, installed, used, or implanted, or where records of results from use of devices are kept);
8. maintain adequate records including:

- a. correspondence with another investigator, an IRB, the sponsor, a monitor, or the FDA;
 - b. records of receipt, use or disposition of a device that relate to the type and quantity of the device, the dates of its receipt, and the batch number or code mark, the names of all persons who received, used, or disposed of each device, why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of;
 - c. each subject's case history and exposure to the device (include the case report forms and supporting data including, for example, the signed and dated consent forms, medical records including progress notes, adverse event reports);
 - d. the protocol and records of any deviations from the protocol; and
 - e. any other records required by the FDA or IRB or relevant to the study;
9. submit reports of unanticipated adverse device effects to the IRB within 48 hours of discovery, in accordance with University policy (see Policy I12F Reporting Adverse Events and Unanticipated Problems); and to the sponsor as soon as possible but within 10 days of becoming aware of the event;
 10. submit a report to the sponsor within 5 days of any withdrawal of IRB approval; and
 11. submit progress reports to the IRB, sponsor, and monitor at least annually.

For additional information on responsibilities in conducting significant risk device investigations investigators should refer to <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm049864.htm>.

I7-INV Investigator-held IND or IDE (Sponsor-Investigator)

Investigators who hold an IND or IDE are required to follow the FDA's requirements for sponsors in addition to those for investigators. Such sponsor-investigators must provide the IRB with documentation from the FDA indicating the IDE number so that the IRB may confirm the validity of the number and FDA approval of the IDE.

I7-INV1 Additional General Requirements for Sponsor-investigator IND Holders

In addition to the responsibilities of investigators, investigators holding an IND assume the responsibilities of sponsors. As the *sponsor*, they are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation, ensuring that the investigation is conducted in accordance with the general investigational plan and protocols contained in the IND, maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug. Additional specific

responsibilities of sponsors can be found in 21 CFR 312 Subpart D (Responsibilities of Sponsors and Investigators).

I7-INV2 Additional General Requirements for Sponsor-investigator IDE Holders

In addition to the responsibilities of investigators, investigators holding an IDE assume the responsibilities of sponsors. In this capacity, they are responsible for selecting qualified investigators and providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, ensuring that IRB review and approval are obtained, submitting an IDE application to FDA, and ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation.. Additional responsibilities of sponsors are described in 21 CFR 812 Subparts B (Application and Administrative Action) and G (Records and Reports).

For additional information on responsibilities as holders of an IDE, sponsor-investigators are advised to refer to

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm049859.htm>.

17-TX-USE Treatment Use of an Investigational or Unlicensed Drug or Device

Clinical investigations may use an investigational drug or device for the treatment or diagnosis of a serious or immediately life-threatening disease or condition in patients for whom no comparable or satisfactory alternative drug, device, or other therapy is available. During the course of drug and device research studies, it may be appropriate to use the drug or device in the treatment of a patient who is not able to enroll in the research, in accordance with a specially developed treatment protocol or treatment IND or IDE (21 CFR 312.34 and 812.36).

The provider in this case is regarded as a treating clinician for the patient and not an investigator for a research participant. The clinician is required to develop and submit a specific protocol application and associated consent document for full IRB review and approval prior to the specifically intended single-patient treatment use of an IND or IDE. The clinician should seek FDA approval for the treatment use of an IND or IDE before requesting IRB review. Treatment may begin 30 days after FDA receives the treatment IND or IDE submission, or on earlier notification by FDA that the treatment use described in the protocol may begin, unless FDA notifies the sponsor in writing earlier than the 30 days that the treatment use may not begin.

I7-TX-USE1 Criteria for Treatment IND or Treatment IDE

FDA will permit an investigational drug or device to be used for treatment under a treatment protocol or treatment IND (or IDE) if the clinician/investigator provides sufficient evidence of safety and effectiveness to support such use, or provides reasonable basis that the drug or device may be effective for its intended use in its intended patient population; or would not expose the patients to whom the

drug is to be administered to an unreasonable and significant additional risk of illness or injury. The clinician/investigator must demonstrate that the criteria listed below are met.

- The drug or device is intended to treat or diagnose a serious or immediately life-threatening disease or condition.
- There is no comparable or satisfactory alternative drug or device or other therapy available to treat (or diagnose) that stage of the disease (or condition) in the intended patient population.
- The drug or device is under investigation in a clinical trial under an IND in effect for the trial (or for the same use under an approved IDE), or all clinical trials have been completed.
- The sponsor of the clinical trial (or investigation) is actively pursuing marketing approval or clearance of the investigational drug or device with due diligence.

To ensure that appropriate safeguards are in place, treatment use of an investigational drug or device is conditioned on the sponsor and clinician/investigator complying with the safeguards of the IND (or IDE) process, including the regulations governing informed consent and prior review and approval by the IRB, and the provisions of 21 CFR 312 (or 21 CFR 812) that include distribution of the drug or device through qualified experts, maintenance of adequate manufacturing facilities, and submission of IND (or IDE) safety reports.

Note: Use of an investigational drug or device under a treatment IND or IDE differs from emergency use. For example, such use under a treatment IND or IDE is subject to all regulations governing use of drugs or devices for research, including the requirement for IRB review and approval before subjects are enrolled.

I7-ER-USE Emergency Use of an Investigational or Unlicensed Drug or Device

Under specific circumstances, the FDA may permit a clinician to use an investigational drug or device in an urgent, life-threatening situation. A patient receiving a test article in an emergency use as defined by FDA regulations may not be considered to be a research subject and is not considered to be involved in research under DHHS regulations and the outcome of such care may not be included in any report of a research activity subject to DHHS regulations. Similarly, VA regulations pertaining to research involving human subjects do not permit data obtained from patients to be classified as human subjects research, nor may the outcome of such care be included in any report of a research activity subject to VA regulations pertaining to research involving human subjects.

I7-ER-USE1 Investigational Drugs or Biologics: FDA Requirements for Emergency Use

The emergency use of an unapproved investigational drug or biologic requires an IND. If the intended subject does not meet the criteria of an existing study protocol, or if an approved study protocol does not exist, the clinician may contact the manufacturer to determine if the drug or biologic may be made available for the emergency use under the company's IND. It may be that the need for an investigational

drug or biologic arises 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 [21 CFR 312.310(d)].

Emergency Use of Drugs or Biologics: Exceptions to Requirements

Specific, proscribed circumstances may result in exceptions to requirements for prior IRB approval and informed consent for emergency use of test articles.

1. Emergency Use Exemption: Requirement for Prior IRB Approval

The emergency use provision in FDA regulations [21 CFR 56.104(c)], exempts the emergency use of test articles from the need to obtain prospective IRB approval. To invoke the exemption for prior IRB review and approval for emergency use of a test article, the three required conditions listed below must exist (21 CFR 56.102(d)).

- The situation is life-threatening*.
- No standard acceptable treatment is available for the situation.
- Insufficient time exists to obtain IRB approval.

*Life-threatening, for the purposes of section 56.102(d), includes the scope of both life-threatening and severely debilitating as follows:

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.

University policy requires that the clinician requesting authorization for emergency use of an investigational drug or biologic provides the IRB Chair (or Vice Chair in the Chair's absence) with information to verify that the three conditions in § 56.102(d) have been met (see above) (i.e., situation is life-threatening, acceptable treatment is lacking, time is insufficient time to obtain IRB approval) and must also agree to the following:

- The clinician will report the emergency use to the IRB within five working days of use.
- Any subsequent use[†] of the test article will be subject to IRB review.

†The IRB may determine that it is 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.

Note: IRB authorization of the specified emergency use of a test article must not be construed as IRB approval.

The University OHRP will use the notification to track the request to ensure that the investigator files a report within the five day time-frame required by the FDA (21 CFR 56.104(c)) and University policy.

2. Emergency Use Exception: Requirement for Informed Consent

Even for an emergency use, the investigator (or clinician) is required to obtain the subject's or her or his legally authorized representative's informed consent. However, due to the peculiarities of emergency use, under certain circumstances FDA allows for an exception to informed consent. For the exception to be invoked, specific conditions must be met [21 CFR 50.23(a)].

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

- The subject (or patient) 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.

Note: If the investigator believes that immediate use of the test article is required to preserve the subject's life, and sufficient time is not available to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and, within five 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. The investigator must notify the IRB within five working days after the use of the test article [21 CFR 50.23(c)].

I7-ER-USE Emergency Use of an Unapproved Medical Device

In general, an unapproved medical device may be used only on human subjects when the device is under clinical investigation and when used by investigators participating in a clinical trial. However, the University recognizes that there may be circumstances under which a health care provider may wish to use an unapproved device to save the life of a patient or to prevent irreversible morbidity when there exists no other alternative therapy.

For investigational devices under an IDE, the IDE regulation permits deviations from the investigational plan without prior approval when necessary to protect the life or physical well-being of a subject in an emergency (21 CFR 812.35(a)). A physician may treat a patient with an unapproved medical device under these conditions:

- The patient has a life-threatening condition that needs immediate treatment.
- No generally acceptable alternative treatment for the condition exists.
- Because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

A physician wishing to use an unapproved device under these conditions must also assess the potential for the patient to benefit from the use of the unapproved device and to have substantial reason to believe that benefits will exist.

In the event that a device is used in circumstances meeting the criteria listed above, the physician should follow as many of the patient protection procedures listed below as possible.

- The treating physician will obtain informed consent from the patient or a legal representative in accordance with University policy, the policy of the treating physician's institution and Nevada state law.
- The treating physician will obtain clearance for the emergency use from the University and the treating physician's institution as specified by their policies.
- The Chair of the University Biomedical IRB will concur with the treating physician's assessment of the situation and benefits.
- The treating physician will obtain an assessment from a physician who is not participating in the study.
- The treating physician will obtain authorization for the emergency use from the IDE sponsor, if an IDE exists for the device.

Reporting requirements for Emergency Use of a Device with an IDE

Prior approval for shipment or emergency use of an investigational device is not required, but within five working days from the time the sponsor holding the IDE learns of the use of the device, the sponsor will report that use to FDA. 21 CFR 812.35(a)(2) and 812.150(a)(4). In the report, the sponsor should provide the following:

- a summary of the conditions constituting the emergency,
- patient outcome information, and
- the patient protection measures that were followed.

Reporting Requirements for Emergency Use of a Device Without an IDE

If no IDE exists for a medical device used in an emergency (as described above), the physician should follow the procedures outlined above and report the emergency use to FDA Center for Devices and Radiological Health or Center for Biologics Evaluation and Research (for emergency use involving biologics).

I7-COM-USE Compassionate Use of an Investigational or Unapproved Device

For devices only, FDA recognizes that there are circumstances in which an investigational device is the only option available for a patient faced with a serious, albeit not life-threatening condition (referred to as "compassionate use"). In these circumstances, FDA uses its regulatory discretion in determining whether such use of an investigational device should occur. Unlike emergency use of an unapproved device, prior FDA approval is required before compassionate use occurs. In order to obtain FDA approval, the sponsor must submit an IDE supplement requesting approval for a protocol deviation under section 21 CFR 812.35(a) in order to treat the patient. (See IRB I7 PR2 Compassionate Use of an Investigational or Unapproved Device.)