UMKC
Office of Research Services

7. Investigational Drugs and Devices in Research

7.1. Policy

7.1.1. Investigational Drug Policy

The UMKC IRB requires investigators to provide a plan to ensure the proper handling of investigational or unlicensed test articles.

All investigational drugs, agents and/or biologics used in human subjects research under the purview of UMKC's IRB shall be stored, handled, and dispensed in compliance with regulations or requirements of the US Food and Drug Administration (FDA), the joint commission as appropriate, Federal, state and other laws and regulations, and the policies and procedures of UMKC. Furthermore, if research is conducted on hospital premises, such research shall be conducted in accordance with applicable hospital and medical staff polices and guidelines.

Protocols involving an investigational drug (IND) or investigational device (IDE) require consideration and satisfaction of the pertinent FDA and DHHS regulations (21 CFR 50).

When the PI is acting as the sponsor of research involving an investigational drug or device, the IRB suggests that the PI review the reporting and record-keeping responsibilities as stated in 21 CFR 312 and 21 CFR 314 (for investigational drugs) or 21 CFR 812 and 21 CFR 814 (for investigational devices).

The PI is responsible for assuring the IRB that investigational drugs and devices are stored in a secure and safe manner and that the storage and safety requirements are consistent with FDA, sponsor, and affiliated research institutions' storage requirements for drugs or devices of the type under study. Whenever possible, the storage of drugs and biologics should be under the supervision of a registered pharmacist and stored in a limited access, locked area. Devices should be stored according to manufacturer's specifications and maintained in a limited access area. Access to the test devices must be limited only to those authorized to use the devices.

The PI is responsible for ensuring that test articles (drugs, biologics, or devices) are controlled so that they are not used outside of a research study. An investigator shall administer the drug or device only to subjects under the PI's personal supervision or under the supervision of a sub-investigator responsible to the PI. The PI shall not supply the investigational drug or device to any person not authorized to receive it.

The protocol for the study should outline the security and storage plan for the test article(s) and indicating, when applicable, that the plan meets the sponsor's storage and security requirements. The plan should include whether or not control will be through a hospital pharmacy and under the supervision of a registered pharmacist or held in a proper and secure storage area by the investigator. The protocol should detail how the test article is used in human subjects, Indicate who may have access to the test article(s) and outline the accountability plan for the test article(s) to ensure that there is no unapproved access to or use of the test article(s).

Protocols involving an IND or IDE will undergo initial and continuing review at a convened meeting that includes at least one physician or pharmacist unless the protocol meets the criteria for expedited review (i.e., all treatment components complete, in follow-up only, data analysis only).

Consent for studies involving an IND and/or IDE will be obtained. FDA regulations allow waiver of consent if research meets the criteria specified in 21 CFR 50.23 or 21 CFR 50.24 or meets the following criteria:

- The clinical investigation involves no more than minimal risk (as defined in 21 CFR 50.3(k) or 56.102(i)) to the subjects;
- The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- The clinical investigation could not practicably be carried out without the waiver or alteration; **and**
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

DHHS regulations allow a waiver of consent if research meets the criteria specified in 45 CFR 46 "waiver of informed consent requirements in certain emergency research," consent is required for all non-emergency research that falls under FDA regulations or involves experimental treatment, tests, or drugs. In addition, the consent form will identify the test article as investigational and will inform participants that the FDA may inspect research records.

Regulations & guidelines: FDA 21 CFR 11; 21 CFR 54; 21 CFR 210; 21 CFR 211; 21 CFR 312; 21 CFR 314; 21 CFR320; 21 CFR 330; 21 CFR 601; 21 CFR807; 21 CFR 812; 21 CFR 814; 21 CFR 820; 21 CFR 860; "IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects; AAHRPP I.5.A.

7.1.2. Definitions

Administer (or "administration" or "administering"): means the direct application of a drug to the body of a patient or research subject by injecting, inhalation, ingestion, or any other means.

Agent(s): are chemical agents that affect the function of living things.

Biologic: a substance made from a living organism or its products and used in the prevention, diagnosis, or treatment of certain health conditions.

Biological products: are a subset of drugs used for the treatment, prevention or cure of disease in humans. FDA regulations and policies have established that biological products include blood-derived products, vaccines, in vivo diagnostic allergenic products, immunoglobulin products, products containing cells or microorganisms, and most protein products. Biological products, like other drugs, can be studied in clinical trials involving human subjects under an IND in accordance with the regulations at 21 CFR 312.

Clinical investigation: means 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 505 of the Federal food, drug, and cosmetic act (the "FDA act") [21 USC. 355] or to, or held for inspection by the food and drug administration ("FDA") as part of an application for a research or marketing permit. [21 CFR 50.3]

Dispense (or dispensing): means the interpretation, evaluation, and implementation of a prescription drug order, including the preparation and delivery of a drug or device to a patient or patient's agent in a suitable container appropriately labeled for subsequent administration to, or use by, a patient. "Dispense" necessarily includes a transfer of possession of a drug or device to the patient or the patient's agent.

Distribute (or distribution): means the delivery of a drug or device other than by administering or dispensing.

Drug: means any substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans, or any substance other than food intended to affect the structure or any function of the body of humans.

Emergency use: is defined as the use of an investigational drug or biological 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. [FDA 21 CFR 56.102(d)]. This is not to be confused with planned emergency research.

Investigational drug (or "investigational new drug"): means a new drug or biological that is used in research. It also includes a biologic used in vitro for diagnostic purposes. The FDA considers the term "investigational new drug" to be synonymous with investigational drug. [FDA 21 CFR 312.2]. However, for purposes of this document, an investigational drug includes the following:

- An approved drug that is being studied for an unapproved or approved use in a controlled, randomized or blinded clinical trial.
- Those new drugs for which the PI or a sponsor has filed an IND application [FDA 21 CFR 312] which are exempt from pre-marketing approval requirements and may be lawfully shipped for use in clinical investigations in human subjects.

A drug that is lawfully marketed in the US that may still be considered investigational and require that an IND be filed if the proposed use of such a drug involves a controlled study aimed towards seeking a significant change in labeling, advertising, route of administration, dosage level, or other factor that affects the risks associated with the use of the product. [FDA 21 CFR 312.3(b)].

Investigational drug application (or "IND"): refers to either an investigational new drug application or to a new drug that is used in clinical investigations. IND is synonymous with "notice of claimed investigational exemption for a new drug." [FDA 21 CFR 312].

Planned emergency research: is the conduct of planned research in life threatening emergencies where the requirement to obtain prospective consent has been waived. [21 CFR 50.24]. The research plan must be approved in advance by the FDA or DHHS and the IRB, and publicly disclosed to the community in which the research will be conducted. This term should not to be confused with emergency use.

Test article: is any drug (including a biological for human use), medical device for human use, human additive, color additive, electronic product, or any other article subject to FDA regulation. [FDA 21 CFR 50.3(j); 21 CFR 56.102(l)].

7.1.3. FDA Exemptions

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

- 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. [FDA 21 CFR 56.104(c)].
- 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 EPA or the food safety and inspection service of the US DOA. [FDA21 CFR 56.104(d)].

7.1.4. IND Requirements

The PI must indicate on the IRB application whether the research involves investigational drugs. If so, the PI must indicate if there is an IND for the research and provide documented assurance from the sponsor that the manufacture and formulation of investigational or unlicensed test articles conform to Federal regulations. Documentation of the IND could be:

- Industry sponsored protocol with IND.
- Letter from FDA.
- Letter from industry sponsor.
- Other document and/or communication verifying the IND.

If the research involves drugs and there is no IND, the PI must provide a rationale why it is not required.

The IRB will review the application and determine:

- Whether there is an IND and if so, whether there is appropriate supporting documentation.
- If the research involves drugs or devices with no IND, and whether the research meets the criteria below.

7.1.4.1. IND Exemption

For drugs, an IND is not necessary if all seven of the following conditions are met:

1. The drug being used in the research is lawfully marketed in the US;
2. The research 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;
3. The research is not intended to support a significant change in the advertising for the product;
4. The research 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;
5. The research is conducted in compliance with the requirements for IRB review and informed consent [FDA 21 CFR parts 56 and 50];
6. The research is conducted in compliance with the requirements concerning the promotion and sale of drugs [FDA 21 CFR 312.7];
7. The research does not intend to invoke 21 CFR 50.24 (exception from informed consent requirements for emergency research).

Note: the following are also exempt from the IND requirements:

- A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND; and
- A drug intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.160.

For clinical investigations involving an in vitro diagnostic biological product, an IND is not necessary if:

- It involves one or more of the following: (a) blood grouping serum, (b)
  - Reagent red blood cells or (c) anti-human globulin;
- It is intended to be used in a diagnostic procedure that confirms the diagnosis
  - Made by another, medically established, diagnostic product or procedure; and
- It is shipped in compliance with 21 CFR 312.160.

7.1.4.2. Responsibilities

This section describes the responsibilities and related responsibilities for handling investigational drugs or unlicensed test articles with respect to pharmacy, inventory control, reporting and documentation.

Regulations & Guidelines: FDA 21 CFR 312.61; 21 CFR 312.62; 21 CFR 312.69; AAHRPP I.5.B.

7.1.4.2.1. Principal Investigator

The PI is responsible for ensuring that the research is conducted according to all regulatory requirements, applicable institution policies, institutional committees, as well as University policies and procedures.

When the PI retains control of investigational drug supplies, the PI is responsible for complying with regulations or requirements of the US food and drug administration (FDA), the joint commission as appropriate, Federal, state and other laws and regulations, and the policies and procedures of the UMKC. Furthermore, if research is conducted on hospital premises, such research shall be conducted in accordance with applicable hospital and medical staff polices and guidelines, including but not limited to the following specific policies.

7.1.4.2.1.1. Drug accountability record

The PI must maintain records of the product's delivery to the study site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product. These records should include dates, quantities, batch/serial numbers, expiration dates, and the unique code numbers assigned to the investigational product(s) and trial subjects. The PI should maintain records that document adequately that the subjects will provide the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

In regard to the "use by each subject", PIs should maintain drug accountability records that document adequately which subject(s) received the drug; when the subject(s) received the drug; the specific dosage the subject(s) received; and any returned amount of the dispensed investigational drug;

7.1.4.2.1.2. Drug storage

Investigational product(s) should be stored as specified by the sponsor and in accordance with applicable regulatory requirement(s). Storage guidelines, include:

- Storage area is large enough for the supply of study drug.
- Storage area can be locked.
- Investigational drug is stored separately from other compounds.
- Non-dispensed drug is stored separately from returned dispensed drug.
    - If the study protocol requires the subject to return the empty investigational drug container or any amount of the unused investigational drug, it is the investigators responsibility to store the returned dispensed investigational drug separately from the non-dispensed investigational drug.
    - It is the responsibility of the PI to deliver the returned dispensed investigational drug to research pharmacy if it is the coordinating and control center for the research drug V. Inventory control procedures are used.
- Any environmental controls are maintained.
- Access is limited to study staff.

7.1.4.2.1.3. Drug Administration

Investigational drugs shall be administered in accordance with any applicable Federal or state laws and regulations and in accordance with any policies or procedures set forth by UMKC. A consent document signed and dated by the subject and the PI must be in place before administering the drug.

Only a person licensed within the state of Missouri and so authorized by their professional scope of practice shall administer an investigational drug to a subject. A PI may designate the responsibility of administering the drug only after the designee has been given and has demonstrated an understanding of basic pharmacologic information about the drug. Investigational drugs are to be administered in accordance with research protocol and in accordance with any other policy pertaining to the administration of investigational drugs.

7.1.4.2.1.4. For Research Involving Investigational New Drugs

The PI will report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug [21 CFR 312 (b)] according to the procedures in the protocol.

The PI will maintain the following:

- Current curriculum vitae ("CV")
- Protocol
- Records of receipt and disposition of drugs
- List of any co-investigators with their CV
- Certification that all physicians, dentists, and/or nurses responsible in the study have appropriate valid licenses for the duration of the investigation, and
- All unexpected adverse effects are reportable; even if the investigator considers that the event is not related to the drug. All unexpected adverse effects shall be reported immediately to the IRB in the manner defined by the protocol and this document.
- IRB letters of approval.

7.1.4.2.1.5. Investigator-Sponsor or Investigator-Initiated Studies

When a PI files an IND or IDE, the PI is considered the sponsor and as such is accountable for all of the FDA regulatory responsibilities and reporting obligations of both the PI and the sponsor, as described in the FDA regulations.

An Individual or group of Individuals or Medical Center is considered a sponsor for an investigation if they hold the IND or IDE. At UMKC these studies are typically called "investigator initiated studies" when they involve the use an investigational drug or device or use an approved drug or device for investigational purposes.

The sponsors' or the investigator as sponsor responsibilities includes the following:

- Selecting qualified investigators
- Providing investigators with the information they need to conduct the investigation properly

- Ensuring proper monitoring of the investigation
- Ensuring that the FDA and any reviewing IRB or all participating investigators are promptly informed of significant new information about an investigation.
- The IRB and RCO will assist investigators holding an IND or IDE on the sponsor regulations.
- The PI shall report all Unanticipated Problem involving risks to subjects or others to the IRB according to the procedures outlined in section 8 and all protocol violations & protocol deviations outlined in section 9. [FDA 21 CFR 312.64].

Regulations & Guidelines: FDA 21 CFR 312.61; AAHRPP III.2.D.

7.1.4.2.2. IRB

The IRB will review the research using the same criteria it would use in considering approval of any research involving an FDA-regulated product. [FDA 21 CFR 56.111].

7.1.5. Emergency Use

7.1.5.1. Definitions

Emergency use: means the use of an investigational drug or biological 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. [FDA 21 CFR 56.102(d)]. The emergency use provision in the FDA regulations [FDA 21 CFR 56.204(c)] is an exemption from prior review and approval by the IRB.

Life threatening: for the purposes of this section, it means both life-threatening and severely debilitating. It includes 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 of 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 at a convened IRB meeting of the IRB infeasible. [FDA 21 CFR 56.102; see also FDA information sheet: emergency use of an investigation drug or biologic].

Severely debilitating: for the purposes of this section, it means diseases or conditions that cause major irreversible morbidity. Examples include blindness, loss of limb, and loss of hearing, paralysis or stroke. [FDA 21 CFR 56.102; see also FDA information sheet: emergency use of an investigation drug or biologic].

7.1.5.2. Emergency Exemption from Prospective IRB Approval

If all conditions described in 21 CFR 56.102(d) exist (i.e., a life threatening situation exists in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval), then the emergency use exemption from prospective IRB approval may be utilized. [FDA 21 CFR 56.104(c)]. The FDA acknowledges 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.

Consent is required unless the conditions for the emergency use exemption are met (see section 7.1.5.3 for details). The IRB must be notified within **5 working days** when an emergency use exemption is used (include a completed **IRB application**). Any subsequent use of the test article at the institution is subject to IRB review. This notification must not be construed as an approval for the emergency use by the IRB. The RCO Director or IRB Chair will review the report to verify that circumstances of the emergency use conformed to FDA regulations.

7.1.5.3. Emergency Waiver of Informed Consent

An exception under FDA regulations permits the emergency use of an investigational drug, device, or biologic without consent where the PI and an Independent physician who is not otherwise participating in the clinical investigation certify in writing all four of the following specific conditions: the subject is confronted by a life-threatening situation necessitating the use of the test article. [FDA 21 CFR 50.23]. Look to see if the following conditions are met:

- 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 legally authorized representative; and
- No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If time is not sufficient to obtain the Independent physician determination before use of the test article, the actions of the PI must be reviewed and evaluated in writing by an Independent physician within 5-6 working days. The IRB must be notified within 5 working days when an emergency waiver is used. This notification must not be construed as an approval for the emergency waiver by the IRB. The IRB Chair (or designee) will review the report to verify that circumstances of the emergency waiver conformed to FDA regulations.

7.1.6. Expanded Access of Investigational Drugs

FDA regulations allow certain Individuals not enrolled in clinical trials to obtain expanded access to investigational drugs, agents, or biologics through the following methods:

7.1.6.1. Compassionate Use: the term "compassionate use" is erroneously used to refer to the provision of investigational drugs outside of an ongoing clinical trial to a limited number of patients who are desperately ill and for whom no standard alternative therapies are available. The term "compassionate use" does not, however, appear in FDA or DHHS regulations. It is preferable, instead, to use the names of the specific access programs when discussing the use of investigational articles outside of formal clinical trials.

7.1.6.2. Group C Treatment Investigational New Drug: a means for the distribution of investigational drugs, agents, or biologics to oncologists for the treatment of cancer under protocols outside controlled clinical trials. Group C drugs, agents, or biologics usually have shown evidence of relative and reproducible efficacy in a specific tumor type. Although the FDA typically grants a waiver for most drugs used in group C treatment IND protocols, UMKC IRB requires prospective IRB review and approval.

7.1.6.3. Open-label Protocol: a study designed to obtain additional safety data, typically done when the controlled trial has ended and treatment continues. The purpose of such a study is to allow subjects to continue to receive the benefits of the investigational drug, agent, or biologic until marketing approval is obtained. Prospective IRB review and approval is required.

7.1.6.4. Parallel Track: a method approved by the FDA that expands the availability of investigational drugs, agents, or biologics as quickly as possible to persons with aids and other HIV-related diseases. These drugs, agents or biologics are utilized in separate protocols that "parallel" the controlled clinical trials and are essential to establish the safety and effectiveness of these new drugs, agents, or biologics. Although the secretary of DHHS may, on a protocol-by-protocol basis, waive the provisions of 45 CFR part 46 where adequate protections are provided through other mechanisms, prospective IRB review and approval is required by the UMKC IRB.

7.1.6.5. Treatment IND or Biologics: a mechanism for providing eligible subjects with investigational drugs (as early in the drug development process as possible) for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. The FDA defines an immediately life-threatening disease as 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. The FDA will permit an investigational drug to be used under a treatment IND after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks. Prospective IRB review and approval is required.

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

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

The FDA identifies two special considerations when a patient is to be treated under a treatment IND:

1. **Consent**: consent is especially important in treatment use situations because the subjects are desperately ill and particularly vulnerable. They will be receiving medications which have not

been proven either safe or effective in a clinical setting. Both the setting and their desperation may work against their ability to make an informed assessment of the risk involved. Therefore, the IRB should ensure that potential subjects are fully aware of the risks involved in participation.

2. **Charging for treatment IND(s)**. The FDA permits charging for the drug, agent, or biologic when used in a treatment IND. Therefore, the IRB committee should pay particular attention to treatment IND(s) in which the subjects will be charged for the cost of the drugs. If subjects will be charged for use of the test article, economically disadvantaged persons will likely be excluded from participation. Charging for participation may preclude economically disadvantaged persons as a class from receiving access to test articles. The IRB should balance this interest against the possibility that unless the sponsor can charge for the drug, it will not be available for treatment use until it receives full FDA approval.

7.1.6.6. Single-patient Use: the use of an investigational drug outside of a controlled clinical trial for a patient, usually in a desperate situation, who is unresponsive to other therapies or in a situation where no approved or generally recognized treatment is available. There is usually little evidence that the proposed therapy is useful, but may be plausible on theoretical grounds or anecdotes of success. Access to investigational drugs for use by a single, identified patient may be gained either through the sponsor under a treatment protocol, or through the FDA, by first obtaining the drug from the sponsor and then submitting a treatment IND to the FDA requesting authorization to use the investigational drug for treatment use. Prospective IRB review and approval is required (see 5 above).

7.1.6.7. Emergency IND: the emergency use of an unapproved investigational drug, agent, or biologic requires an emergency IND. The FDA has established mechanisms and Guidance for obtaining an emergency IND for the use of investigational drugs, agents, or biologics.

Regulations & Guidelines: FDA 21 CFR 312.7(d).

7.1.7. Emergency Waiver of IND

FDA regulations at 21 CFR 312.34, 312.35, and 312.36 address the need for an investigational drug to be used in an emergency situation that does not allow time for submission of an IND. The FDA may authorize shipment of the drug for a specific use in such a circumstance in advance of submission of an IND. Prospective IRB review is required unless the conditions for exemption are met (FDA 21 CFR 56.104(c) and 56.102(d)). Informed consent is required unless the conditions for exemption are met (21 CFR 50.23). All applicable regulations must be met including those at 21 CFR parts 50 and 56, and 21 CFR 312.34 and 312.35.

7.1.8. Waiver of Informed Consent for Planned Emergency Research

The conduct of planned research in life-threatening emergencies where the requirement to obtain prospective consent has been waived is covered by 21 CFR 50.24. The research plan must be approved in advance by the FDA or DHHS and the IRB, and publicly disclosed to the community in which the research will be conducted. Such studies are not allowed under the regulations covering the emergency use of a test article in a life-threatening situation. [21 CFR 56.104(c)].

Investigators should be aware that such planned emergency research involves an extensive approval process that involves, among other requirements, consultation with representatives of the communities in which the research will be conducted and from which participants will be drawn, public disclosure to such communities of plans for the research and its risks and expected benefits, and establishment of an Independent data monitoring committee to exercise oversight of the research. In view of the extensive and stringent requirements for such research, the IRB expects investigators who wish to use the planned emergency exception to the consent requirement to consult with the IRB staff prior to submission of the protocol to the IRB for review.

7.1.8.1. For Research Subject to FDA Regulations

The IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

- The research activity is subject to regulations codified by the FDA at title 21 CFR part 50 and will be carried out under an FDA IND or an FDA IDE.
- The application clearly identifies the protocols that will include subjects who are unable to consent.
- The research subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which might include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.
- Obtaining consent is not feasible because:
    - The subjects will not be able to give their consent as a result of their medical condition.
    - The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible.
    - There is no reasonable way to identify prospectively the Individuals likely to become eligible for participation in the clinical investigation.
- Participation in the research holds out the prospect of direct benefit to the subject because:
    - Subjects are facing a life-threatening situation that necessitates intervention.

  - Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence supported the potential for the intervention to provide a direct benefit to the Individual subjects.
  - Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.
- The clinical investigation cannot practicably be carried out without the waiver.
- The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent.
- The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.
- The IRB has reviewed and approved consent procedures and a consent document consistent with 21 CFR 50.25. These procedures and the consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documentation is feasible.
- The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation.
- Additional protections of the rights and welfare of the subjects will be provided, including, at least:
  - Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn.
  - Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits.
  - Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results.
  - Establishment of an Independent data monitoring committee to exercise oversight of the clinical investigation.
  - If obtaining consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a

legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

- Procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the consent document.
- There is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she might discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible.
- If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.
- The protocol is performed under a separate IND or IDE that clearly identified such protocols as protocols that may include subjects who are unable to consent.
- The submission of those protocols in a separate IND or IDE is required even if an IND for the same drug product or an IDE for the same device already exists.
- If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation.

7.1.8.2. Research not Subject to FDA Regulations

The IRB finds, documents, and reports to DHHS that the following conditions have been met relative to the research:

- The IRB found and documented that the research is not subject to regulations codified by the FDA at title 21 CFR part 50.
- The research subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

- Obtaining consent is not feasible because:
    - The subjects are not able to give their consent as a result of their medical condition.
    - The intervention involved in the research is administered before consent from the subjects' legally authorized representative is feasible.
    - There is no reasonable way to identify prospectively the Individuals likely to become eligible for participation in the research.
- Participation in the research held out the prospect of direct benefit to the subjects because:
    - Subjects are facing a life-threatening situation that necessitated intervention.
    - Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence supported the potential for the intervention to provide a direct benefit to the Individual subjects.
    - The risks associated with the research are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.
- The research could not practicably be carried out without the waiver.
- The proposed research protocol defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact representatives and make this information available to the IRB at the time of continuing review.
- The IRB has reviewed and approved consent procedures and a consent document in accord with 45 CFR 46.116 and 46.117.
    - These procedures and the consent document are to be used with subjects or their legally authorized representative in situations where use of such procedures and documentation is feasible.
    - The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the research consistent with the paragraph of this waiver.
- Additional protections of the rights and welfare of the subjects are provided, including, at least:
    - Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the research is conducted and from which the subjects are drawn.
    - Public disclosure to the communities in which the research is conducted and from which the subjects are drawn, prior to initiation of the research, of plans for the research and its risks and expected benefits.

- Public disclosure of sufficient information following completion of the research to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results.
- Establishment of an Independent data monitoring committee to exercise oversight of the research.
- If obtaining consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the research.
    - The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.
    - Procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remained incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the research, the details of the research and other information contained in the consent document.
    - There is a procedure to inform the subject, or if the subject remained incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
    - If a legally authorized representative or family member is told about the research and the subject's condition improves, the subject is also informed as soon as feasible.
    - If a subject is entered into research with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the research is provided to the subject's legally authorized representative or family member, if feasible.
    - For the purposes of this waiver "family member" means any one of the following legally competent persons: spouses; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any Individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

7.1.9. Investigational Devices in Research

7.1.9.1. Policy

Use of an investigational device in a clinical trial to obtain safety and effectiveness data must be conducted according to FDA's ide regulations found at 21 CFR part 812 and other applicable FDA regulations.

The following procedures describe the use of investigational devices in research under the auspices of the institution's IRB.

Regulations & Guidelines: FDA 21 CFR 812.00; 21 CFR 812.110; 21 CFR 812.140(a); AAHRPP I.5.B.

7.1.9.2. Definitions

Adverse device effect (or "ADE"): is any ae or adverse effect caused by or associated with the use of a device that is unanticipated and has not been included in the protocol or the investigator's brochure.

Device (or medical device): is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related test article, including a component part, or accessory which is (a) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in humans, or (b) intended to affect the structure or any function of the body, and which does not achieve any of its primary intended purposes through chemical action within or on the body, and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

Humanitarian use device ("HUD"): the FDA defines HUD as a device intended to benefit patients by treating or diagnosing a disease that affects fewer than 4,000 Individuals in the US per year. [FDA 21 CFR 814.3(n)].

Investigational device: as defined by the FDA, an investigational device is a device that is the object of a clinical study designed to evaluate the safety or effectiveness of the device. [21 CFR 812.3(g)]. Investigational devices include transitional devices [21 CFR 812.3(r)] that are objects of investigations. However, for the purposes of this document, an investigational device may be an approved device that is being studied for an unapproved use or efficacy.

Investigational device exemption ("IDE"): is an FDA-approval of the application for an exemption that permits an unmarked device to be shipped for the purpose of doing research on the device. [See 21 CFR 812.1 and 812.2 for the scope and applicability].

Non-significant risk device (or NSR device): is an investigational device other than a significant risk device.

Significant risk device ("SR device"): is an investigational device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a human subject;
- 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 human subject;
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or

- Otherwise preventing impairment of human health and presented a potential for serious risk to the health, safety, or welfare or a human subject.

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

7.1.9.3. IDE Requirements

The PI must indicate in the IRB application whether the research involves investigational drugs or devices. If so, the PI must indicate if there is an IND/IDE for the research and provide documented assurance from the sponsor that the manufacture and formulation of investigational or unlicensed test articles conform to Federal regulations. Documentation of the IND/IDE could be a:

- Industry sponsored protocol with IND/IDE;
- Letter from the FDA;
- Letter from industry sponsor; or
- Other document and/or communication verifying the IND/IDE.

For investigational devices, NSR device studies follow abbreviated IDE requirements and do not have to have an IDE application approved by the FDA. If a sponsor has identified a study as non-significant risk, then the PI must provide an explanation of the determination. If the FDA has determined that the study is non-significant risk, documentation of that determination must be provided.

If the research involves drugs or devices and there is no IND/IDE, the PI must provide a rationale why it is not required.

The IRB will review the application and determine:

- Whether there is an IND/IDE and if so, whether there is appropriate supporting documentation; and
- If the research involves drugs or devices with no IND/IDE, and whether the research meets the criteria below.

7.1.9.4. Exempted IDE Investigations

For devices, an IDE is not necessary if:

- 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;
- 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;

- The research involves 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 subject; and
    - Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure;
- 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;
- The research involves a device intended solely for veterinary use;
- The research involves a device shipped solely for research on/or with laboratory animals and labeled in accordance with 21 CFR 812.5(c); and/or
- 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.

7.1.9.5. Responsibilities

7.1.9.5.1. Principal Investigator ("PI")

The PI is responsible for ensuring that the research is conducted according to all regulatory guidelines, and institutional policies and procedures. The PI must obtain approval from the IRB before initiating any research activities or enrolling any subjects in the research.

The PI proposing the device research will be required to provide a plan – to be evaluated by the IRB - that includes storage, security, and dispensing of the device. Elements of a sound control plan include the following:

Storage: all devices received for a study must be stored in a locked environment under secure control with limited access. The area must be within an area of PI's control. 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.

Reporting: the PI shall report all Unanticipated Problems involving risk to subjects or others to the IRB according to the procedures outlined in section 8.

New device requirements: for research involving investigational new device:

- If a device is considered a NSR device by the PI or sponsor, but after review the IRB determines the device to have significant risk, upon receipt of written notice the PI is responsible for notifying the sponsor of the IRB determination. The PI must provide the IRB with confirmation of this action.
- If the PI is storing the devices, he/she must maintain a log indicating the identification/serial number of the device, name of subject, date dispensed, by whom it was dispensed, and amount remaining.
- The PI will maintain the following:
    - Current curriculum vitae ("CV");
    - Protocol of the study;
    - Records of receipt and disposition of devices;
    - List of any co-investigators with their CV;
    - All adverse device effects are reportable;
    - IRB letters of approval;
    - Device training.
- Logs:
    - The **device accountability log** must be completed regarding the receipt, use and/or dispensing of the device and the disposition of remaining devices at the conclusion of the investigation; and
    - After use, the PI must maintain a log regarding the receipt, use and/or re-dispensing of the device and the disposition of remaining devices at the conclusion of the investigation
- **Reporting**: the PI will submit to the sponsor and to the IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

Investigator-sponsor or investigator-initiated studies: when a PI files an IND or IDE, the PI is considered the sponsor and as such is accountable for all of the FDA regulatory responsibilities and reporting obligations of both the PI and the sponsor, as described in the FDA regulations.

An Individual or group of Individuals or Medical Center is considered a sponsor for an investigation if they hold the IND or IDE. At UMKC these studies are typically called "Investigator initiated studies" when they involve the use an investigational drug or device or use an approved drug or device for investigational purposes.

The sponsors' or the investigator as sponsor responsibilities includes the following:

- Selecting qualified investigators;
- Providing investigators with the information they need to conduct the investigation properly;
- Ensuring proper monitoring of the investigation; and

- Ensuring that the FDA and (for devices) any reviewing IRB(s) or (for drugs) all participating investigators are promptly informed of significant new information about an investigation.

The IRB and RCO will assist investigators holding an IND or IDE on the sponsor regulations.

7.1.9.5.2. IRB

The IRB will review the research involving investigational devices in accordance with the following requirements and the same criteria it would use in considering approval of any research involving an FDA-regulated product [21 CFR 56.111].

- Control plan;
- Unless the FDA has already made a risk determination for the study, the IRB will review device studies and determine if the device represents significant or non-significant risk and report the findings to the PI in writing. The IRB will consider the risks and benefits of the medical device compared to the risks and benefits of alternative devices or procedures. NSR device studies do not require submission of an IDE application but must be conducted in accordance with the abbreviated requirements of IDE regulations. If the study that has been submitted as non-significant risk is considered SR, the IRB may approve the study, but the study cannot begin until an IDE is obtained;
- The IRB will not review protocols involving SR devices under expedited review;
- The IRB will document in the minutes and provide written documentation to the PI of the rationale for determining whether a device is classified as NSR device/SR device; and
- If the FDA has already made the SR device or NSR device determination for the study, the agency's determination is final and the IRB does not need to make a risk determination.

7.1.9.6. Emergency Use of Unapproved Medical Devices

An unapproved medical device is defined as a device that is used for a purpose or condition for which the device requires, but does not have, an approved application for pre-market approval under section 515 of the FDA act [21 USC. 360(e)]. An unapproved device may be used in human subjects only if it is approved for clinical testing under an approved application for an investigational device exemption (IDE) under section 520(g) of the act [21 USC. 360(j)(g)] and 21 CFR part 812. Medical devices that have not received marketing clearance under section 510(k) of the FD&C act are also considered unapproved devices which require an IDE.

The FDA recognizes that emergencies arise where an unapproved device may offer the only possible life-saving alternative, but an IDE for the device does not exist, or the proposed use is not approved under an existing IDE, or the investigator/physician or institution is not approved under the IDE. Using its enforcement discretion, FDA has not objected if a physician chooses to use an unapproved device in such an emergency, provided that the investigator/physician later justifies to FDA that an emergency actually existed:

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

FDA expects the investigator/physician to determine whether these criteria have been met, to assess the potential for benefits from the unapproved use of the device, and to have substantial reason to believe that benefits will exist. The investigator/physician may not conclude that an "emergency" exists in advance of the time when treatment may be needed based solely on the expectation that IDE approval procedures may require more time than is available.

Investigator/physicians should be aware that FDA expects them to exercise reasonable foresight with respect to potential emergencies, and to make appropriate arrangements under the IDE procedures far enough in advance to avoid creating a situation in which such arrangements are impracticable.

In the event that a device is to be used in circumstances meeting the criteria listed above, the device developer should notify the Center for Devices and Radiological Health ("CDRH"), program operation staff by telephone (800-638-2041) immediately after shipment is made. [Note: an unapproved device may not be shipped in anticipation of an emergency.] Nights and weekends, contact the FDA Office of Emergency Operations (HFA-615) 301-443-1240.

The investigator/physician is required to follow the subject protection procedures as listed below:

- Obtain an Independent assessment by an uninvolved physician;
- Obtain informed consent from the patient or a legal representative;
- Notify the IRB; and
- Obtain authorization from the IDE holder, if an approved IDE for the device exists.

After an unapproved device is used in an emergency, the investigator/physician must:

- Report to the IRB within five days [FDA 21 CFR 56.104(c)] and otherwise comply with provisions of the IRB regulations [FDA 21 CFR part 56];
- Evaluate the likelihood of a similar need for the device occurring again, and if future use is likely, immediately initiate efforts to obtain IRB approval and an approved IDE for the device's subsequent use; and
- If an IDE for the use does exist, notify the sponsor of the emergency use, or if an IDE does not exist, notify FDA of the emergency use (CDRH program operation staff 800-638-2041) and provide FDA with a written summary of the conditions constituting the emergency, subject protection measures, and results.

Subsequent emergency use of the device may not occur unless the investigator/physician or another person obtains approval of an IDE for the device and its use. If an IDE application for subsequent use has been filed with FDA and FDA disapproves the IDE application, the device may not be used even if the

circumstances constituting an emergency exist. Developers of devices that could be used in emergencies should anticipate the likelihood of emergency use and should obtain an approved IDE for such uses.

An exception under FDA regulations at 21 CFR 50.23 permits the emergency use of an investigational drug, device, or biologic without 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:

- The subject is confronted by a life-threatening situation necessitating the use of the test article;
- 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 legally authorized representative; and
- No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If time is not sufficient to obtain the Independent physician determination before use of the test article, the actions of the investigator must be reviewed and evaluated in writing by an Independent physician within 5-6 working days. The IRB must be notified within 5 working days when an emergency waiver is used. This notification must not be construed as an approval for the emergency waiver by the IRB. The RCO Director or IRB Chair will review the report to verify that circumstances of the emergency waiver conformed to FDA regulations.

Regulations & Guidelines: FDA 21 CFR 50.23; 21 CFR 50.24; 21 CFR 50.25(d); 21 CFR 56.102(d); 21 CFR 56.104(c); FDA Information Sheets: Emergency Use of an Investigative Drug or Biologics; Emergency Use of Unapproved Medical Devices; AAHRPP I.5.C.

7.1.9.7. Humanitarian Use Devices (HUD)

Treatment with a HUD is subject to initial convened IRB review [FDA 21 CFR 814.124]. At the time of initial review the determination may be that continuing review meets criteria for expedited review.

If a physician in an emergency situation determines that IRB approval cannot be obtained in time to prevent serious harm or death to a patient, a (HUD) may be administered without prior IRB approval. In this instance the investigator is required to provide written notification of the use to the IRB within five days after use of the device. The IRB requires that written notification include identification (specification without identifiers) of the patient, the date on which the device was used, and the reason for the use. It is the responsibility of the investigator to notify the FDA if the IRB were ever to withdraw approval for use of a HUD. The FDA should be notified within five days of notification of the withdrawal of approval. Investigators are reminded that humanitarian device exemptions are for clinical use only and HUD(s) can be used only for purposes outlined in the approved IRB application.

Regulations & Guidelines: FDA 21 CFR 20; 21 CFR 814.

Approved by: Lawrence Dreyfus, PhD
Name of University Institutional Official

_____
Signature of University Institutional Official Date