



Institutional Review Board

University of Missouri-Columbia

Standard Operating Procedure

Investigational, Compassionate, Emergency, and
Humanitarian Uses

Investigational, Compassionate, Emergency, and Humanitarian Uses

Effective Date: January 21, 2019
Original Approval Date: January 21, 2019
Revision Date: July 12, 2019
January 21, 2020
March 1, 2020
June 15, 2021
July 20, 2021
June 10, 2022
July 15, 2022
November 18, 2022
May 8, 2023

Michele Kennett

Approved By: Michele Kennett, JD, MSN, LLM
Associate Vice Chancellor for Research

1.0 Purpose

The purpose of this policy is to describe the requirements for studies involving investigational products/substances both FDA regulated and non-FDA regulated, and to describe the requirements for compassionate (expanded access) use, emergency use, and humanitarian device use. The policy specifically covers the following:

- A. Clinical investigations involving investigational FDA regulated test articles
 - i. Drugs/Biologics
 - ii. Medical Devices
- B. Human subject research involving non-FDA regulated products/substances
 - i. Non-FDA Oversight Determination
 - ii. Dietary Supplements, Cosmetics, Food, Other Substance/Product/Item
 - iii. Dosing, Preparation, Administration, and Compounding
 - iv. Accountability, Space, Storage, and Personnel
- C. Humanitarian Use Devices (HUD)
- D. Compassionate/Expanded Access Use
 - i. Drugs/Biologics

- ii. Medical Devices
- E. Emergency Use of a Test Article
 - i. Drugs/Biologics
 - ii. Medical Devices

2.0 Scope

The SOP applies to all human subject research and clinical investigations falling under the purview of the MU Institutional Review Board.

3.0 Policy/Procedure

The use of any investigational product/substance in research or a clinical investigation must comply with applicable regulations and policies.

The Food and Drug Administration (FDA) regulates clinical investigations conducted on drugs, biologics, devices, diagnostics, infant formulas and, in some cases, dietary supplements, cosmetics, and food additives, hereinafter referred to as "FDA regulated test articles." All such investigations must be conducted in accordance with FDA requirements for informed consent and IRB review, regardless of funding source or sponsor.

When an FDA regulated test article is used in a clinical investigation and/or funded by another federal agency, more than one set of regulations may apply. For example, clinical trials involving FDA regulated test articles that are supported by the U.S. Department of Health and Human Services (DHHS), (e.g., the National Institutes of Health (NIH)) fall under the jurisdiction of both the FDA and the DHHS Office for Human Research Protections (OHRP). Such trials must comply with both FDA and DHHS human subject regulations.

The DHHS regulations include specific additional protections for pregnant women, human fetuses, and neonates (Subpart B); prisoners (Subpart C); and children (Subpart D). In April 2004, FDA issued revised regulations to protect children in research (21 CFR 50 Subpart D).

In addition to regulations governing human subject protection, the FDA also has regulations governing the investigational use of drugs and biological drugs (21 CFR 312 and 21 CFR 314) and devices (21 CFR 812 and 21 CFR 814), and regulations governing the emergency use of investigational test articles (21 CFR 56.104(c)).

For research involving investigational products/substances not regulated by the FDA, the DHHS regulations will apply. Additional institutional requirements must be met and are outlined in this policy.

A. Clinical Investigations Involving Investigational FDA Regulated Test Articles

New medical products that have not yet been approved for marketing by the FDA require a special status so they can be legally shipped for the purpose of conducting clinical investigations to establish safety and efficacy.

Drugs (21 CFR 312 and 21 CFR 314)

IND refers to an Investigational New Drug application. ***Investigational New Drug*** means a new drug or biological drug used in a clinical investigation. An investigational drug must have an IND before it can be shipped, unless one of the exemptions outlined in 21 CFR 312.2 is met. (See [FDA Investigational New Drug \(IND\) Application](#))

312.2 (b) Exemptions:

- (1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:
 - (i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
 - (ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;
 - (iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
 - (iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and
 - (v) The investigation is conducted in compliance with the requirements of §312.7.
- (2) (i) A clinical investigation involving an in vitro diagnostic biological product listed in paragraph (b)(2)(ii) of this section is exempt from the requirements of this part if (a) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and (b) it is shipped in compliance with §312.160.
 - (ii) In accordance with paragraph (b)(2)(i) of this section, the following products are exempt from the requirements of this part: (a) blood grouping serum; (b) reagent red blood cells; and (c) anti-human globulin.
- (3) A drug intended solely for tests in vitro or in laboratory research animals is exempt from the requirements of this part if shipped in accordance with §312.160.
- (4) FDA will not accept an application for an investigation that is exempt under the provisions of paragraph (b)(1) of this section.
- (5) A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.
- (6) A clinical investigation involving an exception from informed consent under §50.24 of this chapter is not exempt from the requirements of this part.

An IND is required for experimental drugs if the drugs are used for the purpose of developing information about their safety or efficacy. Approved, marketed drugs may also require an IND if the proposed use in research is different from its previously FDA-approved use or administered by an unapproved route or method of delivery or an altered dosage.

Determining When Non-Drug Products must be Regulated as a Drug:

FDA published guidance for when human research studies can be conducted without an IND. The guidance is found here:

<https://www.fda.gov/downloads/drugs/guidances/ucm229175.pdf>

Certain products, such as cosmetics, food, and dietary supplements may require an IND if they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. The FDA guidance provides information to assist with determining if an IND is required. The investigator should consult the FDA if the intended use is unclear. The IRB will make the final determination if the FDA is not consulted. The IRB may also require the investigator consult with the FDA in these cases and upload documentation to eCompliance.

IND Determination:

The sponsor and/or sponsor-investigator will need to determine if an IND is necessary. This decision will be confirmed by the IRB. If an investigator and/or sponsor consulted with the FDA, all communications with the FDA and the FDA documentation must be uploaded to their IRB submission.

- a. If it is determined an IND is not required, the investigator may proceed with IRB approval. Determinations will be documented in the reviewer checklists and/or minutes.
- b. Prior to full IRB approval if an IND is required, the IRB office will ensure there is valid documentation of the IND (copy of letter from the FDA, FDA application, or IND number included in the protocol from the sponsor). The IRB will utilize the 30 day FDA response time to determine when the study can be opened to enrollment. If a clinical hold is placed by the FDA, the investigator must notify the IRB and enrollment will not be allowed until FDA review and approval is received.

Investigational Pharmacy:

Investigators may be required to use the investigational pharmacy for the control and accountability of research related drugs. Investigators, who arrange with the investigational pharmacy to be exempt from this requirement or are not within the hospital system, are required to submit a plan for drug accountability and storage to the IRB. Approval from the IDS pharmacist is documented in eCompliance for each drug study under their purview.

Medical Devices (21 CFR 812 and 21 CFR 814)

An approved **Investigational Device Exemption** (IDE) permits a device not approved by the FDA to be shipped to conduct clinical investigations of that device. Not all investigational devices need an IDE, if they satisfy the FDA criteria for non-significant risk devices or are determined to be Exempt (see [Device Exemptions](#) below).

Investigators within MU Health will need to work with the Value Analysis Team

(VAT) as well as other offices as applicable to ensure MU Health policies are being followed as they apply to investigational medical devices.

Significant Risk (SR) Device vs. Non-Significant Risk (NSR) Device Determinations:

The sponsor and/or sponsor-investigator makes the initial determination of SR or NSR for the device. However, the IRB will make the final determination for NSR devices. If the IRB disagrees with the NSR device determination and designates the device as SR, the sponsor will be required to submit to the FDA for an IDE. The study will not be fully approved by the IRB until the IDE is obtained. The investigator will be informed of the IRB's determination in writing and the investigator must inform the sponsor. The IRB will utilize the 30 day FDA response time to determine when the study can be opened to enrollment. If a clinical hold is placed by the FDA, the investigator must notify the IRB and enrollment will not be allowed until FDA review and approval is received.

(See FDA Information Sheet on Significant Risk (SR) and Non-Significant Risk (NSR) Medical Device Studies)

Risk Assessment:

In assessing the risk level of a device, the IRB will consider information such as a description of the device and its proposed use, nature 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, reports of prior investigations conducted with the device, the proposed investigational plan, a description of subject selection criteria and monitoring procedures. The IRB should be provided with the sponsor's risk assessment and rationale for its determination as NSR. The sponsor must provide the IRB with the FDA's assessment of the device's risk if such an assessment has been made. The IRB may also choose to consult with the FDA.

FDA considers a device to have an IDE (without the FDA granting the IDE) when all of the following are TRUE: (21 CFR 812.2(b)(1))

- The device is not a significant risk device;
- The device is not a banned device;
- The sponsor labels the device in accordance with §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, informed consent under part 50 and documents it, unless documentation is waived by an IRB under §56.109(c);
- The sponsor complies with the requirements of §812.46 with respect to

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

Device Exemptions:

The investigator will need to determine if the device is exempt. This decision will be confirmed by the IRB. If an investigator and/or sponsor consulted with the FDA, the FDA documentation must be uploaded to their IRB submission. No IDE is required for exempt devices.

A device is exempt from the requirements of an IDE when it falls into one or more of the following categories:

- (1) A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
- (2) A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.
- (3) *A diagnostic device, if the sponsor complies with applicable requirements in §809.10(c) and if the testing:
 - Is noninvasive,
 - Does not require an invasive sampling procedure that presents significant risk,
 - Does not by design or intention introduce energy into a subject, and
 - Is not used as a diagnostic procedure without confirmation 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, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.
- (5) A device intended solely for veterinary use.
- (6) A device shipped solely for research on or with laboratory animals and labeled in accordance with §812.5(c).
- (7) A custom device as defined in §812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

IRB Review of In Vitro Diagnostic Devices and Left Over De-Identified Biospecimens

*When medical device research involves in vitro diagnostics and de-identified tissue specimens, the FDA defines the unidentified tissue specimens as human subjects, and IRB expedited review if required. See the FDA Guidance on “Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable”. The FDA allows a waiver of consent if certain conditions are met.

<https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071265.pdf>

IRB Review of FDA-Regulated Test Articles:

With only a few exceptions, most clinical research being done on FDA-regulated test articles with either an IND or IDE will need initial and continuing review at a convened IRB meeting. (One exception is IRB continuing review of HUD submissions). (See IRB Review of a HUD below)

Research involving FDA-regulated test articles will be fully approved *only* after the IRB:

- Has received documentation that the research will be conducted under an applicable IND or IDE; or
- Has formally determined that satisfactory justification has been provided by the investigator as to why an IND or IDE is not required; or
- Has formally determined and documented that the proposed use of any unapproved device satisfies the FDA criteria for non-significant risk devices.

The IRB will use the guidance provided by 21 CFR 312.2(b) and 21 CFR 812.2(b) in determining if an IND or IDE is required.

Investigators

Under FDA regulations and guidance, investigators (and investigator-sponsors) are responsible for the conduct of the study and for leading the team of individuals conducting the study. Their responsibilities include the following:

- Ensuring informed consent of each subject is obtained
- Ensuring the investigation is conducted according to the investigational plan
- Personally conducting or supervising the investigation
- Protecting the rights, safety, and welfare of participants
- Preparing and maintaining, adequate, current, and complete case histories or records
- Retaining records for two years following the date the marketing application is approved or withdrawn
- Furnishing the required reports to the sponsor, including reports of adverse events and study completion
- Providing timely reports to the IRB, including reports of changes in the research activity needed to avoid immediate hazards to participants or other unanticipated problems involving risks to participants or others, including adverse events to the extent required by the IRB

SOP – Investigational, Compassionate, Emergency, and Humanitarian Uses

Page 8 of 22

- Ensuring changes are not implemented without prospective IRB approval, unless required to eliminate immediate hazard to participants
- Complying with the requirements of the Controlled Substances Act
- Complying with all FDA test article requirements
- Adequately maintaining control of test articles, including appropriate tracking documentation for test articles to the extent that such control and documentation are not centrally administered
- Supervising the use and disposition of the test article
- Disclosing relevant financial information
- Ensuring that all associates, colleagues, and employees assisting in the conduct of the investigation(s) are informed about their obligations in meeting the above commitments.

Sponsors:

The sponsor takes responsibility for initiating the clinical investigation and holding the IND or IDE but does not usually conduct the investigation. Although the sponsor is usually a pharmaceutical, biotech, or medical device company, an individual or group of individuals or medical center can also be considered a sponsor for an investigation. The sponsors' responsibilities include 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 (for devices) any reviewing IRBs or (for drugs) all participating investigators are promptly informed of significant new information about an investigation.

Investigator-Sponsors

In reviewing research involving FDA regulated articles, the IRB determines if the study involves an investigator-sponsor. If so, investigators must meet sponsor responsibilities including reporting requirements to the FDA, (as well as the investigator responsibilities), and are his/her responsibility as required by this Section.

1. Investigator-sponsors who submit protocols to the IRB involving FDA test articles must include all supporting FDA documentation for their IND or IDE and any other required approvals for applying for an IND or IDE. Additionally, if the IND or IDE product will be manufactured at this institution, the Principal Investigator must submit documentation that:
 - The product preparation and manufacture meets the standards for current Good Manufacturing Practice (GMP), or any modification to those standards approved by the FDA in issuing the IND or IDE.
 - The GMP plan has been approved by the applicable Institutional Official.
2. A plan for the IND or IDE product storage, security, and dispensing must be documented

and submitted to the IRB.

3. An investigator-sponsor for an IDE protocol must follow the FDA regulations in 21 CFR 812 applicable to sponsor responsibilities, particularly Subpart C. This includes:
 - the record keeping requirements of 21 CFR 812.140(b), and
 - the required notification under 21 CFR 812.150(b)(1) to the FDA and all participating investigators of any evaluation of an unanticipated device effect within ten (10) working days of first receiving notice of the effect.
4. An investigator-sponsor for an IND protocol must follow the FDA regulations in 21 CFR 312 applicable to sponsor responsibilities, particularly Subpart D. This includes:
 - the record keeping requirements of 21 CFR 312.57, and
 - promptly reporting as required in 21 CFR 312.55(b) to the FDA and all participating investigators of significant new adverse effects or risks with respect to the drug or biologic.

The IRB may perform a site visit with the investigator-sponsor before initiation of the research to determine compliance with these FDA regulatory requirements. If compliance has been demonstrated, the investigator-sponsor may begin the research. The audit may be repeated periodically by the IRB.

Subject Charges for Investigational Test Articles and/or Placebos:

The FDA, under the IDE regulations, allow sponsors to charge for an investigational device, however, the charge should not exceed the amount necessary to recover the costs of manufacture, research, development, and handling of the investigational device. The sponsor/sponsor-investigator must justify the charges in the IDE application and then receive FDA approval.

FDA Guidance: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/charging-investigational-products>

The FDA, under the IND regulations, allows sponsors to charge for an investigational drug when there is compelling justification. The sponsor/sponsor-investigator must receive FDA's written authorization before it can begin charging subjects and/or their insurance. FDA does not decide how charging is to be carried out. FDA does not require authorization to charge for costs of drug delivery, including costs associated with formulation, packaging, instrumentation, monitoring, disposables, setup, and nursing care.

FDA Guidance: <https://www.fda.gov/media/85682/download>

IRB Review of Proposed Charges:

If FDA authorization is required, the authorization must be uploaded to the IRB application. If FDA authorization is not required, there needs to be

rationale in the IRB submission for charging subjects, including whether traditional funding was sought and why other funding sources are not available or appropriate. The IRB reserves the right to deny charges if they are not appropriate and equitable.

Consent: The IRB will review the verbiage in the consent to determine if it adequately informs participants of additional costs to be expected. The consent will need to include individuals whom participants can speak with and to obtain a detailed listing of the potential charges prior to agreeing to participate. These individuals should be knowledgeable of the billing related to the clinical trial as well as pre-authorization or payor/insurance related requirements.

Additional OHRP Guidance – Regulatory & Ethical Issues for Charging for Investigational Products: <https://www.hhs.gov/ohrp/sachrp-committee/recommendations/november-20-2019-attachment-a/index.html>

Data Retention When Participants Withdraw From an FDA Regulated Clinical Trial

When a participant withdraws from a study, the data collected on the participant to the point of withdrawal remains part of the study database and may not be removed. The consent document cannot give the participant the option of having data removed.

A researcher may ask a participant who is withdrawing whether the participant wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the participant would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through noninvasive chart review, and address the maintenance of privacy and confidentiality of the participant's information.

The researcher must obtain the participant's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). The IRB must approve the consent document.

If a participant withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the researcher must not access for purposes related to the study the participant's medical record or other confidential records requiring the participant's consent. However, a researcher may review study data related to the participant collected prior to the participant's withdrawal from the study, and may consult public records, such as those establishing survival status.

See FDA guidance “Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials”:

<https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126489.pdf>

B. Human Subject Research involving Non-FDA Regulated Products/Substances

i. Non-FDA Oversight Determination

Investigators administering non-FDA regulated products/substances are required to complete the supplement/food/cosmetic/other subform associated with the IRB application. Based on information provided in the subform describing the intended uses, the IRB will confirm no IND or IDE is required. If an IND or IDE is determined to be required, the investigator will be required to complete the appropriate subform and remove the item(s) from the supplement/food/cosmetic/other subform.

ii. Dosing, Preparation, Administration, and Compounding

1. Targeted dosing should align with approved/recommended dose unless supportive literature is available to justify change.

2. Preparation of investigational products should follow all local and national guidelines.

a. These guidelines include but are not limited to good pharmacy practice, good manufacturing practice, good laboratory practice, and safe food handling practices.

3. Administration should align with approved/recommended route of administration unless supportive literature is available to justify change.

4. Compounding of investigational products should follow all state guidelines.

a. These guidelines include but are not limited to Missouri compounding standards of practice and Missouri sterile compounding code of state regulations.

b. Drug Compounding

i. Compounding of FDA approved drugs should only be performed by a licensed/certified pharmacist in a state approved pharmacy setting.

c. Supplement Compounding

i. Compounding involving addition of a drug to a supplement should only be performed by a licensed/certified pharmacist in a state approved pharmacy setting.

1. Compounding a supplement and a drug may require submission of an Investigational New Drug Application with the FDA.

iii. Accountability, Space, Storage, and Personnel

1. All equipment should be used in accordance with approved manufacturer guidelines/purposes and have current calibration certificates.

2. Space should be appropriately certified for storage and preparation of investigational products.

- a. A dedicated space should be established for working with investigational products.
 - b. Storage space should include an NIST certified temperature monitor that provides automatic alerts if temperature excursion occurs.
3. Research personnel working with investigational products should have appropriate certifications/training in accordance with local and national requirements.

C. Humanitarian Use Device (HUD)

For an HUD to be used in treatment, diagnosis, or research at MU, the IRB and the FDA must approve it and a Humanitarian Device Exemption (HDE) must be issued by the FDA. While the effectiveness of the device does not have to be demonstrated, the IRB will verify that the device does not pose an unreasonable risk of illness or injury to the recipient, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. The device's labeling must state that the device is a humanitarian use device and that, although the device is authorized by Federal Law, the effectiveness of the device for the specific indication has not been proven or demonstrated.

A HUD being used for research purposes must be submitted on the IRB Application and follow the IRB policies for human subject research review. See Using a HUD for Research Purposes below.

IRB Initial and Continuing Review:

For initial review, the physician must complete the Humanitarian Use Device Form in eCompliance for review along with uploading HUD enclosures listed in the HUD Form.

Initial IRB approval will be performed at a convened IRB meeting. The IRB will not review and approve individual uses of an HUD, but rather the IRB will approve use of the device as it sees fit. That is, the IRB may approve use of the HUD without any further restrictions, under a protocol, or on a case-by-case basis. If restrictions are placed on its use, the HUD acknowledgement letter will state the restrictions and the board minutes.

The IRB will approve the use of the device for a period of time, not to exceed one year. In some higher risk cases, IRBs may approve HUDs for a specific number of patients and have required a summary report before approving the use in additional patients. Continuing review will follow the requirements found at 21 CFR 56, and may be conducted using the expedited review procedures (see 21 CFR 56.110) unless the IRB determines that full board review should be performed. If the IRB determines full board review is required, but there has been no enrollment when the annual review is submitted, it may be reviewed expedited until enrollment is reported on an annual update, then it will be reviewed by the full board.

The HUD Annual Review form must be submitted by the physician by the deadline date to avoid expiration. The MDR reports, if existing, must be submitted on the HUD Annual Review form.

Consent for Clinical Use of a HUD:

The IRB may require informed consent from a patient or legally authorized representative prior to the clinical use of an HUD. Although consent may not be required, the physician must provide the HUD brochure/information packet (prepared by the HDE holder) to the patient and review it with the patient or legally authorized representative.

If informed consent is required by the IRB, the consent document will state that effectiveness for the labeled indication has not been demonstrated. A discussion of the potential risks and benefits of the HUD, and any procedures associated with use of the device, must be included in the consent process. The document must not use the term “research” to refer to the activities associated with this use of the device.

Using an HUD for Research Purposes

When an Investigator seeks to collect safety and effectiveness data about the device, if the use is within the approved labeling, no IDE is needed, but IRB approval is required with the submission of the IRB Application, and informed consent must be obtained, since this constitutes research.

If the Investigator plans to collect data for a new use of the device, then the IDE regulations must be followed, and as described previously, IRB approval is required with the submission of the IRB Application, informed consent must be obtained, and continuing review must occur using the convened IRB according to the Continuing Review of Research SOP.

Considerations for Prompt Reporting

Whenever a physician or health care provider receives or otherwise becomes aware of information from any source that reasonably suggests that an HUD has or may have caused or contributed to the death or serious injury of a patient, the physician or health care provider must report such findings to the FDA, and also the IRB on the HUD Reporting Form within 5 business days. This reporting is in addition to, not a substitute for, FDA and/or manufacturer reporting requirements in accordance with 21 CFR 803.30.

The physician or health care provider shall promptly report any FDA action(s) regarding the HUD to the IRB. Modifications to the HUD are to be promptly reported to the IRB in accordance with the IRB policy for amendments but submitted on the HUD Reporting Form.

Major noncompliance must be reported within 5 business days using the Event Report.

Off-Label Use of a HUD

Physicians should be cognizant that FDA has made a determination of safety and probable benefit for use of the HUD only with its approved indication(s). If a physician wants to use a HUD outside its approved indication(s), FDA recommends that the physician obtain informed consent from the patient and ensure that reasonable patient protection measures are followed, such as devising schedules to monitor the patient, taking into consideration the patient's specific needs and the limited information available about the risks and benefits of the device.

A report regarding the off-label use must be submitted to HDE holder. The HDE holder is required to report to the FDA the total number of devices shipped or sold, no matter how they are used (whether for the approved indication(s), emergency use, or otherwise). (see [FDA Frequently Asked Questions About Medical Devices](#))

Only when the board requires pre-approval of each off-label use, the physician must submit the HUD Reporting Form regarding the off-label use for IRB review with documentation of notification to HDE holder. The HUD approval letter will state if each off-label use must be requested prior to its use.

Emergency Use of a HUD

If there is no time to obtain IRB approval, FDA recommends that the emergency use procedures described for unapproved devices be followed.

If a physician in an emergency situation determines that IRB approval for the use of the HUD at the facility cannot be obtained in time to prevent serious harm or death to a patient, the HUD may be used without prior IRB approval. The following conditions must be present:

1. Patient's life is threatened and patient needs immediate care.
2. No generally accepted alternative exists.
3. There is no time to obtain IRB approval.
4. In such emergency circumstances, the physician should follow as many patient protection procedures as possible. These include:
 - a. Independent assessment of an uninvolved physician, in compliance with the MU Health Policy on Consent for Medical and Surgical Treatment (when the individual is a patient from MU Health)
 - b. Concurrence of the IRB Chair
 - c. Clearance by the institution
 - d. Informed consent from the patient or legal representative
 - e. Authorization from the HDE holder

The HUD may also be used without prior patient consent if a life-threatening emergency exists, the patient lacks the capacity to consent, and a legally authorized representative is unavailable. The term "life-threatening" is meant to include the presence of a serious disease or condition that involves risk of irreversible morbidity, such as loss of eyesight.

In emergency uses at MU Health, physicians must comply with the MU Health Policy: Patient Rights & Responsibilities – Consent for Medical and Surgical Treatment.

Within 5 days of the emergency use, the physician must submit the Emergency Use of a Test Article Form in eCompliance.

Emergency use of a HUD that has IRB approval at the facility does not need to be reported on the Emergency Use of Test Article form. These uses will be reported annually on the HUD Annual Review form.

D. Compassionate Use (Expanded Access)

Compassionate use also known as “expanded access” is the use of investigational drugs, biologics, or medical devices outside the clinical trial setting when the primary purpose is to treat, diagnose, or monitor a patient’s disease or condition. When patient enrollment in a clinical trial is not possible (e.g., a patient is not eligible for any ongoing clinical trials, or there are no ongoing clinical trials), patients may be able to receive the product, when appropriate, through expanded access. Compassionate use must comply with 21 CFR 50 and 56.

Drugs/Biologics: There are Three Categories of Compassionate Use:

1. For individual patients, including emergency use (21 CFR 312.310)
2. For intermediate-size patient populations (generally smaller than those typical of a treatment IND or treatment protocol – a treatment protocol is submitted as a protocol to an existing IND by the sponsor of the existing IND) (21 CFR 312.315)
3. For widespread treatment use through a treatment IND or treatment protocol (designed for use in larger patient populations) (21 CFR 312.320)

Unapproved Drugs/Biologics – Compassionate Uses

- The patient has a life-threatening or severely debilitating illness.
 - 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 patients must be in a life-threatening situation requiring intervention before a chair can concur with the use.*
 - 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.*
- No generally acceptable alternative for the condition exists.
- The patient cannot obtain the drug under another IND or protocol.
- The probable risk to the patient from the drug is not greater than the probable risk from the disease.

- The treating physician will obtain informed consent from the patient or legal representative. Expanded access to an investigational drug for treatment use requires informed consent as described in 21 CFR part 50, unless one of the exceptions found in part 50 applies.

IND Submission:

For each category of expanded access, there are two types of regulatory submissions that can be made: (1) an **expanded access protocol** submitted as a protocol amendment to an existing IND (i.e., an expanded access protocol) or (2) a ***new IND submission**, which is separate and distinct from any existing INDs and is intended only to make a drug available for treatment use (i.e., an expanded access IND).

*A **new IND submission** for expanded access generally should be used when (1) there is no existing IND in effect for the drug or, more commonly, (2) there is an existing IND in effect for the drug, but the sponsor of the existing IND declines to be the sponsor of the expanded access use (e.g., for an individual patient use, the sponsor of the existing IND may prefer that a patient's physician take on the role of sponsor-investigator and submit a separate individual patient IND).

Medical Devices: There are Three Categories of Compassionate Use:

1. For individual patients, including emergency use
2. For individual patients or a small group of patients
3. For treatment use under an approved IDE

Unapproved Medical Devices – Compassionate Uses

- The patient has a life threatening or serious disease or condition.
 - Life-threatening** disease or condition 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 patients must be in a life-threatening situation requiring intervention before obtaining FDA approval.*
 - Serious disease or condition** means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. Serious disease or condition includes sight-threatening and limb-threatening conditions as well as other situations involving risk of irreversible morbidity.*

SOP – Investigational, Compassionate, Emergency, and Humanitarian Uses

Page 17 of 22

- No generally acceptable alternative treatment, diagnostic, or monitoring for the condition exists.
- The probable risk to the patient from the device is not greater than the probable risk from the disease.
- The treating physician has devised an appropriate schedule for monitoring the patient to detect any possible problems arising from the use of the device, taking into consideration the investigational nature of the device and the specific needs of the patient.
- If any problems occur as a result of device use, these will be reported to the IRB as soon as possible.
- The treating physician will obtain informed consent from the patient or legal representative. Expanded access to an investigational device for treatment use requires informed consent as described in 21 CFR part 50, unless one of the exceptions found in part 50 applies.
- The treating physician has obtained clearance from the institution, if any, as required.

IDE Submission:

Individuals/Small Groups Use:

1. If there is an IDE:
 - The IDE sponsor (who may be the device manufacturer or a physician who has submitted the IDE to conduct the clinical study for the device) should submit an IDE supplement requesting approval for a compassionate use under section §812.35(a) to treat the patient.
2. If there is no IDE:
 - A compassionate use request for a single patient may be submitted by the physician or manufacturer to the FDA. The physician should not treat the patient identified in the request until the FDA approves use of the device under the proposed circumstances.

Treatment Use:

During the course of the clinical trial, if the data suggest that the device is effective, then the trial may be expanded under a new treatment IDE to include additional patients with life-threatening or serious diseases.

IRB Submission and Review of Compassionate Use Requests

Prior IRB approval and FDA approval (in the form of an IDE or an IND) are required. The physician must submit the IRB Application in eCompliance for approval. Physicians must also comply with the FDA reporting requirements for compassionate use.

Levels of IRB Review:

1. Administrative (Drugs/Biologics ONLY):
 - Some IND protocols have existing approval from a central IRB to help reduce the administrative burden on local IRBs and allow timely use

of the investigational product. If the use is solely for treatment (i.e. non-research purpose), an FWA and a reliance agreement is not required. Implementation of the protocol may proceed immediately. The MU IRB still requires the submission of the Compassionate Use Form and will be reviewed administratively by the IRB office with the proper documentation provided that clearly delineates no requirement for local IRB review in addition to central IRB review.

2. Expedited (Drugs/Biologics ONLY):
 - A physician submitting an individual patient expanded access IND using Form FDA 3926 may select the appropriate box on that form to request a waiver under 56.105 of the requirements in 56.108(c), which relate to full IRB review. FDA concludes that such a waiver is appropriate for individual patient expanded access INDs when the physician obtains concurrence by the IRB chairperson or another designated IRB member before treatment use begins. A physician submitting an individual patient expanded access IND using Form FDA 1571 may include a separate waiver request with the application.
3. Full Board (Drugs/Biologics and Medical Devices):
 - Drugs/biologics not falling under (1) and (2) above requires review by the full board.
 - All medical devices

Modifications and Annual Updates:

Proposed modifications prior to the treatment use must be submitted on an Amendment Form. If use continues for longer than one year, an Annual Update must be submitted. Any reportable event must promptly be reported according to IRB policies. The IRB must be notified when the use ends.

FDA Guidance:

FDA Guidance for Expanded Access to Investigational Drugs for Treatment Use will be followed:

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM351261.pdf>

FDA Guidance for Expanded Access for Medical Devices will be followed:

<https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051345.htm>

E. Emergency Use of a Test Article:

The FDA regulations for the protection of human subjects and patients allow for an investigational drug or device to be used in emergency situations without prior IRB approval [21 CFR 56.102(d), 21 CFR 56.104(c)]. The emergency use provision in the FDA regulations is an exemption from prior review and approval by the full IRB.

Under FDA regulations, the emergency use of a test article, other than a medical device, is a clinical investigation, the patient is a participant, and the FDA may require data from an emergency use to be reported in a marketing application. Under VA requirements, emergency use regulated by FDA is not considered to be involved in research and is not a research participant.

All the following conditions for emergency use must be met:

- Subject is facing a life-threatening condition, for which there is no conventional treatment;
- There is insufficient time to obtain IRB approval prior to administration;
- The subject to receive the test article will not be enrolled in a research study involving the test article; and
- The physician has legitimate access to a test article and believes that there is reasonable likelihood that its use may be advantageous to the life-threatening condition.

Approval of an emergency use of a test article will be granted for only one (1) patient. If subsequent use of the test article is contemplated on the same subject or others, a complete IRB application must be submitted for full board review prior to any additional use of the test article. An investigator cannot carry out a research project on a case-by-case basis under an emergency use premise.

To be exempt from the requirement for IRB review for the emergency use of a test article in a life threatening situation, a physician must not use the data in a systematic investigation designed to develop or contribute to generalizable knowledge. To comply with this limitation, physicians must follow these three rules:

1. Do not use the emergency use exemption to circumvent the general requirement for prior IRB review;
2. Do not use data from an emergency in a prospective research study; and
3. Do not report data from an emergency use in a retrospective research study, unless granted specific approval by the IRB.

In emergency uses at MU Health, physicians must comply with the MU Health Policy: Patient Rights & Responsibilities – Consent for Medical and Surgical Treatment.

Procedures for Emergency Use – Drugs/Biologics

1. IND status:
 - a. The physician must contact the sponsor and FDA and upload the approval/supportive documentation of this 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 usual procedure is to contact the manufacturer

and determine if the drug or biologic can be made available for the emergency use under the company's IND.

- b. The need for an investigational drug or biologic may arise in an emergency situation that does not allow time for submission of an IND. In such a case, FDA may authorize shipment of the test article in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means [21 CFR 312.310(d)].
2. Document the IND number.
3. Document that the human subject is 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.
 - a. Life-threatening, for the purposes of section 56.102(d), includes the scope of both life-threatening and severely debilitating, as defined here. Life threatening 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.
4. Document the emergency use request, including the subject's history, and rationale for the use of the drug or biologic.
5. Document the consent process with the patient or LAR.
 - a. If consent will not or was not obtained from the subject or their legally authorized representative, both the physician and another physician who is not otherwise participating in the clinical investigation must certify in writing all of the following (please upload this certification): (1) the subject is confronted by a life-threatening situation necessitating the use of the test article; (2) informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from the subject; (3) time is not sufficient to obtain consent from the subject's legal representative; and (4) no alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.
 - b. EXCEPTION: If, in the physician's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical physician should make the determination and, within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

Procedures for Emergency Use – Medical Devices

1. IDE Status: Emergency use may apply if the investigational device is being studied in a clinical trial under an IDE: if a physician needs to use the device in a manner inconsistent with the approved investigational plan; or a physician who is not part of the clinical study, wishes to use the device to treat a patient with a life-threatening or serious disease or condition. Emergency use of an investigational device may occur before an IDE is approved and when a device is not being studied under an IDE.
2. Document the IDE number.
3. Document how the patient has a life-threatening or serious disease or condition that needs immediate treatment, no generally acceptable alternative treatment for the condition exists; and because of the immediate need to use the device, there is no time to use existing procedures to obtain FDA approval for the use. FDA approval is not required prior to emergency use of a medical device. If all the criteria here are met, an unapproved device may be used in an emergency situation without prior approval by the FDA.
4. Document the potential for benefit from the use of the unapproved device, and provide reasons to believe that benefits will exist.
5. Document the consent process, or if consent was not obtained and why.
6. Document the independent assessment of an uninvolved physician, or why one was not obtained.
7. Document the authorization from the device manufacturer, or why it was not obtained.
8. Report to the FDA
 - a. If there is an IDE for the device, the IDE sponsor must notify the FDA of the emergency use within 5 days through submission of an IDE Report (§812.35(a)(2)). This follow-up report should include a summary of the conditions constituting the emergency, the patient protection measures that were followed, and patient outcome information.
 - b. If no IDE exists, the physician should submit a follow-up report on the use of the device (description of device used, details of the case, and the patient protection measures that were followed) to:
Food and Drug Administration
Center for Devices and Radiological Health
10903 New Hampshire Ave
Document Control Center
WO66 Rm G-609
Silver Spring, MD 20993

IRB Submission and Review of Emergency Use:

1. If the Chair or IRB administrative office cannot be contacted in advance, the physician may administer the drug/biologic or device as long as s/he obtains informed consent from the subject (see above for consent requirements) and submits the Emergency Use of a Test Article Form within five (5) days of the test article administration.

SOP – Investigational, Compassionate, Emergency, and Humanitarian Uses

Page 22 of 22

- a. The Chair (or physician designee if the chair is not a physician) and IRB administrative office will review the request for emergency use for acceptability. If review by the convened board is possible within the time available, it will be reviewed by the convened board.
- b. If the request is approved, a determination will be sent to the physician through the eCompliance system.

Reporting Requirements

The physician must submit the Emergency Use of a Test Article Form within five (5) days of the test article administration.

All unanticipated problems associated with Emergency Use must be reported to the IRB within 5 business days of the occurrence according to the Unanticipated Problems SOP.

References:

Combined Policies January 21, 2019:

Investigational and Unlicensed Test Articles

Approval Dates: December 1, 2006; June 10, 2010; July 1, 2011; March 1, 2015;
July 1, 2015; June 8, 2017; May 3, 2018

Emergency Use of a Test Article

Approval Dates: January 22, 2001; April 19, 2002; February 24, 2006; December 1, 2006; June 10, 2010; July 1, 2011; March 1, 2015; July 1, 2015; June 8, 2017