TITLE: Institutional Review Board Special Considerations  
SC 507 Clinical Research Involving Investigational Devices

POLICY STATEMENT: The use of an Investigational Device in research is subject to the United States Code of Federal Regulations Title 21 - Food & Drugs Part 812 - Investigational Device Exemption (IDE). This policy defines the applicability of the Code of Federal Regulations and the procedures the Mercy Health IRB follows to determine whether an IDE is needed for a clinical investigation, outlines the responsibilities of the investigator who holds the IDE and establishes procedures for the proper control, storage, use and handling of investigational devices.

For purposes of maintaining a uniform process in the control of non-standard of care use devices at Mercy Health, Humanitarian Use Devices must also be controlled as outlined in this policy. Humanitarian Use Device review process is outlined in policy SC 513.

GENERAL PROVISIONS:
Under FDA regulations 21 CFR 812.2(a) all clinical investigations that involve determining the safety or efficacy of a medical device must have an Investigational Device Exemption, unless the device meets one of the exemptions from the requirement for an IDE in 21 CFR 812.2(b).

There are two ways that a medical device can have an Investigational Device Exemption:

1. FDA issues an Investigational Device Exemption.

2. The device meets the requirements for an abbreviated Investigational Device Exemption.

Research that meets all of the elements of the following category is considered to have an abbreviated Investigational Device Exemption and does not need an FDA-issued Investigational Device Exemption: [21 CFR 812.2(b)]

Abbreviated Investigational Device Exemption:
The device is not a significant risk device:

- Is not intended as an implant and does not present a potential for serious risk to the health, safety, or welfare of a subject;
- Is not purported or represented to be for a use in supporting or sustaining human life and does not present a potential for serious risk to the health, safety, or welfare of a subject;
- Is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Does not present a potential for serious risk to the health, safety, or welfare of a subject.
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- The device is not a banned device.
- The sponsor labels the device in accordance with 21 CFR 812.5;
- The sponsor obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;
- The sponsor ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator’s care, 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 21 CFR 812.46 with respect to monitoring investigations;
- The sponsor maintains the records required under 21 CFR 812.140(b)(4) and (5) and makes the reports required under 21 CFR 812.150(b)(1)-(3) and (5)-(10);
- The sponsor ensures that participating investigators maintain the records required by 21 CFR 812.140(a)(3)(i) and make the reports required under 21 CFR 812.150(a)(1)(2)(5) and (7); and
- The sponsor complies with the prohibitions in 21 CFR 812.7 against promotion and other practices.

There are seven categories where research involving a medical device is exempt from the requirement for an Investigational Device Exemption: [21 CFR 812.2(b)]

Exemption #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.

Exemption #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 21 CFR 807 in determining substantial equivalence. (I.e., “FDA-approved device”)

Exemption #3:
- A device is a diagnostic device.
- The sponsor complies with applicable requirements in 21 CFR 809.10(c).
- The testing is noninvasive.
- The testing does not require an invasive sampling procedure that presents significant risk.
- The testing does not by design or intention introduce energy into a subject.
- The testing is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

Exemption #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.

Exemption #5: A device intended solely for veterinary use.

Exemption #6: A device shipped solely for research on or with laboratory animals and labeled in accordance with 21 CFR 812.5(e).

Exemption #7: 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.
In accordance with FDA requirements, it is the policy of Mercy Health IRB that a determination of Significant Risk (SR) or Non-Significant Risk (NSR) for a medical device is made prior to consideration of approval of the medical device study. The Significant Risk versus Non-Significant Risk determination must be made by the convened IRB. The criteria for approval of device studies are the same as for any FDA-regulated study.

All devices with an Investigational Device Exemption number require full Board approval. If the IRB determines, or concurs with the assessment of the sponsor that a device study involves a Significant Risk, then it would be governed by the Investigational Device Exemption regulations at 21 CFR 812. The determination of the risk status of the device should be based on the proposed use of the device in the investigation. The IRB may review any of the following materials:

- A description of the device;
- Reports of prior investigations conducted with the device;
- The proposed investigational plan;
- A description of subject selection criteria;
- Monitoring procedures; and
- The sponsor risk assessment and the rationale used to make the sponsor's risk determination;
- The IRB may also request additional information if necessary from the sponsor or investigator or ask the FDA to provide a risk assessment.

The IRB determination of the risk status of the device will be indicated in formal IRB minutes and correspondences to the investigator (sent via normal mechanisms), and when applicable, will identify that the IRB determination of risk status differs from that submitted by the investigator/sponsor in the application materials. When required, this determination will also be forwarded to the sponsor.

In accordance with FDA regulations 21 CFR 812.3, and Good Clinical Practice (GCP) guidelines; the requirements applicable to a sponsor-investigator under part 812 include both those of an investigator and a sponsor. The responsibilities include the following:

- Maintaining the Investigational Device Exemption
- Obtaining Qualified Investigators and Monitors
- Providing Necessary Information and Training for Investigators
- Monitoring the Investigation
- Controlling the Investigational Agent
- Reporting Significant Adverse Events to FDA/Investigators
- Maintaining and Retaining Accurate Records
- Implementing and maintaining quality assurance with written Standard Operating Procedures (SOP’s)

When a Mercy Health Investigator is the sponsor of the Investigational Device Exemption (sponsor-investigator), the Mercy Health IRB requires the investigator to meet with a representative of the Office of Research and Innovation to review his/her FDA responsibilities as a sponsor-investigator. The Office of Research and Innovation or assigned designee is responsible for providing the Mercy Health IRB with documentation in writing that the review has taken place, and that the investigator understands his/her FDA Investigational Device Exemption responsibilities. Approval to initiate the research is contingent upon receipt of written documentation from the Office of Research or assigned designee.

In accordance with FDA regulations 21 CFR 812 and Mercy Health policies, the Sponsors and/or Investigators are responsible for the proper ordering, handling, storage and disposition of investigational devices in clinical trials at Mercy Health.

**Ordering**

Ordering of an investigational device must be done by the Principal Investigator or designated study personnel according to the terms of the executed agreement and only after the protocol has been approved by the IRB.

**Receipt**

Investigational devices may only be received by the Principal Investigator or designated study personnel at a Mercy Health business address. Receipt should be recorded in a device accountability log.

**Storage/Labeling**

Investigational devices used in conjunction with a research protocol must be kept in a locked and secured area and must be labeled “Caution: Investigational Device-Limited by Federal Law (or United States) Law to Investigational Use.”
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If a device is FDA approved and is provided to Mercy Health specifically to be used for research purposes, the device should be labeled with the "Investigational Device" label to ensure the investigational device stock is recorded, stored and distributed appropriately.

Access to investigational devices must be limited to the Principal Investigator or designated study personnel.

Study device supplies must be labeled as investigational by the manufacturer and maintained and stored separately from general use devices.

Dispensing
The investigational device may not be provided to any physician or physician's staff member who is not a member of the research team trained and responsible for accountability, distribution and use of the device. The investigational device may not be used for any patient that has not consented and signed a specific research informed consent document for the study requiring use of the device. The Principal Investigator must not supply the investigational device to any Mercy Health colleague not authorized to have access to the device for research purposes. For accountability purposes an investigational device accountability log(s) must be kept for all investigational device studies. Documentation of the following elements should be recorded for each device used:

- The type of device
- Model Number
- Serial Number
- Lot Number (if applicable)
- Date received
- Research subject name and Mercy Health ID number (for internal tracking purposes)
- Research subject study ID number
- Date implanted or used

Personnel may not remove any device(s) from the standard device inventory and substitute them for an investigational device, even if the device, under study, is approved and used in practice. If the sponsor provides an investigational device accountability log, research personnel must review the log to determine if the required elements are included on the log. If the log provided by the sponsor does not include all of the required elements, a separate log including those elements must be maintained.

Billing
If the research study involves billing for services or procedures provided to subjects, investigators must ensure that the appropriate process and forms are used for correct billing to occur. The IRB does not review billing practices. The IRB will require that the investigator have a written plan for informing the participant of billing practices, expectations and potential cost to the participant. Standardized research billing procedures for inpatient and outpatient services and ancillary testing are outlined in Mercy Health system policies.

Maintaining an Investigational Device Log(s)
Investigational device logs must be maintained in the study’s regulatory binder for the period of time required by the federal regulations or terms of the agreement, whichever is longer. The full names, titles/positions, signatures and/or initials of all Mercy Health personnel responsible for maintaining or documenting in the log(s) must be indicated on either a cover sheet or in the log itself. The Principal investigator or designated study personnel must regularly review the device logs to ensure that there is an adequate amount of devices or the appropriate type of devices available (i.e. sizes) to conduct the scheduled procedures.

Disposition
Upon conclusion or termination of the clinical investigation, or by the sponsor’s request, the principal investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device(s) as the sponsor directs. Investigational device(s) should not be destroyed by the principal investigator or study personnel without obtaining advanced written permission from the sponsor. Documentation of why, when, and the personnel involved is required. In the event of research software, disposition must include the date the software was deprogrammed or removed from the device(s).
Radioactive Materials
Radioactive Material in a Radiation Delivery Device: Obtain approval from the Mercy Health Radiation Safety Committee (RSC) for all research protocols involving a radioactive device.
Radiation Generating Equipment: Contact Radiation Safety regarding new and transferred radiation generating equipment (e.g. x-ray unit). Radiation Safety must be involved in the protocol feasibility review process and must also be notified at least 3 weeks prior to delivery of the equipment to allow time for planning. New and transferred radiation safety equipment must be tested and accepted by a Mercy Health Radiation Expert in Radiology or Radiation Oncology, as appropriate, prior to use on a human research subject.

Maintenance and Cleaning:
All investigational devices must be properly maintained and cleaned according to instructions supplied by the sponsor and/or manufacturer.

DEFINITIONS:
Research: As defined by the Department of Health and Human Services (DHHS), any systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

Under FDA regulations activities are “research” when they involve:
   a. Use of a drug other than the use of an approved drug in the course of medical practice (21 CFR 312.3(b)).
   b. Use of a medical device other than the use of an approved (means approved by the FDA for marketing) medical device in the course of medical practice (Food, Drug and Cosmetic Act 530(g)(3)(a)(ii)).

Humanitarian Use Device: (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. A device manufacturer’s research and development costs could exceed its market returns for diseases or conditions affecting small patient populations. The HUD provision of the regulation provides an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting these populations.

To obtain approval for an HUD, a humanitarian device exemption (HDE) application is submitted to FDA. An HDE is similar in both form and content to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA. An HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury 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. Additionally, the applicant must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that they could not otherwise bring the device to market.

An approved HDE authorizes marketing of the HUD. However, an HUD may only be used in facilities that have established a local institutional review board (IRB) to supervise clinical testing of devices and after an IRB has approved the use of the device to treat or diagnose the specific disease. The labeling for an HUD 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 demonstrated.

Investigational Device: The US FDA defines an investigational device as “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.”

Please note: Software (e.g. software that controls a pacemaker) is considered a device.
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Significant Risk(s): A significant Risk (SR) device study is defined as a study of a device that presents a potential for serious risk to health, safety, or welfare of a subject and (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise prevents a potential for serious risk to the health, safety, or welfare of a subject. If the Institutional Review Board (IRB) determines the study to be SR, the sponsor must obtain an Investigational Device Exemption (IDE) from the Food and Drug Administration (FDA) before proceeding with the study.

Non-Significant Risks: The non-significant risk (NSR) category was created to avoid delay and expense where the anticipated risk to human subjects did not justify the involvement of the FDA. If the IRB determines that the study is NSR, no submission to or review by the FDA is necessary before starting studies in humans. Note: It is very important to note that the terms "non-significant risk" and "minimal risk" are defined separately, and are not synonymous.

510(k): A 510(k) Device is a new device that the FDA agrees is substantially equivalent to a device already on the market. 510(k) devices can be marketed without clinical testing. However, if clinical data are necessary to demonstrate equivalence, any clinical studies must be conducted in compliance with the requirements of the IDE, IRB review and informed consent regulations. Because 510(k) devices under clinical investigation fall under the IDE regulations, reporting of adverse or unanticipated 510(k) device effects will follow the same requirements.

Investigational Device Exemption(s) (IDE): An Investigational Device Exemption (IDE) allows the investigational device to be used in a clinical trial in order to collect safety and effectiveness data required to support a Pre-market Approval application (PMA) or a Pre-market Notification [510(k)] submission to the FDA. An IDE permits a device to be shipped lawfully for purposes of conducting investigations of that device. (21CFR 812.1). The FDA assigns each investigational device exemption (IDE) to either category A or B. All clinical investigations of devices must have an approved IDE or be exempt from the IDE regulation, see 21 CFR 812.2.

Investigational Device Exemption(s) (IDE) Number: The FDA assigns a special identifier that corresponds to each device granted an IDE.

FDA category A Device: Experimental/Investigational. Category A devices are novel first of a kind technology: an innovative device for which the absolute risk of the device has not been resolved.

FDA category B Device: Non-experimental/Investigational. Category B devices are new generations of proven technology.

Sponsor: Means a person who initiates, but who does not actually conduct, the investigation, that is, the investigational device is administered, dispensed, or used under the immediate direction of another individual. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

Sponsor-Investigator: Means an individual who both initiates and actually conducts, alone or with others, an investigation, that is, under whose immediate direction the investigational device is administered, dispensed, or used. The term does not include any person other than an individual. The obligations of a sponsor-investigator under this part include those of an investigator and those of a sponsor.

Transitional Device: Transitional device is a device subject to section 520(l) of the FD&C Act and which FDA previously regulated as a new drug or an antibiotic drug before May 28, 1976.

REFERENCE:
21 CFR 807
21 CFR 809.10
21 CFR 812
21 CFR 814 Subpart H - Humanitarian Use Devices
FDA Device Advice: http://www.fda.gov/cdrh/devadvice/
http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/HDEApprovals/default.htm

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ATTACHMENTS:
SC 507-A Worksheet for Review of Research Involving Investigational Devices

PROCEDURE: All Mercy Health Campuses

Responsibility
IRB Specialist/IRB Coordinator

Action
1. Review incoming submissions and
determine if the proposal includes use of an
investigational device.
2. Notify the IRB Chairperson that the study
includes use of an investigational device.
3. Add study to the next IRB Meeting
agenda
4. Provide reviewers with appropriate
protocol review worksheets and/or
checklists.
5. Upload completed checklists into the IRB
Manager system when they are returned. If
reviewers indicate they have comments or
questions related to use of the
worksheet, pass the information along to the
IRB Chairperson for further review and
consideration.
6. Provide the completed checklists (and
worksheets when appropriate) to the
Investigator for review and response.
7. Issue correspondence as advised by the
IRB Chairperson.

IRB Chairperson or Designee

1. Select reviewers with appropriate
expertise for the research to be reviewed.
2. Ensure all reviewers’ findings have been
addressed and prepare to discuss reviewer
findings with the IRB Committee.
3. Inform IRB Coordinator/IRB Clinical
Research Assistant of outcome and the
proper correspondence to be issued.

IRB Member or Designated Reviewer

1. Review research proposal and summarize
findings on appropriate protocol review
worksheet and/or checklists.
2. Ascertain whether any special
considerations exist that may influence the
review of a proposal.
3. Ascertain whether the evidence exists that
third party verification of submitted
information is needed.
4. Prepare summary of findings and
recommendations for presentation at the
next convened IRB meeting.
5. Return review materials and
recommendation documentation to the IRB
Chairperson.
6. Upon request of the IRB Chair,
communicate with the investigator to
resolve reviewer findings.
7. Provide Chairperson with documentation
of reviewers’ satisfaction with investigators
response to reviewers’ comments.
8. If reviewers findings are not addressed by the investigator, reviewer is to inform the chair of outstanding findings that still need to be addressed.

IRB Committee

1. Review the proposed research and all submitted materials.
2. Be prepared to debate issues and to make difficult determinations that are required to meaningfully influence the protection of human research participants.
3. Ensure the device regulations have been met for review and approval.
4. Vote "for", "against", "abstain" or "recuse the research proposal during the IRB meeting.

Principal Investigator

1. Ensure that the study is conducted according to the approved protocol and all applicable federal, state, and local regulations and Institutional policy;
2. Permit an investigational device to be used only with participants under the investigator’s supervision. Ensure an investigational device is not supplied to any person not authorized to receive it;
3. Upon completion or termination of a clinical study, return to the manufacturer any remaining supply of the device or otherwise disposition of the unused supplies of the device according to the study sponsors directions and institutional policy;
4. If a device is approved for marketing and does not have an IDE number, the investigator must provide to the IRB the exemption category [21 CFR 812.2] and justification that the research meets the criteria in that category, or;
5. Provide justification to the IRB that the abbreviated requirements for an IDE are met. [21 CFR 812.2(b) or (c)(1-7);
6. Maintain accurate, complete, and current records as required in 21 CFR 812.140(a) and maintain those record for 2 years after either: The date in which the study is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. [21 CFR 812.140(d);
7. An investigator who has authority to grant access shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held;
8. Permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation [21 CFR 812.145(b]
9. Permit authorized FDA employees to inspect and copy records that identify participants, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted to the IRB have not been submitted or are incomplete, inaccurate, false, or misleading. [21 CFR 812/145;]
10. Prepare and submit the following complete, accurate, and timely reports [21 CFR 812.150(a):]
   - A report to the IRB of any unanticipated adverse device effect occurring during a study as soon as possible, but in no event later than 10 working days after the investigator first learns of the event.
   - A report to the manufacturer, within 5 working days when a withdrawal of approval by the reviewing IRB occurs.
   - A report to the IRB of any deviation from the investigational plan to protect the life or physical well-being of a participant in an emergency as soon as possible, but no later than 5 days after the emergency occurred. Except in cases of emergency, prior approval by the IRB is required.
   - A final report to the IRB within 10 days after termination or completion of the study.

CONCURRENT CONSENTS: [Signature]
Institutional Official [Signature]