

Human Research Protection Program (HRPP) Handbook

Standard Operating Procedures (SOP)

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1.0 IRB COVID-19 MEMORANDUM

(Last Updated 01/07/2022)

The interim guidance on human subjects-related research, Principal Investigators may determine it necessary to make changes to study procedures of existing IRB-approved projects to eliminate an apparent immediate hazard and/or limit exposure to COVID-19. **Examples** may include allowing:

- *Study Visits by Telephone*
- *Laboratory Assessments to be completed at a Participant's Local Lab*
- *Shipment of Oral Drug*
- *Vital signs obtained by the Participant's Local Primary Care Physician*
- *The Omission of a Study Procedure*

In cases where the Principal Investigator has made such a determination, the human research regulations allow for changes necessary to eliminate immediate hazard to be implemented prior to IRB approval. After the changes have been instituted, the Principal Investigator should submit a report within five days to inform the Saint Luke's Health System IRB. The report should include sufficient detail on the temporary changes being made and the harm being mitigated.

If you have a COVID-19 specific new project, expanded access protocol, or emergency use request, please submit in iMEDris adding to standard IRB submission procedures and send an email with the IRB project number to IRB@saint-lukes.org. We will be prioritizing these requests.

The HRPP office is closely monitoring guidance on responding to COVID-19 and will update the research community with any changes in our office operation.

Every effort is being made to address the COVID-19 situation in a way that is seamless while upholding our mission to protect human research participants.

If you have any questions, you can contact the IRB at IRB@saint-lukes.org.

Thank you,

Saint Luke's Health System HRPP office

1.1 OHRP GUIDANCE ON COVID-19

(This guidance represents the current thinking of the Office for Human Research Protections (OHRP) on this topic.)

This guidance does not create or confer any rights for or any person and does not operate to bind OHRP or the public. OHRP guidance should be viewed as recommendations unless specific regulatory requirements are cited.

The use of the word "must" in OHRP guidance means that something is required under the Department of Health and Human Services (DHHS) regulations at 45 CFR part 46. The use of the word "should" in OHRP guidance means that something is recommended or suggested, but not required. An institution may use an alternative approach if the approach satisfies the requirements of 45 CFR part 46.

As a general matter, OHRP wants to reassure the research community that OHRP will take into account the specific circumstances that institutions and Investigators are experience and will use available flexibility in its decision making as institutions and Investigators are experiencing and will use available flexibility in its decision making as

institutions and Investigators implement actions necessary to protect public health, while still appropriately protecting research subjects.

Public Health and Clinical Activities:

Actions taken for public health or clinical purposes, and not for research purposes, are not research procedures and therefore do not require institutional review board (IRB) approval before being implemented. *For example, if a hospital implements mandatory clinical screening procedures related to COVID-19 for all people who come to that institution, including research subjects, these screening procedures do not need to be reviewed by an IRB before they may be implemented.* Further, as these activities are not research procedures, the hospital does not need IRB review in order to share the screening results with a public health authority or the research subjects, although other permissions or notice may be necessary under applicable law or policy.

Excluded Public Health Surveillance Activities:

Some types of public health surveillance activities, including collection and testing of information or bio-specimens, conducted, supported, requested, ordered, required, or authorized by a public health authority, are explicitly excluded from the Revised Common Rule (2018 Requirements) (45 CFR 46.102(l)(2)).

(Note: that FDA regulations may apply if this involves use of an investigational in vitro diagnostic device.)

The following is an example of an activity that could be conducted under 45 CFR 46.102(l)(2) as a public health surveillance activity.

Example:

If a public health authority authorizes general screening for COVID-19 for public health surveillance purposes and requests test results be shared as necessary with a public health authority to allow the public health authority to identify, monitor, assess or investigate the COVID-19 outbreak, an Investigator may incorporate these activities into an existing research study visit without prior IRB review and approval.

Legally Required Reporting:

When required by law to provide information related to an individual's COVID-19 test results to a public health authority, including individually identifiable information about individuals who are research subjects, the HHS protection of human subjects regulations do not prevent Investigators or institutions from fulfilling this requirement (even if doing so would be inconsistent with statements made in the study's consent form). The existence of a Certificate of Confidentiality does not alter an Investigator's ability to disclose a research subject's COVID-19 test results when required by federal, state, or local laws. *For example, if a research subject tests positive for COVID-19, an Investigator may provide this test result to a public health authority if required to do so under applicable state or federal law.* In such circumstances, Investigators should inform the participant of the required reporting of results.

Research Changes to Eliminate Apparent Immediate Hazards:

Investigators may implement changes to approved research prior to IRB review and approval if the changes are necessary to eliminate apparent immediate hazards to the subject (45 CFR 46.108(a)(3)(iii) under the 2018 Requirements and 45 CFR 46.103(b)(4)(iii) under the pre-2018 Requirements). *For example, we expect that Investigators are cancelling or postponing non-essential study visits or conducting phone visits instead of in-person visits to reduce COVID-19 transmission risks.* In these situations, Investigators may make such changes to the research to reduce risks without prior IRB approval, but they should report those changes to the IRB when possible.

Proposing and Reviewing Study Changes:

Investigators may submit any proposed changes to previously approved research to the IRB at any time. The IRB may use an expedited review procedure to review and approve those changes if the changes are minor (45 CFR 46.110(b)(1)(ii) under the 2018 Requirements and 45 CFR 46.110(b)(2) under the pre-2018 Requirements).

Whether Suspensions of Research Must be Reported:

Please note, that only IRB suspensions or terminations of approved research are required to be reported to OHRP. If an Investigator or an Institutional Official (IO) suspends or terminates approved research, such actions are not required to be reported to OHRP under 45 CFR 46.113.

1.2 FDA GUIDANCE ON CONDUCT OF CLINICAL TRIALS OF MEDICAL PRODUCTS DURING COVID-19 PANDEMIC FOR INDUSTRY, INVESTIGATORS AND INSTITUTIONAL REVIEW BOARDS

(This guidance is being issued to address the Coronavirus Disease 2019 (COVID-19) public health emergency.)

This guidance is being implemented without prior public comment because the Food and Drug Administration (FDA or the Agency) has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 10.115(g)(2)).

For the full PDF version visit: <https://www.hhs.gov/ohrp/sites/default/files/fda-covid-guidance-2apr2020.pdf>

The Food and Drug Administration (FDA or Agency) plays a critical role in protecting the United States from threats including emerging infectious diseases, including the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to providing timely guidance to support continuity and response efforts to this pandemic.

FDA is issuing this guidance to provide general considerations to assist sponsors in assuring the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity during the COVID-19 pandemic.

This policy is intended to remain in effect only for the duration of the public health emergency related to COVID-19 declared by the Department of Health and Human Services, including any renewals made by the HHS Secretary in accordance with section 319(a)(2) of the Public Health Services (PHS) Act.

In general, FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance's describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named "SARS-CoV-2" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19). On January 31, 2020, the Department of Health and Human Services issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS. In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.

FDA recognizes that the COVID-19 pandemic may impact the conduct of clinical trials of medical products. Challenges may arise, *for example, from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product, or other considerations if site personnel or trial subjects become infected with COVID-19.* These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing. FDA recognizes that protocol modifications may be required, and that there may be unavoidable protocol deviations due to COVID-19 illness and/or COVID-19 control measures. Although the necessity for, and impact of, COVID-19 control measures on trials will vary depending on many factors, including

the nature of disease under study, the trial design, and in what region(s) the study is being conducted, FDA outlines the following general considerations to assist sponsors in assuring the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity. The appendix further explains those general considerations by providing answers to questions about conducting clinical trials that the Agency has received during the COVID-19 pandemic.

Considerations for ongoing trials:

- Ensuring the safety of trial participants is paramount. Sponsors should consider each circumstance, focusing on the potential impact on the safety of trial participants, and modify study conduct accordingly. Study decisions may include those regarding continuing trial recruitment, continuing use of the investigational product for patients already participating in the trial, and the need to change patient monitoring during the trial. In all cases, it is critical that trial participants are kept informed of changes to the study and monitoring plans that could impact them.
- Sponsors, in consultation with clinical Investigators and Institutional Review Board (IRB)/Independent Ethics Committees (IECs), may determine that the protection of a participant's safety, welfare, and rights is best served by continuing a study participant in the trial as per the protocol or by discontinuing the administration or use of the investigational product or even participation in the trial. Such decisions will depend on specific circumstances, including the nature of the investigational product, the ability to conduct appropriate safety monitoring, the potential impact on the investigational product supply chain, and the nature of the disease under study in the trial.
- Since trial participants may not be able to come to the investigational site for protocol-specified visits, sponsors should evaluate whether alternative methods for safety assessments (e.g., phone contact, virtual visit, alternative location for assessment, including local labs or imaging centers) could be implemented when necessary and feasible, and would be sufficient to assure the safety of trial participants. Sponsors should determine if in-person visits are necessary to fully assure the safety of trial participants (*for example, to carry out procedures necessary to assess safety or the safe use of the investigational product appropriately*); in making the decision to continue use or administration of the investigational product, the sponsor should consider whether the safety of trial participants can be assured with the implementation of the altered monitoring approach.
- In some cases, trial participants who no longer have access to investigational product or the investigational site may need additional safety monitoring (e.g., withdrawal of an active investigational treatment).
- The need to put new processes in place or to modify existing processes will vary by the protocol and local situation. *For example, this assessment could include consideration of whether it is appropriate to delay some assessments for ongoing trials, or, if the study cannot be properly conducted under the existing protocol, whether to stop ongoing recruitment, or even withdraw trial participants.*
- COVID-19 screening procedures that may be mandated by the health care system in which a clinical trial is being conducted do not need to be reported as an amendment to the protocol even if done during clinical study visits unless the sponsor is incorporating the data collected as part of a new research objective.
- Changes in a protocol are typically not implemented before review and approval by the IRB/IEC, and in some cases, by FDA. Sponsors and clinical Investigators are encouraged to engage with IRB/IEC as early as possible when urgent or emergent changes to the protocol or informed consent are anticipated as a result of COVID-19. Such changes to the protocol or investigational plan to minimize or eliminate immediate

hazards or to protect the life and well-being of research participants (e.g., to limit exposure to COVID-19) may be implemented without IRB approval or before filing an amendment to the IND or IDE, but are required to be reported afterwards.⁴ FDA encourages sponsors and Investigators to work with their IRB to prospectively define procedures to prioritize reporting of deviations that may impact the safety of trial participants.

- The implementation of alternative processes should be consistent with the protocol to the extent possible, and sponsors and clinical Investigators should document the reason for any contingency measures implemented. Sponsors and clinical Investigators should document how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted.
- Changes in study visit schedules, missed visits, or patient discontinuations may lead to missing information (e.g., for protocol-specified procedures). It will be important to capture *specific* information in the case report form that explains the basis of the missing data, including the relationship to COVID-19 for missing protocol-specified information (e.g., from missed study visits or study discontinuations due to COVID-19). This information, summarized in the clinical study report, will be helpful to the sponsor and FDA.
- If scheduled visits at clinical sites will be significantly impacted, certain investigational products, such as those that are typically distributed for self-administration, may be amenable to alternative secure delivery methods. For other investigational products that are normally administered in a health care setting, consulting FDA review divisions on plans for alternative administration (e.g., home nursing or alternative sites by trained but non-study personnel) is recommended. In all cases, existing regulatory requirements for maintaining investigational product accountability remain and should be addressed and documented.
- With respect to efficacy assessments, FDA recommends consultation with the appropriate review division regarding protocol modifications for the collection of efficacy endpoints, such as use of virtual assessments, delays in assessments, and alternative collection of research-specific specimens, if feasible. For individual instances where efficacy endpoints are not collected, the reasons for failing to obtain the efficacy assessment should be documented (e.g., identifying the specific limitation imposed by COVID-19 leading to the inability to perform the protocol-specified assessment).
- If changes in the protocol will lead to amending data management and/or statistical analysis plans, the sponsor should consider doing so in consultation with the applicable FDA review division. Prior to locking the database, sponsors should address in the statistical analysis plan how protocol deviations related to COVID-19 will be handled for the pre-specified analyses.
- If planned on-site monitoring visits are no longer possible, sponsors should consider optimizing use of central and remote monitoring programs to maintain oversight of clinical sites.

In general, and if policies and procedures are *NOT* already in place for applicable trials:

Sponsors, clinical Investigators, and IRB should consider establishing and implementing policy and procedures, or revise existing policy and procedures, to describe approaches to be used to protect trial participants and manage study conduct during possible disruption of the study as a result of COVID-19 control measures at study sites. Changes to policy and procedures could address, but not be limited to, impact on the informed consent process, study visits and procedures, data collection, study monitoring, adverse event reporting, and changes in Investigator(s), site staff, and/or monitor(s) secondary to travel restrictions, quarantine measures, or COVID-19 illness itself. Policy and procedures should be compliant with applicable (regional or national)

policy for the management and control of COVID-19. Depending upon the nature of the changes described above, a protocol amendment may be required under the applicable regulations.

For all trials that are impacted by the COVID-19 pandemic:

Sponsors should describe in appropriate sections of the clinical study report (or in a separate study-specific document):

- Contingency measures implemented to manage study conduct during disruption of the study as a result of COVID-19 control measures.
- A listing of all participants affected by the COVID-19 related study disruption by unique subject number identifier and by investigational site, and a description of how the individual's participation was altered.
- Analyses and corresponding discussions that address the impact of implemented contingency measures (e.g., trial participant discontinuation from investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data) on the safety and efficacy results reported for the study.

Robust efforts by sponsors, Investigators, and IRB/IECs to maintain the safety of trial participants and study data integrity are expected, and such efforts should be documented. As stated above, FDA recognizes that protocol modifications may be required, including unavoidable protocol deviations due to COVID-19 illness and/or COVID-19 control measures. Efforts to minimize impacts on trial integrity, and to document the reasons for protocol deviations, will be important.

Questions and Answers:

Q1. What are some of the key factors that a sponsor should consider when deciding whether to suspend or continue an ongoing study or to initiate a new study during the COVID-19 pandemic?

Central to any decision should be ensuring that the safety of clinical trial participants can be maintained. Sponsors, in consultation with clinical Investigators and Institutional Review Board (IRB)/Independent Ethics Committees (IECs), should assess whether the protection of a participant's safety, welfare, and rights is best served by continuing a study participant in the trial as per the protocol or by discontinuing the administration or use of the investigational product or even participation in the trial. Such decisions will depend on specific circumstances, including the nature of the investigational product, the ability to conduct appropriate safety monitoring, the potential impact on the investigational product supply chain, and the nature of the disease under study in the trial. As part of this assessment, sponsors should carefully consider the following aspects of clinical trial conduct when deciding how or whether to proceed with a clinical trial:

- *Assessing whether the limitations imposed by the COVID-19 pandemic on protocol implementation pose new safety risks to trial participants, and whether it is feasible to mitigate these risks by amending study processes and/or procedures.*
- *Assessing the continued availability of the clinical Investigator/sub-Investigators to provide oversight of the trial, and properly assess and manage safety issues that may emerge.*
- *Assessing whether there will be sufficient clinical trial support staff given the evolving COVID-19 situation and its impact on staff availability. Are there appropriately trained staff that could be available to handle the expected tasks? Is there adequate equipment and materials for clinical trial support staff?*
- *Assessing whether clinical Investigator sites will remain open to trial participants for required in-person assessments or whether the clinical Investigator has the ability to provide required in-person assessments*

at an acceptable alternate location(s), or whether such protocol- specified in-person assessments can instead be conducted virtually.

- Assessing the continued availability of clinical trial supplies and continued operations of vendors, especially related to supply of the investigational product and/or to clinical trial supplies that are essential to maintaining appropriate safety monitoring or other key trial procedures. This should include consideration of product stability (shelf life) if the treatment schedule is revised, or if the clinical site is unable to properly store the product for the needed duration.*
- Assessing the continued availability of, and support for, information technology systems and any other technological tools that are needed to support the trial. Are current contingency plans adequate for the types of disruptions that might be anticipated? What other plans can be put in place to minimize any potential disruptions?*
- Assessing whether there will be continued operations of, and adequate communications with, IRB) IEC and Data Monitoring Committee (DMC) staff, if applicable, to support trial needs.*
- Assessing whether it is feasible to conduct the trial in light of any COVID-19 public health measures implemented by Federal and State authorities to control the virus.*

Involvement of a study's DMC, if one has been established, can provide support for the assessments discussed above. Since a primary responsibility of the DMC is assuring the safety of participating trial participants, the DMC's assessment of the impact of modifications of trial conduct due to COVID-19 on patient safety is important to consider.

The risks and benefits of continuing a trial are likely different than a decision to initiate a trial (other than trials intended to evaluate investigational treatments or vaccines for COVID-19). Given the evolving situation, with likely increasing impacts on Investigators, staff, and supply chains, sponsors should carefully consider the ability to effectively mitigate risks such that patient safety and trial integrity are assured. In addition, it is important to consider whether initiation of the trial could interfere with public health measures implemented by Federal and State authorities to control the virus.

Q2. What key factors should sponsors consider when deciding whether to continue administering or using an investigational product that appears to be providing benefit to the trial participant during the COVID-19 pandemic?

There may be circumstances in which an investigational product (either a drug, biological product or medical device) appears to be providing benefit to the trial participant. A sponsor deciding whether to continue administering or using such a product during the COVID-19 pandemic should carefully consider context-dependent issues, including whether a trial participant appears to be benefitting from treatment with the investigational product, whether there are reasonable alternative treatments, the seriousness of the disease or condition being treated, and the risks involved in switching to an alternative treatment if necessary. FDA recognizes that in some circumstances it may be necessary (e.g., based on lack of product supply or inability to administer or ensure the safe use of the investigational product) to discontinue investigational product administration in a trial. If there are individual trial participants for whom discontinuing the investigational product might present a substantial risk (e.g., trial participants perceived by the Investigator as having a clinical benefit to the investigational product), the sponsor should consider amending the protocol, after discussion with the relevant review division, to limit investigational product use to those patients with apparent benefit and discontinue investigational product use to other participants. In all cases, if a trial

participant is discontinued from an investigational therapy, it is important that there be appropriate management after discontinuation.

Q3. How should sponsors manage protocol deviations and amendments to ongoing trials during the COVID-19 pandemic?

FDA recognizes that during the COVID-19 pandemic, sponsors of clinical trials may need to modify protocol-specified procedures. As in discussed in the main body of this guidance, for protocol deviations necessitated by the impact of the current COVID-19 pandemic, the sponsor should document the specific protocol deviation and the reason for the deviation. The sponsor can document protocol deviations using its standard processes, or given the larger expected number of such deviations, use alternative documentation approaches. For example, if visits are to be conducted by telephone/video contact rather than at the investigational site as specified in the protocol, documentation that provides a listing of all study visits (e.g., listing study reference number, patient ID, date of visit) that are deviations from the protocol due to the current COVID-19 situation generally would be acceptable.

For a study-wide change in protocol conduct, protocol amendments that are necessary to prevent imminent hazards to trial participants can generally be immediately implemented with subsequent submission and formal approval by the IRB and notification to FDA through filing a protocol amendment to the IND or IDE.

Q4. How should a sponsor submit a change in protocol that results from challenges related to the COVID-19 pandemic?

For IND studies, the sponsor should submit a formal amendment to its IND, with the following information added to the cover letter in the subject line:

PROTOCOL AMENDMENT – COVID-19

TITLE OF PROTOCOL

Sponsors should summarize the major changes made to the protocol related to COVID-19 in the cover letter and should include a tracked changes version of the protocol to facilitate review. As with other protocol amendments, sponsors may implement protocol amendments due to COVID-19 upon submission to FDA if approved by the IRB. Sponsors seeking FDA input prior to implementation should indicate that in the cover letter.

For IDE studies, the sponsor should submit a supplement to its existing IDE, with the following information added to the cover letter in the subject line:

CHANGE IN PROTOCOL SUPPLEMENT- COVID-19 or NOTICE OF IDE CHANGE – COVID-19, as applicable

TITLE OF PROTOCOL

The submission to the IDE should contain a tracked changes version of the protocol to facilitate review.

Q5. Can a sponsor initiate virtual clinical trial visits for monitoring patients without contacting FDA if there is an assessment by the sponsor and Investigator that these visits are necessary for the safety of the trial participant, and it will not impact data integrity?

FDA regulations allow for changes to be made to the investigational plan or protocol without prior FDA review or approval, if the change is intended to eliminate an apparent immediate hazard or to protect the life and well-being of subjects.⁴ Therefore, changes in protocol conduct necessary to immediately assure patient safety, such as conducting telephone or video contact visits for safety monitoring rather than on-site visits, can be immediately implemented with subsequent review by the IRB and notification to FDA. Since this reflects a

protocol deviation (until the amendment is approved), documentation of the required deviations, as described above, would generally be acceptable (i.e., a document that lists each deviation (study reference ID, patient ID, and date)). For example, documenting that all protocol-specified visits will be done by telephone contact rather than on-site visits, and that procedures requiring in-person visits will either not be conducted, or performed by other means (specified, as appropriate). Since the change to telephone or video contact visits would likely result in some protocol-required procedures not being conducted (e.g., vital signs, blood samples for safety laboratory studies, etc.), the sponsor must evaluate the potential impact on patient safety, and consider how to mitigate risks to patients, including the need to discontinue the investigational product.

For IDE studies, sponsors are required to report deviations implemented to address the imminent safety risk to FDA within 5 working days after learning of the deviations. We recognize that challenges related to the COVID-19 pandemic may make it difficult to meet this timeframe. Sponsors may consolidate implemented deviations when submitting 5-day reports and should update FDA as soon as possible.

Q6. With the rapid changes in clinical trial conduct that may occur due to the COVID-19 pandemic, including multiple deviations to address patient safety, what is the best way for sponsors and Investigators to capture these data?

As noted in the main body of this guidance, it is important to capture specific information for individual participants that explains the basis for missing protocol-specified information that includes the relationship to COVID-19 (e.g., from missed study visits or study discontinuations due to COVID-19). This information, summarized in the clinical study report, will be helpful to the sponsor and FDA. If it is not possible to capture this information in the case report form(s), sponsors may develop processes that enable systematic capture of these data across the sites in a manner that enables the appropriate analysis when the data are submitted to FDA. Sponsors may also develop processes to capture site-level status, site-level or vendor-level protocol deviations, and process deviations.

Q7. If patients are currently dispensed investigational product through a pharmacy for self-administration at home, can a sponsor switch that to home delivery without amending the protocol?

If there is concern about risk of exposure to COVID-19, home delivery of investigational product that would not raise any new safety risks may be implemented to protect patients from coming to clinical trial sites. In all cases, requirements under FDA regulations for maintaining required investigational product storage conditions and investigational product accountability remain; these requirements must be addressed and documented (21 CFR 312.60; 312.62, and 812.140). If the protocol indicates pharmacy dispensing for self-administration at home, and this is changed to direct-to-patient shipments, then a protocol amendment would be required to permit home delivery of investigational product. If the extent of home delivery is limited to certain participants and not the entire population described in the protocol, documenting the change in the mechanisms of distribution of investigational product administration through protocol deviations may also be acceptable. If the change in the mechanisms of investigational product distribution is then included in a protocol amendment, such a change may be part of a “cumulative” amendment that includes a number of changes that accrue, rather than an urgent protocol change.

Q8. If patients are currently receiving an investigational product infusion at the clinical trial site, can a sponsor switch to home infusion?

Sponsors should consider the safety risk to trial participants who would miss an investigational product infusion because of the inability to come to the clinical trial site. In general, for investigational product that is usually administered in a health care setting, consulting the appropriate FDA review divisions is recommended regarding plans for alternative sites for administration (e.g., home nursing or alternative sites by trained but

non-study personnel). For example, consulting FDA would be strongly advised for complex investigational products (e.g., cellular therapy and gene therapy products) where potentially altered storage and handling conditions could adversely affect product stability. In all cases, applicable requirements for maintaining required investigational product storage conditions (prior and after reconstitution), investigational product reconstitution specifications per the Investigational Brochure, and investigational product accountability remain and must be addressed and documented. Storage conditions and investigational product accountability should be considered if the protocol is amended to permit alternative site infusions. Defining circumstances when discontinuing investigational product treatment, while continuing study participation albeit with potentially delayed assessments, may be an appropriate option when suitable alternative arrangements cannot be made.

Q9. Considering that there will be likely delays to on-site monitoring of clinical trials during the COVID-19 pandemic, what are FDA's expectations in such circumstances?

FDA recognizes that monitors may not be able to access the trial sites for on-site visits in a timely manner during the COVID-19 pandemic. Sponsors should work to find alternative approaches to maintain trial participant safety and trial data quality and integrity, such as enhanced central monitoring, telephone contact with the sites to review study procedures, trial participant status, and study progress, or remote monitoring of individual enrolled trial participants, where appropriate and feasible. FDA recognizes that delays in on-site monitoring may result in delayed identification of GCP non-compliance (including major protocol deviations) at the clinical trial site(s) (including protocol deviations not due to the impact of COVID-19). Sponsors should carefully document situations where monitors were unable to access, or had to delay, monitoring of a clinical site. Sponsors/monitors should also include in their documentation of protocol deviations, or other GCP non-compliance issues identified at clinical sites whether delayed identification was due to postponed monitoring. FDA recognizes that unique situations at clinical sites will occur due to COVID-19 control measures and will consider these circumstances when evaluating inspectional observations.

Q10. How do I obtain a signed informed consent from a patient who is in isolation and the COVID-19 infection control policy would prevent us from removing a document signed by the patient from their hospital room?

FDA regulations generally require that the informed consent of a participant be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent (21 CFR 50.27(a)). In light of COVID-19 infection control measures, the following procedure would satisfy documentation of this requirement if the patient signing the informed consent is in COVID-19 isolation.

- If the technology is available, electronic methods of obtaining informed consent should be considered.
- When it is not possible to obtain informed consent electronically, the sponsor should consider taking the following steps:
 - An unsigned consent form is provided to the patient by a health care worker who has entered the room
 - If direct communication with the patient in isolation is not feasible or safe, the Investigator (or their designee) obtains the patient's phone number and arranges a three-way call or video conference with the patient, an impartial witness, and if desired and feasible, additional participants requested by the patient, (e.g., next of kin)
 - To ensure that patients are approached in a consistent fashion, a standard process should be used that will accomplish the following:
 - Identification of who is on the call

- *Review of the informed consent with the patient by the Investigator (or their designee) and response to any questions the patient may have*
- *Confirmation by the witness that the patient's questions have been answered*
- *Confirmation by the Investigator that the patient is willing to participate in the trial and sign the informed consent document while the witness is listening on the phone*
- *Verbal confirmation by the patient that they would like to participate in the trial and that they have signed and dated the informed consent document that is in their possession.*

If the signed informed consent document cannot be collected from the patient's location and included in the study records, FDA considers the following two options acceptable to provide documentation that the patient signed the informed consent document:

- *Attestations by the witness who participated in the call and by the Investigator that the patient confirmed that they agreed to participate in the study and signed the informed consent*

OR

- *A photograph of the informed consent document with attestation by the person entering the photograph into the study record that states how that photograph was obtained and that it is a photograph of the informed consent signed by the patient.*

A copy of the informed consent document signed by the Investigator and witness should be placed in the patient's trial source documents, with a notation by the Investigator of how the consent was obtained, e.g., telephone. The trial record at the investigational site should document how it was confirmed that the patient signed the consent form (i.e., either using attestation by the witness and Investigator or the photograph of the signed consent). The note should include a statement of why the informed consent document signed by the patient was not retained, e.g., due to contamination of the document by infectious material.

If the patient is unable to provide informed consent and there is a legally authorized representative, Investigators must obtain consent from the participant's legally authorized representative in accordance with 21 CFR 50.27(a).

1.3 EFFECTS OF DISASTERS ON HUMAN RESEARCH PROTECTION PROGRAMS GUIDANCE

(This document provides guidance on the oversight of ongoing human research protections programs in affected areas after disasters.)

The Office for Human Research Protections (OHRP) understands that the effects of disasters (e.g., hurricanes, tornados, earthquakes) can be devastating to the affected areas. As a result, some human subject protection programs at institutions in the affected areas may be interrupted and unable to function and may be unable to do so for some time.

Oversight on Ongoing Research:

OHRP has been asked how such institutions should handle institutional oversight of ongoing, IRB approved research. One option is to rely on another IRB that is not affected by the disaster. IRB authorization agreements still must be executed. However, depending upon the breadth of a disaster, IRB records may not be available to send to another IRB for review. OHRP understands that it may not be possible or practical to prevent expiration of IRB approval. Investigators should be cognizant of when IRB approval for their research expires. Of course, any research that is determined to be in the best interest of already enrolled subjects may continue after expiration of

IRB approval. When Investigators determine that it is in the best interest of subjects to continue with the research, they are expected to notify the IRB, when possible.

OHRP encourages reasonable attempts to rely on another IRB. However, if extraordinary circumstances make relying on another IRB untenable, OHRP will take into account the situation at institutions that are affected by such disasters and will use available flexibility in its decision making if an institution failed to conduct continuing review at least annually. This flexibility will continue during the time that the devastation prevents the IRB from either conducting continuing review or temporarily relying on another IRB to conduct continuing review.

Research Activities:

It is difficult to provide generalized advice on the steps that affected Investigators, IRB, institutions, and sponsors should take. In some instances, it may be appropriate to terminate the conduct of a study where doing so would not endanger the subjects. In other instances, it may be appropriate to attempt to find a qualified Investigator and IRB outside the affected area to take over the conduct and oversight of the study in order to permit the study to continue, particularly where doing so would be in the best interest of subjects (*for example, treatment protocols*). Unfortunately, in some instances, studies may be disrupted, subjects and study staff so dispersed, and IRB records and research data so compromised that it may take some time to sort through these issues.

An institution holding an OHRP-approved assurance may extend their assurance to cover two types of collaborating individual Investigators: collaborating independent Investigators and collaborating institutional Investigators.

Another option is to make other individuals "agents" under their FWA for the purpose of carrying out some aspect of a research study on behalf of an engaged institution holding an FWA. Agents can include staff, students, contractors, and volunteers, among others, regardless of whether the individual is receiving compensation.

2.0 HRPP PURPOSE AND SCOPE

Saint Luke's Health System (SLHS) fosters a research environment that promotes the respect for the rights and welfare of individuals recruited for, or participating in, research conducted by or under the auspices of the Organization. In support of this, SLHS has established a Human Research Protection Program (HRPP). The SLHS Human Research Protection Program, in partnership with its research community, is responsible for ensuring the ethical and equitable treatment of all human subjects in research conducted under SLHS auspices.

The SLHS Human Research Protection Program is guided by the ethical principles regarding research involving human participants as set forth in the [Belmont Report](#). SLHS assures that all of its research involving human participants will comply with the Terms of Assurance for Protection of Human Subjects for Institutions within the United States (<http://www.hhs.gov/ohrp/assurances/index.html>). Research conducted outside of the jurisdiction in which SLHS resides is also subject to the same ethical and regulatory requirements, in addition to country/region specific requirements. This fundamental commitment to the protection of human participants applies to all SLHS research involving human participants, regardless of the funding source and regardless of the location of the research.

SLHS requires that all human research projects in which SLHS is *engaged* must be reviewed and approved by an SLHS IRB or an appropriate IRB within the HRPP prior to initiation. SLHS becomes *engaged* in human research when its employees (1) intervene or interact with living individuals for research purposes; (2) obtain individually identifiable private information for research purposes; or (3) all projects involving patients, personnel or resources (property or services) of SLHS.

The mission of the HRPP is to:

- Safeguard and promote the health and welfare of human research subjects by ensuring that their rights, safety and well-being are protected;
- Provide guidance and support to the research community in the conduct of research with human subjects;
- Assist the research community in ensuring compliance with relevant regulations;
- To provide timely and high quality education, review and monitoring of human research projects; and
- To facilitate excellence in research with human subjects.

The HRPP includes mechanisms to:

- Monitor, evaluate and continually improve the protection of human research participants
- Exercise responsible oversight of human subjects research
- Educate IRB Members, Investigators, and staff about their ethical responsibility to protect research participants
- When appropriate, intervene in research and respond directly to concerns of research participants.

2.1 ORGANIZATIONAL AUTHORITY

The SLHS Human Research Protection Program operates under the direction of the Director, HRPP and the SLHS HRPP standard guidance. SLHS policies serve as the governing framework for the conduct and review of all human research conducted under the auspices of the Saint Luke's Health System posted on the IRB website ([Institutional Review Board Standard Guidance and Education | Saint Luke's Health System \(saintlukeskc.org\)](#)).

The SLHS Human Research Protection Program supports the administration of the Saint Luke's Health System Institutional Review Board (hereafter referred to as the "SLHS IRB" or "IRB"). The SLHS IRB has the authority to review, approve, disapprove or require changes in research or related activities involving human subjects. As stated in [45 CFR 46.109](#), the IRB has the authority to:

- Review and approve, require conditions in (to secure approval), or disapprove all research activities covered by this standard guidance.
- Require that information given to subjects as part of informed consent is in accordance with [45 CFR 46.116](#).
- Require documentation of informed consent or waive documentation in accordance with [45 CFR 46.117](#).
- Notify Investigators in writing of its decision to approve or disapprove the proposed research activity, or of modification required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it will include in its written notification a statement of the reasons for its decision; however, a detailed critique of the protocol is not provided. The Investigator may rewrite and submit the study as a new protocol.
- Conduct continuing review of research covered by this standard guidance at intervals appropriate to the degree of risk, but not less than once per year.
- Have authority to observe or have a third party observe the consent process or the research and to review the research documentation.

The IRB also has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with serious harm to subjects ([45 CFR 46.113](#)). Any suspension or termination of approval will include a statement of the reasons for the IRB's action and will be reported promptly to the Investigator.

The IRB does not have the authority to grant retroactive approval should a research study be initiated without prior IRB review.

No institutional official at SLHS can reverse IRB decisions that involve disapproval, deferral, suspension, or termination of a research study. However, the SLHS Institutional Official (IO), SLHS Chief Executive Officer (CEO), or an Officer as designated by the SLHS CEO can disapprove an IRB approved protocol for activation or continuation at SLHS.

The IRB operates under the rules set forth under DHHS FWA00000922 for Protection of Human Subjects and the Code of Federal Regulations ([45 CFR 46](#)) as well as FDA regulations for the performance of all research activities that involve human subjects ([21 CFR 50 and 56](#)).

The responsibilities of the Institutional Review Board are:

- To protect human subjects from undue risk and deprivation of human rights and dignity.
- To disapprove studies of no scientific merit ([Belmont Report](#) – Respect of Persons).
- To ensure that participation by subjects is voluntary, as indicated by a voluntary and fully informed consent.
- To ensure equitable selection of subjects ([Belmont Report](#) – Justice).
- To maintain an equitable balance between potential benefits of the research to the subjects and/or society and the risks assumed by the subject ([Belmont Report](#) – Beneficence).
- To determine that the research design and study methods of a protocol are appropriate to the objectives of the research and the field of study.
- To assist the Investigator by providing peer review and institutional approval.
- To ensure compliance of protocols with the regulations of the FDA, DHHS, and other funding agencies when appropriate.

2.2 HRPP OFFICE RESPONSIBILITIES

Institutional Oversight of Federalwide Assurance:

A complete copy of the current SLHS Federal-wide Assurance (FWA) is maintained by the HRPP office and is available on the SLHS website, <https://www.saintlukeskc.org/human-research-protection-program>. The SLHS Chief Executive Officer (CEO) has ultimate responsibility for the institutional commitment made in the institution's Federalwide Assurance (FWA); and is the designated Signatory Official for the Institution and the HRPP.

In addition, the Chief Executive Officer (CEO) of SLHS possess knowledge about the requirements of Federal regulations, applicable state law, the institution's Assurance, and institutional policies and procedures for the protection of human subjects. The Chief Executive Officer (CEO) has full responsibility for leading the strategic planning, operational management, quality improvement, and development of all research conducted at, administrated by or affiliated with SLHS.

The SLHS Assurance is based on the following principles in order to safeguard the rights and welfare of human participants in research and other research activities.

- SLHS staff, which comprise its departments, divisions, and facilities, are subject to the Assurance and this Standard guidance. This includes any research for which an Assurance or another formal agreement (e.g., IRB Authorization Agreement) identifies the SLHS IRB as the IRB of Record.
- SLHS agrees to uphold the ethical principles of the Belmont Report to all proposed research involving human participants. The ethical principles set forth in the Belmont Report are:

- Respect for Persons: Recognition of the personal dignity and autonomy of individuals and special protection for those persons with diminished autonomy
- Beneficence: Obligation to protect persons from harm by maximizing anticipated benefits and minimizing possible risk of harm
- Justice: Fairness in the distribution of research benefits and burdens
- SLHS further agrees to apply additional regulations such as the U.S. Food and Drug Administration Human Subject Regulations ([21 CFR 50, 56, 312 and 812](#)), DHHS regulations ([45 CFR 46](#)), and the Health Insurance Portability and Accountability Act of 1996 (HIPAA), when applicable, to research involving human participants.
- This Assurance applies to research conducted within the jurisdiction with which SLHS resides (both local jurisdiction, state jurisdiction and US jurisdiction) as well as to research outside of the jurisdiction of SLHS (international human subject research in which SLHS faculty/staff/personnel are “engaged”).

2.3 IRB STANDARD GUIDANCE REVIEW

The SLHS HRPP maintains written policies and procedures reflecting the current practices of the IRB in conducting reviews and approvals under its Assurance. Policies and procedures are developed and revised by the HRPP office. As appropriate, the revisions are reviewed and approved by the IRB fully convened meeting of each Board.

Resource Evaluation:

On an annual basis, the Institutional Official (IO), the Director, HRPP, and the Manager will evaluate whether the number of IRBs is appropriate to the volume and types of human research being reviewed, so that reviews are accomplished in a thorough and timely manner.

In addition, the IRB administrative personnel and budget will be reviewed on an annual basis by the Institutional Official (IO), the Director, HRPP and the Manager. Modifications in space, facilities, and staff will be made as necessary to accommodate the volume and types of research reviewed.

Referral Process:

The Director, HRPP, Manager, and IRB Chair have the authority to consider whether a protocol requires expert consultation and/or a local context reviewer.

3.0 INSTITUTIONAL OFFICIAL

The Institutional Official (IO) is the individual who is legally authorized to act for the institution and, on behalf of the institution, obligates the institution to the Terms of the Assurance. The IO is responsible for ensuring that the HRPP functions effectively and that the institution provides the resources and support necessary to comply with all requirements applicable to research involving human subjects. The IO represents the institution named in the Federalwide Assurance (FWA). The IO should be an individual of sufficient rank who has the authority to ensure that all obligations of the HRPP are carried out effectively and efficiently. This person is usually the President, Chancellor, Director General, Chief Executive Officer, or Chief Operating Officer for the legal entity that constitutes the institution conducting research. The IO should be at a level of responsibility sufficient to allow authorization of necessary administrative or legal action should that be required. Thus, department Chairs, division directors or other officials who only have authority over one portion of the institution would generally not be an appropriate IO. Similarly, OHRP recommends that the IO not be the Chair or member of any IRB designated under the FWA.

What are the general administrative obligations of the IO?

- Designating one or more Institutional Review Board (IRB) that will review research covered by the institution's FWA;
- Providing sufficient resources, space, and staff to support the IRB's review and record keeping duties;
- Providing training and educational opportunities for the IRB and Investigators;
- "Setting the tone" by promoting an institutional culture of respect and conscience, so that the ethical conduct of human subjects research is supported at the highest levels of the organization;
- Ensuring effective institution-wide communication and guidance on human subjects research
- Ensuring that Investigators fulfill their responsibilities;
- Encouraging that all staff engaged in the conduct or oversight of human subject research participate in education activities
- Serving as a knowledgeable point of contact for OHRP and other federal agencies, or delegating this responsibility to another appropriate individual;
- Depending on the organizational structure at a given institution, other administrative arrangements may be appropriate.

What can the IO or designee NOT do?

- Approve research that has been disapproved (or not yet approved) by the IRB.

What are some responsibilities that may be delegated by the IO to a designee?

- The IO may delegate the performance of certain oversight and operational duties to one or more individuals. Any delegation of duty must be in writing. Upon designation of a new IO, all delegation letters must be reviewed and renewed by the new IO if the new IO chooses to maintain delegation.
- Appointing IRB Members. Suspending or terminating the IRB Membership of any individual for whom it has been determined that he/she is not fulfilling membership responsibilities and or obligations;
- Appointing the IRB Chair or Co-Chairs. Suspending or terminating the appointment of any Chair or co-Chair who is fulfilling his/her responsibilities and or obligations;
- Performing periodic evaluation of the performance of the IRB Chair and Co-Chairs and administrative staff;
- Managing and administering funds. Ensuring that adequate personnel, space and other resources are allocated to the HRPP;
- Reviewing and signing memoranda of understanding and cooperative agreements between the institution and other organizations, including those that establish reliance on IRB of record for collaborative research (e.g., IRB Authorization Agreements, Individual Investigator Agreements);
- Being the point of contact for correspondence addressing human subjects research with the OHRP, FDA and other agencies as applicable, including reports to federal agencies;
- Ensuring that IRB Members and Investigators are knowledgeable to conduct research in accordance with ethical standards and all applicable regulations;
- Developing and implementing an educational plan for IRB Members, staff and Investigators;
- Ensuring that IRB Members and Investigators are knowledgeable to conduct research in accordance with ethical standards and all applicable regulations;
- Performing periodic evaluation of the performance of the IRB Members and administrative staff;
- Recruiting qualified members to include expert, non-scientific and unaffiliated representation on the IRB;
- Reviewing and approving Standard Operating Procedures (SOPs) for the IRB and HRPP;
- Overseeing daily operations of the IRB and HRPP in accordance with the SOPs.

What responsibilities should NOT be delegated by the Institutional Official to a designee?

- *Signatory authority for the FWA;*
- *Completing recommended Assurance training for the IO;*
- *Ensuring that the IRB functions independently and that its Chair or co-Chairs and members have direct access to the IO for appeal if they experience undue influence or if they have concerns about the function of the IRB;*
- *Ensuring that adequate resources, including funds, space, and personnel are provided to support the operation of the HRPP.*

4.0 BOARD MEETINGS

The SLHS HHRP has under its jurisdiction two SLHS IRB committees that is responsible for reviewing any research involving human subjects conducted by staff or faculty of SLHS, as well as any other research involving human subjects as needed. The committee is constituted appropriately according to the Federal Regulations to review research with the sole purpose of protecting the rights and welfare of human subjects recruited to participate in research activities conducted under the auspices of the institution. Meetings of the IRB are held and documented in accordance with Federal regulations and guidelines for the review of research as denoted below.

Meetings of the IRB:

SLHS has two IRB committees who is charged with reviewing general biomedical and behavioral research. The committees meet on the second and fourth Tuesday of each month (except holidays). Protocols that require Board review are scheduled for a meeting once the pre-review conducted by the HRPP staff is complete. The agenda, along with meeting materials, is sent to IRB Members seven days in advance of the meeting.

Protocols may be submitted to the IRB at any time. Protocols are not reviewed by the committees unless the submission is complete.

IRB Members will utilize either paper or electronic copies of all items to be reviewed during the scheduled meeting. Both paper and electronic versions of materials meet regulatory requirements for IRB review. In addition, IRB Members will have access to the full IRB protocol file (either paper and/or electronic versions) during discussion and voting for each action on the meeting agenda. Criteria for approval are provided during each meeting as a) part of the mandatory IRB Reviewer Checklist and b) as handouts for reference during meeting discussions and voting. IRB meetings are conducted in person on the above noted schedule. An IRB meeting may be convened “ad hoc” in the event of an emergency and may be conducted in person as well as via teleconference (as long as quorum requirements are met).

Initial Review:

(Information Received and Reviewed by IRB Members)

The primary and secondary reviewer will receive and conduct an in-depth review of the protocol application, proposed informed consent documents, recruitment materials, the full protocol, any relevant grant applications, the Investigator’s Brochure (when one exists), the DHHS-approved sample informed consent document (when one exists) and the complete DHHS-approved protocol (when one exists).

All other IRB Members will receive and review the following: the protocol, application, proposed informed consent documents, and recruitment materials. These members are required to review the material in enough depth to be familiar with them and prepared to discuss them at the convened meeting.

Continuing Review:

(Information Received and Reviewed by IRB Members)

All IRB Members will receive:

- Continuing review application which includes information about study progress since the last review.
- A summary since the last IRB continuing review of all:
 - Amendments
 - Unanticipated problems involving risks to participants or others, protocol deviations, subjects complaints, or other reportable events
 - Data and Safety Monitoring Committee/Board and Data and Safety Monitors' reports, including interim findings and recommendations
- Current IRB approved consent documents.
- Any newly proposed consent documents.
- Current IRB approved protocol.
- Any newly proposed protocol modifications.

Primary and secondary reviewers are assigned and are charged with conducting an in-depth review of all submission materials. All other members are required to review the material in enough depth to be familiar with them and prepared to discuss them at the convened meeting.

If a study has expired because the IRB has *NOT* granted continuing approval by the expiration date (regardless of whether the application materials have been received by the expiration date), a member of the HRPP staff will send correspondence to the Investigator to inform them that all research activities must cease once the study expires. In addition, clarification as to whether any research activities have occurred after the expiration date is requested from the Investigator. The correspondence, together with the Investigator response is placed in the IRB record. The information is copied and distributed to all IRB Members at the IRB meeting when the study is reviewed; or in case of expedited review, it is provided to the IRB Member performing the review.

Amendments/Modifications to Previously Approved Research:

(Information Received and Reviewed by IRB Members)

The primary and secondary reviewer will receive and conduct an in-depth review of the amendment application (Investigator checklist), all modified documents with the changes highlighted, all relevant currently IRB approved documents (approved consent, research plan) the Investigator's written explanation for the changes, and a clean copy of the revised documents. All other IRB Members will receive

and review the amendment application (Investigator checklist), all modified documents with the changes highlighted, all relevant currently IRB approved documents (approved consent, current protocol), the Investigator's written explanation for the changes, and a clean copy of the revised documents in enough depth to be familiar with them and be prepared to discuss them at the convened meeting.

Additional Information Available to IRB Members:

Before and after the meeting IRB Members may come to the HRPP office to obtain the complete IRB protocol record, meeting minutes, and information provided to the primary reviewers. HRPP staff will make these items available to them upon request.

During the meeting, IRB Members may ask the HRPP staff for a copy of the protocol file, meeting minutes, and information provided to the primary reviewers. HRPP staff will make these items available.

Each month a copy of the Report of Administrative Actions for the preceding month is distributed to the members of the IRB for review.

Reviewer System:

Each protocol on an IRB agenda will be assigned a primary and secondary reviewer. The HRPP staff will assign a primary and secondary reviewer to each protocol and is responsible (in consultation with the IRB Chair when necessary) to ensure that at least one of these two reviewers has the required scientific and scholarly expertise required to review the protocol. If the research is a treatment protocol, the HRPP staff must assign a physician or nurse as the primary reviewer. If a primary or secondary reviewer with the appropriate scientific or scholarly expertise and background is not available, the HRPP Manager either refers the protocol to another IRB in the local affiliated HRPP or will utilize an appropriate consultant.

The primary reviewer is responsible to review all materials in depth and present the research proposal at the meeting of the IRB. The secondary reviewer is responsible to review all materials in depth, substitutes for the primary reviewer if the latter is absent at the meeting, and otherwise provides an additional level of review and discussion. After the primary and secondary reviewers have presented their comments, all Board Members discuss the documents received for review and add their comments.

Quorum and Voting:

Each action to be reviewed and voted upon during an IRB Committee meeting requires a “quorum”, which is defined “as the presence of at least 51% of the voting members as required by the Federal Regulations”. This includes the requirement to have at least one member whose primary concerns are in nonscientific areas, one member who is not affiliated with the institution and one member who represents the general perspective of the research participants present at a convened IRB meeting during the review and voting for each action. The non-scientific member, the non-affiliated member, and the person representing the general perspective of the research participants may be the same person.

In addition, if the IRB reviews research that involves categories of participants vulnerable to coercion or undue influence (e.g., decisional impaired or prisoners), one or more individuals who are knowledgeable about or experienced in working with such individuals must be present as part of quorum during the discussion and voting for any action as it relates to that specific research protocol.

A protocol must receive approval by a majority of the members present at a meeting for it to be approved. The IRB Chair or a member of the IRB Administration Office is responsible for monitoring the members present at convened meetings to ensure that the meetings remain appropriately convened. When quorum is lost during a meeting, the IRB cannot take further actions or votes until the quorum is restored. If the quorum cannot be restored, the meeting will be adjourned. Individuals choosing to abstain from voting on a particular action count toward maintaining quorum but not toward the required majority necessary for protocol approval. The IRB Chair abstains on each voted action but counts towards meeting the quorum. However, if the vote “for” or “against” an action is tied, the Chair will cast the deciding vote i.e., to vote “for” or “against” an action.

Criteria for IRB Approval of Research:

Initial Review Procedures:

Except for research that is exempted or waived under [45 CFR 46.101\(b\)](#) or [45 CFR 46.101\(i\)](#), all human subject research conducted under the jurisdiction of the HRPP will be reviewed, prospectively approved and subjected to continuing oversight and review at least annually by the IRB.

For the IRB to approve research it must determine that all of the following requirements are satisfied ([45 CFR 46.111](#) and [21 CFR 56.111](#)):

- Risks to subjects are minimized (i) by using procedures which are consistent with sound research design, and which do not unnecessarily expose subjects to risk; and (ii) whenever appropriate, by using procedures already being performed on subjects for diagnostic or treatment purposes.
- Risks are reasonable in relation to anticipated benefits, if any, and the importance of the knowledge that may reasonably be expected to result.
- Selection of subjects is equitable, taking into account the purposes of the research and the setting in which it is conducted.
- Informed consent will be sought from each prospective subject or the subject's legally authorized representative in accordance with [45 CFR 46.116](#).
- Informed consent will be appropriately documented in accordance with [45 CFR 46.117](#).
- The research plan appropriately monitors the data collected to ensure safety of subjects.
- The subject's privacy is appropriately protected, and confidentiality of the subject's data is maintained.
- Appropriate safeguards are included to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, decisional impaired, mentally disabled persons, or economically or educationally disadvantaged persons.

4.1 ACTIONS OF THE IRB

The IRB has established the following categories of actions to be taken on protocols (including new protocols, approved protocols at continuing review and amendments), reviewed at a convened IRB meeting:

Approved:

The protocol is approved as submitted with no changes. Approval is usually for one year; however, under certain circumstances (e.g., in high-risk studies in which the risks and benefits of the approved research cannot be fully anticipated) the IRB may limit the approval interval to a shorter period of time or require that the research be reviewed after a specific number of subjects are studied.

Approved with Conditions:

The protocol is approved pending receipt and administrative review of additional information, which can include minor clarification or modification of the protocol, consent form, or supporting materials. To qualify for this category, the IRB must, assuming that the conditions are satisfied, be able to make all determinations required for IRB approval (see Criteria for IRB Approval of Research above), including determinations about research risks and benefits, adequacy of privacy and confidentiality protections, and adequacy of the informed consent process. If the IRB cannot make determinations required for approval, it can either disapprove the project or defer or table the project for further review at a future date. Conditions of approval may include (1) confirmation of specific assumptions or understandings on the part of the IRB regarding how the research will be conducted (e.g., confirmation that the research excludes children); (2) submission of additional documentation (e.g., certificate of ethics training); (3) precise language changes to protocol or informed consent documents; or (4) substantive changes to protocol or informed consent documents along with clearly stated parameters that the changes must satisfy. Written notification of required conditions for approval will be sent to the Investigator. The Investigator

must provide responsive materials that, point by point, confirm that all such conditions have been satisfied. If a consent form is modified, two copies of the new consent form must be returned with one copy showing all deleted and inserted text. The other copy must incorporate all the changes. The Investigator's responses and requested modified documents will be administratively reviewed by the IRB Chair or another IRB Member designated by the Chair, on behalf of the IRB; and if all conditions for approval have been satisfied, an approval will be granted.

Deferred:

A protocol is deferred when the changes proposed, or questions raised by the Board are significant enough to warrant re-review of the protocol at a subsequent Board meeting. The Investigator will receive notification of the issues the IRB needs addressed or changed. If a protocol is deferred, it will usually be reconsidered by the same Board that deferred it. In addition to deferring the protocol the IRB may ask for additional review by expert consultants, or it may refer the protocol for an ethics consultation.

At the time of initial review, the IRB may approve some components of a proposed study and allow the Investigator to initiate research activities related to those approved components, while deferring, taking action on other components of the proposed study. In these circumstances, the approved components must be scientifically valid and satisfy all criteria required for IRB approval.

Disapproved:

If the protocol is judged to be lacking in scientific merit, if it raises ethical questions that cannot be resolved, or if it is decided that the risks outweigh the benefits to the subjects, the protocol will be considered unacceptable and disapproved. The Investigator will be notified in writing by the IRB including the reason(s) for the disapproval; however, a detailed critique of the protocol is not provided. The Investigator may appeal to the IRB regarding the decision or rewrite and submit the study as a new protocol.

Tabled:

The SLHS IRB consists of two committees that are equally constituted. The two committees are referred to as Board One and Board Two. The committees meet on the second and fourth Tuesday of the month (except holidays) at 2:00 PM Central.

Please note submissions may be "tabled" for the following reasons:

- Lack of meeting time to conduct thorough review of the item
- Loss of quorum
- Insufficient information to make a determination
- Other reasons as determined by the Chair
- The Investigator will not initiate any new research activities or implement proposed changes to previously approved research until the application has subsequently been reviewed by the IRB and they have received written notification of IRB approval.

4.2 SPECIAL DETERMINATIONS BY THE IRB

At Board meetings special determinations will be made, if appropriate, regarding pediatric risk, waiver of assent, waiver of informed consent, and waiver of signed consent, waiver of consent in Emergency Settings, and Emergency Use of Drug, Device or Biologic .

Pediatric Risk:

All studies involving children require IRB review in accordance with the provisions of [45 CFR 46 Subpart D](#). The IRB will determine the pediatric risk level of a protocol and document its determination by the appropriate Federal citation number in the minutes of the IRB meeting. The following determinations may be made according to Federal regulations.

- [45 CFR 46.404](#) **Research *NOT* involving greater than minimal risk to the children.** To approve this category of research, the IRB must make the following determinations:
 - The research presents no greater than minimal risk to the children.
 - Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in DHHS regulations at [45 CFR 46.408](#).
- [45 CFR 46.405](#) **Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research.** To approve research in this category, the IRB must make the following determinations:
 - The risk is justified by the anticipated benefits to the subjects.
 - The relation of the anticipated benefit to the risk presented by the study is at least as favorable to the subjects as that provided by available alternative approaches.
 - Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in DHHS regulations at [45 CFR 46.408](#).
- [45 CFR 46.406](#) **Research involving greater than minimal risk and no prospect of direct benefit to the individual child subjects involved in the research, but likely to yield generalizable knowledge about the subject's disorder or condition.** In order to approve research in this category, the IRB must make the following determinations:
 - The risk of the research represents a minor increase over minimal risk.
 - The intervention or procedure presents experiences to the child subjects that are reasonably commensurate with those inherent in their actual, or expected medical, dental, psychological, social, or educational situations.
 - The intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or amelioration of the disorder or condition.
 - Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in DHHS regulations at [45 CFR 46.408](#).
- [45 CFR 46.407](#) **Research that the IRB believes does not meet the conditions of [45 CFR 46.404](#), [46.405](#), or [46.406](#), but finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.**

If the IRB believes that DHHS supported research does not meet the requirements of [45 CFR 46.404](#), [46.405](#), or [46.406](#), but finds that it presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, it may refer the protocol to DHHS for review. Before submitting a protocol to OHRP, the IRB must determine that, in addition to meeting the requirements of [45 CFR 46.407\(a\)](#) and other applicable sections of subpart D, the proposed research also meets all of the requirements of [45 CFR part 46, subpart A](#). The research may proceed only if the Secretary, DHHS, or his or her designee, after consulting with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and following an opportunity for public review and comment, determines either: (1) that the research in fact satisfies the conditions of [45 CFR 46.404](#), [46.405](#), or [46.406](#), or (2) the following:

- The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.
- The research will be conducted in accordance with sound ethical principles.
- Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in DHHS regulations at [45 CFR 46.408](#).

Recent [OHRP guidance](#) for review of research classified as 407 by the IRB now states that OHRP will only review DHHS funded research. The DHHS position is: “DHHS will consult with a panel of experts under 46.407 only when the proposed research is conducted or supported by DHHS. Note that if an institution has elected in its assurance to apply all of the subparts of 45 CFR part 46 to all of its human subjects’ research regardless of the source of support, and the IRB finds that the proposed research meets the conditions for review under 46.407, the IRB is not required to submit the protocol to OHRP for review if the research under consideration is not supported by DHHS. In such cases, OHRP recommends that the institution consult with appropriate officials at the relevant federal agency or department supporting the research. When such research is supported by a non-federal sponsor, OHRP recommends that the institution consider convening an independent panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and provide an opportunity for review and comment by the local community where the research is to be conducted before deciding whether to proceed with the research.” Protocols meeting the conditions of [45 CFR 46.407](#) also may be subject to Food and Drug Administration regulations under [21 CFR 50.54](#) if the protocols involve a clinical investigation of an FDA-regulated product. Other protocols may be subject to FDA regulation at [21 CFR 50.54](#) but not subject to DHHS regulations at [45 CFR 46.407](#). The reader is advised to consult with The FDA should be consulted in the event that the review process falls within FDA’s regulatory purview.

Waiver of Assent:

The assent plan and documentation of assent for minors must be recorded in the meeting minutes. The IRB will determine if the assent may be waived for all or some of the population, based on the justification provided by the Investigator, and according to Federal regulations ([45 CFR 46.408](#)). This determination will be documented using the Federal citation number in the minutes of the Board meeting.

Alteration or Waiver of Consent:

- Alteration/Waiver of Consent Approved under [45 CFR 46.116\(c\)](#):

The research could not practicably be carried out without waiver or alteration.

- Alteration/Waiver of Consent Approved under [45 CFR 46 116\(d\)](#):

Involves no more than minimal risk, does not adversely affect rights and welfare of subjects, research could not be carried out without waiver or alteration, and subjects may be provided with information regarding the study.

Waiver of Signed Consent:

- Waiver of Signed Informed Consent Approved under [45 CFR 46.117\(c\) \(1\)](#):

The only record linking the subject and the research would be the consent document and the principal risk would be a breach of confidentiality.

- Waiver of Signed Informed Consent Approved under [45 CFR 46.117\(c\) \(2\)](#):

Research presents no more than minimal risk and involves no procedures for which written consent is normally required outside of the research context.

Waiver of Consent in Emergency Settings:

The IRB will consider protocols that require waiver of informed consent for emergency research. There is a limited class of research that may be carried out in human subjects who are in a life-threatening situation and in need of emergency therapy for whom, because of the subject's medical condition and the unavailability of legally authorized representatives of the subjects, no legally effective informed consent can be obtained. In these situations, a waiver of consent may be granted. The IRB has developed a detailed guidance in these situations. Protocols that request waiver of informed consent for research in emergency settings will always receive convened Board review. These research activities must be conducted in accordance with FDA regulation 21 CFR 50 and will be carried out under an FDA investigational new drug application (IND) or an FDA investigational device exemption (IDE). The research plan and all associated research protocol materials must clearly identify that will include subjects who are unable to consent and provide ample justification (in compliance with 21 CFR 50) as to why these subjects should be enrolled in the research.

Because of the special regulatory limitations relating to research involving pregnant women, fetuses and human in-vitro fertilization ([45 CFR 46, Subpart B](#)), and research involving prisoners ([45 CFR 46, Subpart C](#)), this waiver is inapplicable to these categories of research. The policies are stated in FDA regulation [21 CFR 50.24](#) and the joint publication by DHHS and the FDA of "Waiver of Informed Consent Requirements in certain Emergency Research, Federal Register, 61:51531-3, 1996." See also FDA Draft Guidance for Institutional Review Boards, Clinical Investigators and Sponsors: Exception from Informed Consent Requirements for Emergency Research Federal Register, 71:51198-9, 2006.

The waiver, under the following conditions below, can only be applied to all subjects in a protocol and never to only some study participants and always requires SLHS Law Department concurrence with IRB determination.

- If the research is FDA-regulated, it must meet the requirements of [21 CFR 50.24](#), Exception from informed consent requirements for emergency research.

Waiver of Consent for Emergency Use of Investigational Drug, Biologic or Device (subject to FDA regulation):

The IRB may review and approve a clinical investigation without requiring that informed consent of all research subjects be obtained if 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 human 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 informed consent is not feasible because:** The subjects will not be able to give their informed 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; and 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 subjects 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 support the potential for the intervention to provide a direct benefit to the individual subjects; and 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 could not 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 shall 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 informed consent procedures and an informed consent document consistent with Federal Regulations. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible.
- 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; and If obtaining informed 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 informed consent document, and 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 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.

- All clinical investigation records, including IRB determinations and regulatory files, shall be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by the regulatory authorities, as applicable.
- Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols to the FDA in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments to the existing IND/IDE.
- If an IRB determines that it cannot approve a request for exception from informed consent requirements in emergency research because the clinical investigation does not meet the criteria in the applicable Federal regulations 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, which must disclose the information as required by applicable regulations.

Waiver of Consent for Emergency Use of Investigational Drug, Biologic or Device (Not Subject to FDA Regulation):

The IRB may review and approve a clinical investigation without requiring that informed consent of all research subjects be obtained if 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 is not subject to FDA regulations
- AND**
- Item # 1 through item #8 as stated in the Requirements for Emergency Research Subject to FDA regulation as satisfied.

Review of Sponsor-Investigator:

Investigator-sponsors are required to be knowledgeable of the additional regulatory requirements of sponsors and knew how to comply with them. In order to ensure the Investigator-sponsor is knowledgeable about the additional regulatory requirements of sponsors and knows how to follow them, the IRB coordinator will verify that all Investigators and key study personnel have completed the required training upon receipt of a new IRB application. The IRB may request from the Principal Investigator (PI) additional documentation to assure the Investigators and key study personnel have adequate knowledge, processes, personnel, and facilities to conduct human subject research of investigational drugs, agents, biologics, and devices.

The IRB coordinator will not process IRB applications until all Investigators and key study personnel have completed the required training. The IRB coordinator will contact the PI or study contact when required training of all Investigators and key study personnel is incomplete and inform the PI that the study cannot be processed by the IRB until required training is complete. The IRB coordinator will document the name of the person called, the date called, the discussion and the response in the IRB database.

Other items reviewed during Convened Board Meetings:

The following additional items may be considered for approval, acceptance, or discussion during a convened IRB meeting as needed/available:

Chairperson's Report:

The Chairperson's Report is a discussion of general IRB matters which are of interest to the members. These include the addition or resignation of Board Members; articles related to IRB issues for education purposes; continuing education meetings; and the Board review and approval of IRB policies and submission forms.

Report of Administrative Actions:

The Report of Administrative Actions is a monthly report of the actions taken by the IRB outside of a convened meeting, including submissions determined not to qualify as "human subject research" (Non-Human Research Determinations), protocols reviewed via expedited review procedures ((new studies; continuing reviews; and addenda to approved protocols), protocol determined to be "exempt" from IRB review, adverse events that did not increase risk to subjects, unanticipated problems/protocol deviations that did not increase risk to subjects, information to File, and closures of previously IRB approved studies. Each month, the report is provided to both Boards prior to a convened meeting. At the convened meeting, members have the opportunity to ask any questions related to these items and request that any item be brought to a convened meeting for discussion and review. If members do not have any questions or concerns with any items within the report, the meeting minutes will reflect that the report was presented and no further action is required.

Determination on Non-Compliance Issue or Allegation:

The IRB will review issues or allegations of non-compliance. If the IRB determines that an issue or allegation of non-compliance is Serious or Continuing Non-Compliance, this determination will be documented in the minutes and the non-compliance will be promptly reported to the corresponding regulatory agency when applicable.

4.3 MINUTES OF A CONVENED BOARD MEETING

It is the standard practice of IRB that the minutes of a convened Board meeting will contain the relevant information as stipulated by Federal regulations ([45 CFR 46.115\(a\) \(2\)](#) and [21 CFR 56.115\(a\) \(2\)](#)).

Procedures for Documentation of IRB meeting Minutes:

An HRPP staff member will attend each committee meeting and will draft detailed notes to document the discussions and determinations of the Board for each agenda item. The Minutes of each IRB meeting will document the separate deliberations, actions, and votes for each protocol undergoing initial or continuing review by the convened IRB, and the vote on all IRB actions including the number of members voting for, against, and abstaining. The minutes must be sufficient in detail to demonstrate:

Attendance at the meeting for each IRB action, to include:

- If an alternate is present and who they are representing.
- The initial and continued presence of a majority of members (quorum), including at least one non-scientist.
- If a consultant is present

For each protocol discussed, the minutes must document:

- If a Committee Member is excused from the meeting due to a conflict of interest during the discussion and vote on the study. The name of the Committee Member is also recorded.
- Actions taken by the IRB (e.g., approved; conditions required to secure approval; deferred; and disapproved)

- The discussion of any controverted issues and their resolutions, and documentation of a consultant’s findings.
- The basis for required changes in research; the basis for disapproving research.
- The level of risk involved in the research (e.g., minimal, or greater than minimal risk).
- The approval period for initial and continuing review.
- Justification for any change in study design or risk level for amendments, including those submitted with the continuing review.
- The vote on the actions including the number of voting “for; against; and abstaining.” In order to document the continued existence of a quorum, votes should be recorded in the minutes using the following format: Total = xx, For: xx, Against: xx, and Abstained: xx. (Board Members who abstain are identified by name in the minutes.) Determinations required by the regulations (e.g., waiver or alteration of informed consent; research involving pregnant women, human fetuses, or neonates; research involving prisoners; research involving children; research involving individuals with diminished capacity); and protocol specific findings justifying those determinations.
- The IRB’s rationale for significant risk/non-significant risk device determinations.
- Justification of deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample informed consent document.

When the suspension of an approved protocol is considered, documentation of the discussion to allow for continued treatment of enrolled subjects must be included.

Distribution and Approval of the Minutes:

Draft minutes will be prepared by a member of the HRPP staff and forwarded to the HRPP Manager for review. After review by the HRPP Manager, the HRPP Analyst will make the necessary revisions and create a final electronic version of the document. The Board Members will receive copies of the minutes with a subsequent meeting packet. The minutes will be reviewed at a convened meeting of the Board that generated the minutes. Any requested revisions will be discussed and incorporated in the minutes. Once members have reviewed and no further revisions are requested, the meeting minutes will reflect that no more revisions are requested and the previous meeting minutes will be finalized.

4.4 NOTIFICATION OF ACTION AND REVIEW OF RESPONSES

When the IRB takes an action on a submission, written notification of the action, together with the rationale for the decision as well as a list of major or minor modifications/clarifications (when required) are sent to the Principal Investigator (and Study Coordinator when requested) from the SLHS HRPP Office. The results of IRB actions are conveyed via the electronic IRB submission system (iMEDris) usually within one week of the meeting at which the protocol was considered. Furthermore, when a primary reviewer (either through Full Board or expedited review) determines that additional modifications or clarifications are required, these are also forwarded in writing to the Responsible/Principal Investigator. All communications are sent by the IRB Administrative staff.

The Investigator must respond to all IRB requests using the electronic submission system (a limited number of protocols are still maintained in paper). When an Investigator responds to the IRB actions, these correspondences are reviewed by the IRB Members to determine whether the information provided satisfies the Board’s requests and the criteria for IRB approval. The information can be reviewed administratively by expedited review (when the Investigator has agreed to the changes requested by the IRB or the protocol is eligible for review using the expedited procedure). Otherwise, the modifications are reviewed by the convened IRB.

When the IRB disapproves a protocol, the Principal Investigator is provided with written notification for the reason(s) for the disapproval; however, a detailed critique of the protocol is not provided. The Investigator is instructed to contact the HRPP office with any questions. An Investigator may rewrite and submit the study as a new protocol if they wish but must take in to account the Board's concerns and reason(s) for the disapproval of the protocol.

When the IRB approves research with conditions, the IRB will document in IRB minutes and inform the Investigator of the following:

- All conditions that must be satisfied
- AND**
- Date when IRB Chair or designated person determines that all conditions of approval have been satisfied, the date when initial approval becomes effective, and date when continuing review must occur.

A copy of all findings and actions of the IRB, either during Full Board or Administrative review, are available to the Institutional Official (IO) upon request. The Institutional Official (IO) on the SLHS Federalwide Assurance, is also the President and Chief Executive Officer for SLHS, and a member of the SLHS Clinical Council.

Investigators at IRB Meetings:

IRB meetings are not routinely open to Investigators. The IRB may invite an Investigator to attend during part of the discussion of his or her protocol to respond to questions from members of the IRB or provide additional information. The Investigator is not present during the final discussion about the protocol or the protocol vote.

Visitors at IRB Meetings:

A visitor is anyone who is not a voting or non-voting member of the IRB, or member of the SLHS HRPP. Visitors may attend an IRB meeting with the approval of the Chair of the meeting. Visitors may not be present during discussions and voting on compliance issues. Visitors who attend meetings of the IRB must sign a "Visitor Confidentiality Agreement". Copies of signed Confidentiality Agreements will be kept on file in the IRB Administration Office.

Study Withdrawal for Lack of Response:

If a protocol has been given contingent approval with a request for minor changes; or has been deferred, a written letter outlining the required changes or reasons given for the action will be sent to the Investigator. The Investigator has 90 days from the time of the IRB meeting at which the protocol was considered to respond in writing to the changes requested by the IRB. If the Investigator does not respond in writing within 60 days from the time of the IRB meeting, a reminder letter will be sent. If the Investigator does not respond in writing in 90 days, the protocol will be closed by the IRB. A written notice of Withdrawal for lack of response will be sent to the Investigator and placed in the protocol file. If the Investigator wishes to seek approval for the study, a new protocol must be submitted and approved. If there are unusual circumstances that prevent a timely response to requested changes, the principal Investigator can request an extension of time to respond.

Length of Time of Approvals:

The DHHS and FDA regulations require reevaluation of approved research at intervals that are appropriate to the degree of risk, but not less than once a year [45 CFR 46.109\(e\)](#) and [21 CFR 56.109\(f\)](#). At SLHS, the maximum approval period for new protocols and the re-approval of studies at continuing review, is one year minus one day.

It is important to note, that IRB approval is a temporary authority and may be withdrawn at any time if warranted by the conduct of the research activities.

When determining the approval period of protocols at initial and continuing review, the Board determines whether the estimate of the Investigator's assessment of the anticipated results, risks and procedures are reasonable; whether the risk/benefit ratio is appropriate and accurate; and whether there is an adequate plan for monitoring the data collected to ensure subjects safety.

The IRB recognizes that protecting the rights and welfare of subjects sometimes requires that research be reviewed more often than annually. *For example, when a highly vulnerable subject population is being researched, the risks may not be completely known at initial review.* The IRB shall monitor the research project closely and require more frequent than annual review. The IRB shall consider the following factors in determining the criteria for which studies require more frequent review and what the timeframes generally will be:

- Probability and magnitude of anticipated risks to subjects.
- Likely psychological condition of the proposed subjects.
- Overall qualifications of the Principal Investigator (PI) and other members of the research team.
- Specific experience of the PI and other members of the research team in conducting similar research.
- Nature and frequency of adverse events observed in similar research at this and other facilities.
- Vulnerability of the population being studied.
- Other factors that the IRB deems relevant.

In specifying an approval period of less than one year, the IRB may define the period with either a time interval or a maximum number of subjects (i.e., after 3 months or after three subjects enrolled). OHRP recommends that the minutes clearly reflect these determinations regarding risk and approval period.

The approval date is determined by the date which the research was reviewed and approved by the full Board. If the full Board requests modifications to secure approval which can be administratively approved, the approval date is calculated from the date that the protocol was reviewed at full Board approval, and not the date the changes were administratively approved. The expiration date is one day less than the period of approval, e.g., if the approval period is for one year starting April 14, 2006 then the study will expire at midnight on April 13, 2006.

For protocols approved by expedited review, the expiration date is also one day less than the period of approval that is awarded by the IRB Chair or a designated senior IRB Member. When amendments are approved, the expiration date of the protocol does not change. The approved consent form will have the IRB approval stamp stating the expiration date of the protocol.

Authorized Signatures:

The Chair of the IRB is authorized to sign outcome letters for actions taken on behalf of the IRB. In the absence of the Chair, the HRPP Manager of SLHS or designated IRB Member or HRPP staff may sign an IRB approval.

Research Conducted at Multiple Sites:

SLHS may rely upon an IRB outside of the SLH HRPP as per an executed IRB Authorization Agreement (or Inter-Institutional Amendment) in effect between the collaborating institutions. The decision of which IRB to rely on for review of a particular protocol is made by the Director, HRPP in consultation with the Institutional Official (IO).

Institutions external to SLH may rely on the SLH IRB if there is an executed IRB Authorization Agreement in effect between the institution and the SLH IRB. The decision of whether the SLH IRB will serve as the IRB of record for an external institution is made by the Director, HRPP in consultation with the Institutional Official (IO).

5.0 IRB CHAIR

The SLHS IRB is guided by the ethical principles regarding research involving human participants as set forth in the [Belmont Report](#). SLH assures that all of its research involving human participants will comply with the Terms of Assurance for Protection of Human Subjects for Institutions within the United States (<https://www.hhs.gov/ohrp/>).

IRB Chair will be appointed to 3-year terms and are eligible for reappointment at 3-year intervals. During the appointment period, an IRB Chair may be removed at the discretion of the Institutional Official (IO). In addition to their authorities and responsibilities as IRB Chairs, such individuals serve as members of the IRB and are counted for the quorum. They shall have voting privileges and other authorities and responsibilities of members including the responsibility to review, make motions, participate in discussions and vote on approval/disapproval of studies.

Appointment:

The Institutional Official (IO) appoints the Chair of the IRB.

Conflict of Interest Disclosure:

The IRB Chair with a conflicting interest in a protocol must disclose the conflict and leave the room during the discussion of the protocol and the related vote, except if they are providing information at the request of the IRB. The IRB Chair will remind the IRB Members of the importance of disclosure of conflict of interests and review relevant policies as often as necessary.

Compensation:

The IRB Chair will be compensated for their IRB duties and responsibilities by protecting their time at the discretion of the Institutional Official (IO) and will consider the professional background of the individual and the expected time commitment of the appointed position to IRB activities.

IRB Review:

The IRB Chair is responsible for the following IRB Review duties including but not limited to:

- Maintain a thorough understanding of federal regulations pertaining to human subject protections, the SLH IRB Policies and Procedures, and other applicable SLH Clinical Policies, state, and local regulations;
- Review and approve, when appropriate, expedited submissions in accordance with regulatory requirements under 45 CFR 46.110 and 21 CFR56.111;
- Review and approve, when appropriate, research that is considered “exempt” in accordance with regulatory requirements 45 CFR 46.101;
- Review (or assign the review to other IRB Members as appropriate) adverse event reports (AEs) and unanticipated problems/protocol deviations (U/D) to determine if the event affecting the safety of subjects and, the conduct of the trial. As warranted, the IRB Chair may also determine course of immediate action to address the safety of subjects; and if necessary and in consultation with the Institutional Official (IO), convene an emergency meeting of the IRB with the assistance of the IRB Administration Office;

- Appoint qualified staff members from the HRPP office or from the SLH Clinical Research Community as IRB designees with review and signature authority as defined in these Policies and Procedures;
- Assure that regulations and policies are applied in all IRB matters with a commitment to foster ethically and scientifically sound human subject research;
- Respect the diverse backgrounds, perspectives, and sources of expertise of all IRB Members and foster such respect among the IRB Members and;
- Uphold IRB judgments no matter how these are received or perceived by Principal Investigators

IRB Meetings:

The IRB Chair has the overall responsibility for the oversight of the IRB meeting.

With the assistance of HRPP staff, the IRB Chair is responsible for monitoring the members present at convened meetings to determine that the meetings are appropriately assembled and remain appropriately convened.

The Chair abstains on each voted action but counts towards meeting the quorum. However, if the vote “for” or “against” an action is tied, the Chair will cast the deciding vote i.e., to vote “for” or “against” an action.

The IRB will set conditions as recommended by OHRP and the FDA, for the approval of research at a convened meeting. In cases where the convened IRB requests substantive clarifications or modifications regarding the protocol or informed consent documents that are directly relevant to the determinations required by the IRB in accordance with regulatory requirements under 45 CFR 46.111 and 21 CFR 56.111, IRB review of the proposed research will be deferred, pending subsequent review by the convened IRB of responsive material. When the convened IRB stipulates specific revisions requiring simple concurrence by the Investigator, the IRB Chair or another IRB Member as designated by the Chair, may subsequently approve the revised research on behalf of the IRB under an expedited review process.

IRB Chair Responsibilities Prior to Each Convened Meeting:

The IRB Chair, with assistance from the HRPP staff, will ensure meeting coverage when not able to serve as Chairperson for the meeting as scheduled.

Prior to each convened meeting the IRB Chair is responsible for the meeting will:

- Review IRB meeting schedule and agenda;
- Provide guidance to the HRPP staff on the assignment of reviewers to studies requiring convened IRB review if requested;
- Assist the IRB reviewers and other IRB Members with any concerns in preparing for the meeting, as necessary and;
- Recommend consults and/or external reviews when appropriate to assist in IRB reviews.

IRB Chair Responsibilities during IRB Meetings:

During each convened meeting the IRB Chair with the assistance of HRPP staff, will be responsible for the following:

- Preside over IRB meetings and ensure that meetings are conducted in an efficient, orderly, and fair manner with respect given to the opinions of all members;
- Ensure a quorum for each study review and ensure that this quorum is properly documented;

- Ensure that all regulatory-required elements of review are addressed during the meeting and that there is meaningful and substantive discussion of relevant matters and/or questions;
- Ensure that assigned reviewers present a clear and concise review of study materials including consent documents and recruitment items and process;
- Ensure that all IRB-required changes to consent and other documents are documented;
- Ensure that the IRB discusses specific findings, as required by regulations, whenever there is the involvement of vulnerable populations, e.g., children, prisoners, pregnant women, and fetuses;
- Accept appropriate motions from voting members of the IRB;
- As necessary, ensure that the specific elements pertaining to the motion are clearly understood by the IRB and accurately recorded in the meeting minutes;
- Ensure that IRB decisions are made in accordance with federal, state, and local regulations and with the SLH IRB Policies and Procedures and;
- Review the minutes of IRB meetings and votes of the IRB Members to ensure it accurately reflects discussions and actions.

6.0 IRB MEMBERSHIP

The SLHS IRB and HRPP are guided by the ethical principles regarding research involving human participants as set forth in the [Belmont Report](#). The HRPP assures that all of its research involving human participants will comply with the Terms of Assurance for Protection of Human Subjects for Institutions within the United States (<https://www.hhs.gov/ohrp/>).

The purpose of this guidance is to describe the responsibilities of IRB Members and a recommended approach for conducting a thorough review of items, including initial, amendments, continuing reviews, and reportable events.

Each IRB Member's primary responsibility is the protection of the rights and welfare of the individual human beings who are serving as the subjects of research. In order to fulfill these responsibilities, IRB Members are expected to be versed in regulations governing human subject protection, biomedical and behavioral research ethics, and Saint Luke's Health System IRB policies and procedures.

Appointment:

- The appointment or re-appointment of an IRB panel member including their designation as either a scientist or non-scientist, affiliation status and representative capacity is thoroughly vetted and approved by the HRPP Manager, or designee.
- IRB Members/alternatives are appointed for a three-year term. Members/alternatives are eligible for re-appointment at the end of their term.
- The HRPP Manager is responsible for the appointment and re-appointment of members to an IRB Roster.
- The HRPP Manager is responsible for determining the IRB Member's status on the IRB Roster at the time of appointment and re-appointment.
- HRPP office Staff will assist the HRPP Manager with these responsibilities by collecting required documentation, scheduling interviews, and managing correspondence.

IRB Composition:

Each IRB has at least five members with varying backgrounds to promote complete and adequate review of research commonly conducted at Saint Luke's Health System (SLHS).

- Each IRB includes at least one Registered Nurse (RN) with voting privileges to meet the requirements of the American Nurses Association (ANA) Magnet Recognition Program.
- Each IRB is sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.
- Every nondiscriminatory effort is made to ensure that no IRB consists entirely of men or entirely of women.
- No IRB consists entirely of members of one profession.
- Each IRB includes at least one member whose primary concerns are in scientific areas (scientific member).
- Each IRB includes at least one member whose primary concerns are in nonscientific areas (non-scientific member).
- Each IRB includes at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution (non-affiliated member). This member represents the perspective of research subjects.
- No IRB has a member participate in the IRB's initial or continuing review of any research project in which the member has a conflicting interest, except to provide information requested by the IRB.
- An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals do not vote with the IRB.
- Each IRB is able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice.
- For each IRB that reviews research involving vulnerable subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration is given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those human subjects.
- For all research projects that involve prisoners as a vulnerable category, at least one member who is a prisoner representative is required to participate in the review of any research involving prisoners as subjects.
- Several IRB Members serve as an alternate for other members. The list of IRB Members must identify the member(s) for whom each alternate member may substitute.

IRB Roster:

- IRB Administration identifies new replacement members for existing members who rotate off the IRB Committees and submits the names of the members comprising the IRB Committees to the Institutional Official (IO) for review and approval.
- IRB Administration is responsible for maintaining a current roster of all members serving on the IRB. Current rosters are accessible on the IRB's website. Upon request, copies may be provided to external study sponsoring organizations, regulatory agencies, and/or representatives of each.
- The IRB roster shall include, at a minimum, the following:

- Initial
- Earned Degree(s)
- Primary area of expertise or specialty
- Alternate status and which member(s) or class of primary members the alternate may replace

Conflict of Interest Disclosure:

IRB Member’s with a conflicting interest in a protocol must disclose the conflict and leave the room during the discussion of the protocol and the related vote, except if they are providing information at the request of the IRB. The IRB Chair will remind the IRB Members of the importance of disclosure of conflict of interests and review relevant policies as often as necessary.

Assigned Reviewers:

For each item to be considered by a convened IRB meeting, assigned reviewers are selected from the regular or alternate members of that specific IRB. Assigned reviewers may be designated as *primary* reviewers or *additional* reviewers.

The *primary* reviewer conducts a comprehensive review of all submitted materials for the assigned item, presents findings resulting from that review, provides an assessment of the criteria for approval, and recommends specific actions to the IRB. The primary reviewer leads the discussion of the assigned item.

One or more *additional* reviewers is assigned to new applications and to selected continuing reviews and revisions. Additional reviewers also conduct comprehensive reviews to supplement those provided by the primary reviewer, focusing on areas or issues not otherwise addressed. The additional reviewer may serve as the discussion leader in the unexpected absence of the primary reviewer.

All assigned reviewers are authorized and expected to contact Investigators or other study personnel (if appropriate) to resolve questions or concerns whenever possible prior to the convened IRB meeting.

It is recommended that assigned reviewers use the IRB Reviewer Checklists and/or Reviewer Worksheets to assist in organizing and documenting reviews for presentation to committee members.

Assigned reviewers are expected to document reviews prior to the convened IRB meeting. This provides all members sufficient time to read the reviewer findings and recommendations, to be familiar with any issues, to contribute to the discussion, and to prepare to vote.

Assigned reviewers perform a comprehensive review of each assigned item and make recommendations for consideration by the IRB. The reviewers assess whether:

- The ethical principles of research with human subjects are upheld;
- All criteria at 45 CFR 46.111 (Criteria for Approval of Research) and 21 CFR 56.111 (as applicable) have been met;
- The research includes enrollment of vulnerable subjects and if appropriate safeguards are in place;
- The research involves use of an FDA-regulated product(s) and the regulatory status of the product(s);
- The consent process, as described by the Investigator, is appropriate;
- The consent document is understandable and contains all the required and additional elements as appropriate;
- The study requires data and safety monitoring to ensure the safety of subjects;
- The interval for continuing review of the research is appropriate.
- The research fulfills the criteria for referral for continuing review by expedited review procedures;

- The research design and scientific merit are appropriate (often informed by departmental research scientific review recommendations);
- Conflict(s) of interest exist for any study team member(s) and, if present, there are adequate provisions to protect human subjects from any additional significant risk and to maintain the integrity of the research;
- Ad hoc expertise (i.e., use of a consultant) is needed to assist in the review of issues which require expertise beyond or in addition to that available on the IRB.

As applicable to each new application under review:

- At least one member assesses whether the proposed research is consistent with any corresponding Department of Health and Human Services funding application(s),
- AND**
- At least one member reviews the DHSS-approved consent document.

Amendment to Previously Approved Research:

For convened IRB review of revisions to previously approved research:

- All members (including alternates in attendance) have access to and review the revised materials
- Assigned reviewers are selected from the regular or alternate members scheduled to attend the specific convened IRB meeting.
- Each assigned reviewer conducts a review of the request for revisions in accordance with the criteria for approval and assesses whether the proposed revisions are consistent with ensuring the continued protection of subjects. In addition, assigned reviewers consider whether:
 - Any new significant findings have arisen that may impact the subject's willingness to continue participation.
 - Any new information resulting from the revisions or from other sources necessitates an adjustment to the IRB's prior determination(s), such as inclusion of protected or vulnerable populations and findings regarding FDA-regulated products.
 - The proposed revisions to the research require revision of the consent document(s), and if so, whether the revised consent documents are accurate and understandable to the subject population.
 - The revisions warrant re-consenting of currently enrolled subjects or notification of subjects who have completed research interventions.
 - Continuing review should occur more frequently than previously determined.
- Assigned reviewers present findings and recommendations during the convened IRB meeting.

Continuing Review:

For continuing review of research by a convened IRB:

- Assigned reviewers are selected from the regular or alternate members scheduled to attend the specific convened IRB meeting.
- Each assigned reviewer conducts a comprehensive review of the ongoing research and status report, including the:
 - Full protocol, a current consent document(s) (as applicable), and revisions previously approved by the IRB and any occurring since the last IRB review

AND

- Progress and findings to date as reported in the Investigator's continuing review application.
- At a minimum, assigned reviewers assess:
 - Whether the research continues to meet the criteria for approval, and if any new information resulting from the specific research under review or from other sources necessitates an adjustment to the IRB's earlier determination(s)

AND

- The appropriate interval for continuing review.
- Assigned reviewers present findings and recommendations during the convened IRB meeting.

Guideline for Reviewer Presentations at Convened IRB Meetings:

Oral presentations conducted by the primary reviewer should include:

- A succinct summary of the research study
- An overview of the population of subjects being studied, including protocol specific findings pertaining to adequacy of protections for any vulnerable subjects
- As applicable, a description of the FDA-regulated product(s) under study and the regulatory status of the product(s), including recommendations for significant/ non-significant risk device determinations
- A recommendation regarding whether or not the criteria for approval of research (45 CFR 46.111, and as applicable 21 CFR 56.111) are met
- Enough background to justify the performance of the research
- Information necessary for the members to make an informed decision on the approvability of the research
- A critique that includes pertinent deficiencies or criticisms of the application
- Comments regarding the consent process and the content of the consent document
- Points that should be changed by the Investigator in sufficient detail so that other members and support staff understand what is needed in meeting minutes and notifications to the Investigator
- A motion for a determination on the item.

Additional reviewers should focus on areas of disagreement with the previous reviewer(s) or on additional findings not previously covered.

7.0 DEPARTMENT AND ANCILLARY REVIEW

It is the standard guidance of the IRB that an individual and/or committee in each department reviews all protocols prior to submissions to the IRB. The review address scientific merit, ethical issues, and the availability of departmental resources to carry out the research. Department review allows the Chair/Director of the Department to be aware of research activities.

Investigators must first submit to their Department Chair/Director and/or Research Review Committee for review and approval. This applies to new protocols and when directed by the IRB protocols submitted for continuing review, and amendments with major study design changes or changes that alter the level of risk to subjects.

The IRB does not review or approve any protocol that has not been reviewed and approved by the Principal Investigator's department.

Protocols originating in nursing are reviewed by the Nursing Research Council prior to submission to the IRB.

Functions of a Department Chair/Director or Department Research Review Committees:

- Review the scientific merit of a protocol
- Review the available resources (including qualified staff, appropriate population, and adequate facilities) to carry out the proposed research within the department
- Review the proposed time to conduct and complete the research
- Review ethical concerns related to the study risk especially as it relates to the discipline represented by the department
- Review the protocol, consent forms and other study related documents
- When IRB directed, review amendments to approved protocols if the amendment adds significant risk to the subjects or significantly alters the study design or procedures
- Serve as an educational resource for faculty and staff of the department on human subject protections

Each Department Chair/Director or Research Review Committee:

- Ensures timely and prompt review of protocols submitted for review
- Organizes a timely and efficient review process for protocols submitted
- Does not need to have a convened meeting if the department sends protocols to committee members individually for review
- Refers protocols to an Ethics Committee for review and recommendations when either the Chair/Director or committee members believe it is appropriate

Appointment and Members of Department Research Review Committee:

- The Chair/Director of the clinical department may appoint members to a Department Research Review Committee from among the department's faculty.
- A Department Review Committee has a minimum of two faculty members
- Members may be appointed to a Department Research Review Committee for any length of service considered appropriate by the department
- Members of a Department Research Review Committee do not participate in the review or vote on their own protocols.

(Note: The Vice President of Research will review and approve protocols of which the Department Chair/Director is the Principal Investigator.)

Chair of Department Research Review Committee:

The Chair/Director of the department appoints a Chair of the Department Research Review Committee from among the members of the committee. A Department Chair/Director may be a member of the Department Research Review Committee and may Chair the committee. The Chair of the Department Research Review Committee should have experience in clinical research and be familiar with Federal regulations governing human subject research and IRB standard guidance. The Chair also serves as a resource for the department members who have questions about IRB issues.

Secondary Department Reviews:

- Protocols involving medical care or treatment of subjects not under the primary care of the Principle Investigator's Department must also obtain approval from the Department responsible for the subjects' care.
- If a protocol includes a Co-Investigator from the responsible Department, review by that additional Department is at the discretion of the IRB and will depend on the nature of the study.

Additional Required Reviews:

Human subject research protocols may require review and approval from entities not represented by the Principal Investigator's under the HRPP policies. Human subject research conducted at SLHS which involve any of the following procedures (experimental or otherwise) will require additional review from the appropriate departments of committees prior to IRB approval:

- Biosafety
- Department Pathology
- Department of Radiology
- Electrical Safety
- Grants and Contracts
- Investigational Pharmacy
- Nursing Research Council
- Radiation Safety
- Research Information Technology (IT)
- Scientific Review
- Special Care Units

Biosafety:

Biosafety is responsible for assessing containment level for research involving recombinant DNA and synthetic nucleic acid molecules. Biosafety will oversee research with other potentially hazardous biologics such as; Recombinant DNA and synthetic nucleic acid molecules (this includes human gene transfer studies), infectious agents, biological toxins, human-derived tissues, fluids, cells, certain animal-derived tissues, fluids, cells and federally regulated select agents, experiments with Dual Use Research of Concern potential and research requiring BSL3 containment.

Department of Pathology:

Protocols that include research use of surgical tissue that is sent to the Department of Pathology may require approval of the Department of Pathology. This requirement does not apply if a member of Pathology faculty in an Investigator on the protocol, or if the tissue is obtained under an IRB approved protocol for tissue banking.

Department of Radiology:

The Department of Radiology must review protocols originating in Radiology and protocols that contain radiological tests. This requirement does not apply if a member of Radiology faculty in an Investigator on the protocol.

Electrical Safety:

If the protocol involves subject contact with new or nonstandard (non-FDA approved) electrical equipment, the equipment and the protocol must be submitted for approval to the Electrical Safety Office. Electrical Safety is also a requirement when the equipment's grounding is attached to the unit's casing. Each protocol must include sufficient information to determine whether electrical safety is an issue. The protocol must identify all experimental or investigational electrical equipment used in subject contact by manufacturer model and serial number (if known) and an IDE number (if applicable). The protocol must describe how the equipment is to be used,

as well as its location. All equipment must be approved before use on subjects. Approval should be submitted to the IRB with the protocol.

Grants and Contracts:

The Grants and Contracts Office must review all industry-sponsored protocols and research contracts for the purposes of ensuring coordination of legal review, ensuring that Investigators follow fiscal guidelines, and ensuring regulatory compliance with research billing policies. Grants and Contracts Office approval is not required prior to IRB submission although approval is required prior to subject enrollment.

Investigational Pharmacy:

Investigational Pharmacy has the sole responsibility for the procurement, storage, distribution, and control of all medications for patients at SLHS. The Department provides information and assistance on the clinical use, pharmacokinetics, administration, and adverse reactions of medications.

Investigational Pharmacy dispenses investigational only in accordance with the current protocol approved by the IRB. All investigational products are dispensed through Investigational Pharmacy unless an exception has been reviewed and approved by the Investigational Pharmacy and Research Services.

Investigators using an investigational product as part of their protocol must contact Investigational Pharmacy to discuss how and by whom the drugs will be dispensed, whether an investigational new drug (IND) application with the FDA should be considered, and to review any other special considerations for feasibility assessment.

Nursing Research Council:

Protocols originating in nursing are reviewed by the Nursing Research Council prior to submission to the IRB. This is done to facilitate the process of conducting nursing research and evidence-based practice within SLHS, ensure compliance with SLHS Office of Research Services (ORS), collaborate with quality structure to support research and quality scholarship and sharing, assist in the distribution of nursing research funds allocated for SLHS nursing research, evaluate nursing research proposals to be carried out within SLHS and forward recommendations to the appropriate individuals, support the IRB by approving credentials of primary nurse Investigators, and ensuring scientific merit of nursing research projects prior to submission to the IRB, provide support for the dissemination and utilization of nursing research results, and to collaborate within the shared governance structure to maintain a structure and an environment that integrates nursing research and evidence-based practice into the practice of nursing.

Radiation Safety:

Protocols that use ionizing radiation (such as x-ray, CT, scintigraphy, PET, SPECT, etc.) in human subjects for research purposes outside standard clinical care require review and approval by Radiation Safety (RS) of the institution in which the procedure is to be performed.

This requirement is based not on the nature of the procedure but on whether the person would receive the radiation only because he/she is participating in the research. (Conversely, if the person would receive the radiation for his/her clinical care, regardless of the enrollment status, RS review is not required.)

If there is any question if radiation exposure is part of a subject's standard of care, Investigators or the IRB may ask for a determination by either (1) submitting a written, signed report from the review committee of the department that performs the procedure which exposes humans to radiation or, (2) submitting the protocol to RS for its determination.

In the event of a disagreement whether the proposed radiation use is within the standard of care, the matter is brought to RS for evaluation. This evaluation includes input from the department proposed to perform the procedure that exposes humans to ionizing radiation.

Research Information Technology (IT):

Research IT reviews all protocols with (1) previously un-approved methods of data storage; (2) protocols involving the use of an electronic application; (3) all methods of electronic consent; or (4) any other data storage / extraction / transmission methods that have not been previously approved. Protocols involving the aforementioned study procedures are required to undergo Research IT review prior to IRB approval. REDCap is the preferred storage method for research data.

Special Care Units:

Protocols involving subjects in areas of special care, such as intensive care units or respiratory care units, require the approval of the director of that area, as well as the approval of the Department Chair.

Signatures:

- After the Department Chair/Director and/or Research Review Committee has reviewed a protocol and is satisfied a signature is provided.
- The Department Chair/Director does not sign for protocols on which he/she is the Principal Investigator. The Vice President of Research will review and approve protocols of which the Department Chair/Director is the Principal Investigator to ensure available resources (including qualified staff, appropriate population, and adequate facilities) to carry out the proposed research within the department are satisfied.

(Note: an alternate from the respective department is also required to review the protocol for scientific merit and concerns related to the study risk especially as it relates to the discipline represented by the department.)

- The staff of the IRB ensures that the review has taken place and the criteria for review by the Department Chair/Director and/or Research Review Committee have been addressed prior to formal IRB review of the research.

8.0 ENGAGEMENT IN HUMAN RESEARCH

An organization is considered engaged in human research when its employees or agents, for the purposes of nonexempt research project, obtain:

- Data about the subjects of the research through intervention or interaction with them;
- Identifiable private information about the subjects of the research;
- The informed consent of human subjects for the research; or when the institution receives a direct federal award to conduct human subject research, even when all activities involving human subjects are carried out by a subcontractor (that is, employees or agents of another institution).
 - Institutions that receive an award through a grant, contract, or cooperative agreement directly from HHS for the non-exempt human subject's research (i.e., awardee institutions), even where all activities involving human subjects are carried out by employees or agents of another institution.

- Institutions whose employees or agents intervene for research purposes with any human subjects of the research by performing invasive or noninvasive procedures.
Examples of invasive or noninvasive procedures include drawing blood; collecting buccal mucosa cells using a cotton swab; administering individual or group counseling or psychotherapy; administering drugs or other treatments; surgically implanting medical devices; utilizing physical sensors; and utilizing other measurement procedures.
- Institutions whose employees or agents intervene for research purposes with any human subject of the research by manipulating the environment.
Examples of manipulating the environment include controlling environmental light, sound, or temperature; presenting sensory stimuli; and orchestrating environmental events or social interactions.
- Institutions whose employees or agents interact for research purposes with any human subject of the research.
Examples of interacting include engaging in protocol-dictated communication or interpersonal contact; asking someone to provide a specimen by voiding or spitting into a specimen container; and conducting research interviews or administering questionnaires.
- Institutions whose employees or agents obtain for research purposes identifiable private information or identifiable biological specimens from any source for the research. It is important to note that, in general, institutions whose employees or agents obtain identifiable private information or identifiable specimens for non-exempt human subject's research are considered engaged in the research, even if the institution's employees or agents do not directly interact or intervene with human subjects. In general, obtaining identifiable private information or identifiable specimens includes, but is not limited to:
 - observing or recording private behavior;
 - using, studying, or analyzing for research purposes identifiable private information or identifiable specimens provided by another institution;
 - using, studying, or analyzing for research purposes identifiable private information or identifiable specimens already in the possession of the Investigators.

In general, OHRP considers private information or specimens to be individually identifiable as defined in 45 CFR 46.102(f) when they can be linked to specific individuals by the Investigator(s) either directly or indirectly through coding systems.

Institutions *NOT* Engaged in Human Subject Research:

Institutions would be considered not engaged in non-exempt human subject's research project the involvement of their employees or agents in that project is limited to one or more of the following.

The following are scenarios describing the types of institutional involvement that would make an institution not engaged in human subject's research; there may be additional such scenarios:

- Institutions whose employees or agents perform commercial or other services for Investigators provided that all of the following conditions also are met:
 - the services performed do not merit professional recognition or publication privileges;
 - the services performed are typically performed by those institutions for non-research purposes; and
 - the institution's employees or agents do not administer any study intervention being tested or evaluated under the protocol.

- The following are **examples**, assuming the services described would not merit professional recognition or publication privileges:
 - *An appropriately qualified laboratory whose employees perform routine serum chemistry analyses of blood samples for Investigators as a commercial service.*
 - *A transcription company whose employees transcribes research study interviews as a commercial service.*
 - *A hospital whose employees obtain blood through a blood draw or collect urine and provide such specimens to Investigators as a service.*
 - *A radiology clinic whose employees perform chest x-rays and send the results to Investigators as a service.*
- Institutions (including private practices) not selected as a research site whose employees or agents provide clinical trial-related medical services that are dictated by the protocol and would typically be performed as part of routine clinical monitoring and/or follow-up of subjects enrolled at a study site by clinical trial Investigators (e.g., medical history, physical examination, assessment of adverse events, blood test, chest X-ray, or CT scan) provided that all of the following conditions also are met:
 - the institution's employees or agents do not administer the study interventions being tested or evaluated under the protocol;
 - the clinical trial-related medical services are typically provided by the institution for clinical purposes;
 - the institution's employees or agents do not enroll subjects or obtain the informed consent of any subject for participation in the research; and
 - when appropriate, Investigators from an institution engaged in the research retain responsibility for:
 - overseeing protocol-related activities

AND

 - ensuring appropriate arrangements are made for reporting protocol-related data to Investigators at an engaged institution, including the reporting of safety monitoring data and adverse events as required under the IRB-approved protocol.
- Institutions (including private practices) not initially selected as a research site whose employees or agents administer the study interventions being tested or evaluated under the protocol limited to a one-time or short-term basis (e.g., an oncologist at the institution administers chemotherapy to a research subject as part of a clinical trial because the subject unexpectedly goes out of town, or is unexpectedly hospitalized), provided that all of the following conditions also are met:
 - an Investigator from an institution engaged in the research determines that it would be in the subject's best interest to receive the study interventions being tested or evaluated under the protocol;
 - the institution's employees or agents do not enroll subjects or obtain the informed consent of any subject for participation in the research;
 - Investigators from the institution engaged in the research retain responsibility for:
 - overseeing protocol-related activities;
 - ensuring the study interventions are administered in accordance with the IRB-approved protocol; and

- ensuring appropriate arrangements are made for reporting protocol-related data to Investigators at the engaged institution, including the reporting of safety monitoring data and adverse events as required under the IRB-approved protocol; and
 - an IRB designated on the engaged institution’s FWA is informed that study interventions being tested or evaluated under the protocol have been administered at an institution not selected as a research site.
- Institutions whose employees or agents:
 - inform prospective subjects about the availability of the research;
 - provide prospective subjects with information about the research (which may include a copy of the relevant informed consent document and other IRB approved materials) but do not obtain subjects’ consent for the research or act as representatives of the Investigators;
 - provide prospective subjects with information about contacting Investigators for information or enrollment; and/or
 - seek or obtain the prospective subjects’ permission for Investigators to contact them.

Example of this would be a clinician who provides patients with literature about a research study at another institution, including a copy of the informed consent document, and obtains permission from the patient to provide the patient’s name and telephone number to Investigators.

- Institutions (e.g., schools, nursing homes, businesses) that permit use of their facilities for intervention or interaction with subjects by Investigators from another institution.

Examples would be a school that permits Investigators from another institution to conduct or distribute a research survey in the classroom; or a business that permits Investigators from another institution to recruit research subjects or to draw a blood sample at the work site for research purposes.

- Institutions whose employees or agents release to Investigators at another institution identifiable private information or identifiable biological specimens pertaining to the subjects of the research.

Note that in some cases the institution releasing identifiable private information or identifiable biological specimens may have institutional requirements that would need to be satisfied before the information or specimens may be released, and/or may need to comply with other applicable regulations or laws. In addition, if the identifiable private information or identifiable biological specimens to be released were collected for another research study covered by 45 CFR part 46, then the institution releasing such information or specimens should:

- ensure that the release would not violate the informed consent provided by the subjects to whom the information or biological specimens pertain (under 45 CFR 46.116)
- OR**
- if informed consent was waived by the IRB, ensure that the release would be consistent with the IRB’s determinations that permitted a waiver of informed consent under 45 CFR 46.116 (c) or (d).

Examples of institutions that might release identifiable private information or identifiable biological specimens to Investigators at another institution include:

- *Schools that release identifiable student test scores;*
- *HHS agency that releases identifiable records about its beneficiaries; and*
- *Medical centers that release identifiable human biological specimens.*

(Note: in general, the institutions whose employees or agents obtain the identifiable private information or identifiable biological specimens from the releasing institution would be engaged in human subject’s research.)

- Institutions whose employees or agents:
 - obtain coded private information or human biological specimens from another institution involved in the research that retains a link to individually identifying information (such as name or social security number); and
 - obtain coded private information or human biological specimens from another institution involved in the research that retains a link to individually identifying information (such as name or social security number); and
 - are unable to readily ascertain the identity of the subjects to whom the coded information or specimens pertain because, *for example*:
 - *the institution's employees or agents and the holder of the key enter into an agreement prohibiting the release of the key to those employees or agents under any circumstances;*
 - *the releasing institution has IRB-approved written policies and operating procedures applicable to the research project that prohibit the release of the key to the institution's employees or agents under any circumstances; or*
 - *there are other legal requirements prohibiting the release of the key to the institution's employees or agents.*

For purposes of this document, *coded* means that:

Identifying information (such as name or social security number) that would enable the Investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, and/or combination thereof (i.e., the code); and a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

- Institutions whose employees or agents access or utilize individually identifiable private information only while visiting an institution that is engaged in the research, provided their research activities are overseen by the IRB of the institution that is engaged in the research.
- Institutions whose employees or agent's access or review identifiable private information for purposes of study auditing (e.g., a government agency or private company will have access to individually identifiable study data for auditing purposes).
- Institutions whose employees or agents receive identifiable private information for purposes of satisfying U.S. Food and Drug Administration reporting requirements.
- Institutions whose employees or agents author a paper, journal article, or presentation describing a human subject's research study.

9.0 REVISED COMMON RULE

The "Common Rule" is the popular term for the [Federal \(U.S.\) Policy for the Protection of Human Subjects, 45 CFR part 46](#), which outlines the criteria and mechanisms for IRB review of human subjects research.

On January 18, 2017, the Federal Policy for the Protection of Human Subjects, or Common Rule, was updated for the first time since its publication in 1991. The Common Rule was amended twice to delay the date that regulated

entities must comply with the revised version of the rule. The Office of Human Research Protection (OHRP) refers to this version as the "revised Common Rule," the "2018 Requirements," or the "2018 Rule."

The general compliance date of the 2018 Common Rule remains January 21, 2019. This revision of the Common Rule has been adopted by the U.S. Department of Health and Human Services and 15 other Federal Departments and Agencies.

This means that HHS-conducted or supported research initiated on or after January 21, 2019, will need to comply with the revised Common Rule. The term "initiated" refers to the date on which: (1) research was initially approved by an IRB; (2) IRB review was waived pursuant to §46.101(i); or (3) a determination was made that the research was exempt.

What studies are affected?

New studies that are federally funded or federally conducted will fall under the new rule.

- *New = First-time submissions that have not received IRB approval as of January 21, 2019*
- *Federally funded = Receiving funds directly from a federal funding agency (not indirectly)*
- *Federally conducted = Study takes place at a federal site, e.g., the VA Medical Center or a National Laboratory*

What studies that are *NOT* affected?

- *Studies that are not federally funded or federally conducted*
- *Studies that have been approved by the IRB **before** January 21, 2019 (regardless of funding source)*

What are the main changes?

- **Continuing Review** – Some new, minimal risk studies will no longer require annual review.
- **Informed Consent** – Several new standard statements are required in the consent form.
- **Exemptions** – Several exempt categories have been broadened, and one new category has been added: Benign behavioral interventions.

Transitioning Studies:

Institutions ***are not*** required to take action in transitioning studies initiated before January 21, 2019 to the pre-2018 Common Rule.

Institutions may make the **voluntary determination** for studies that were initiated before January 21, 2019 to comply with the revised Common Rule on a per-study basis or for a group of studies. The institution or IRB must document and date the institution's determination to transition a study to the revised Common Rule. Beyond that requirement, the transition provision does not prescribe how institutions must document these decisions as long as the decision is dated.

SLHS Transitioning Process:

Effective January 21, 2019, the Saint Luke's Health System Institutional Review Board voluntarily began the process of transitioning applicable studies to the revised Common Rule.

Existing Studies:

For existing “minimal risk” studies that were approved on or before January 20, 2019 and for full board studies that no longer involve subject intervention/interaction, the SLHS IRB evaluated the need for continuing review, new exemption category and possible revisions to the informed consent during an internal audit process.

During this audit the IRB will conduct a comprehensive review of current IRB documentation, current review/approval, specific categories, review all regulatory documents i.e., informed consent, protocol, data collection, etc.,

If a study was identified as a study that may qualify for limited IRB review, the research team received a memo requesting specific study information that assisted the IRB in determining a new review under the Revised Common Rule. Once a final determination has been made the research team will receive a new IRB approval letter.

New Studies:

Studies approved on or after January 21, 2019, the SLHS IRB will follow the new Rule.

New Process:

(Annual Reminder of Study Team Responsibilities & Project Termination)

Even when continuing review is not required for a project, the study team is still required to:

- Submit amendment for projects changes
- Report Adverse Events, Protocol Deviations and/or Unanticipated Problems
- Termination when the project ends, or when personal identifiers are removed from the data/biospecimens, and all codes and keys are destroyed

Definition changes:

Research: The revised Common Rule adds a provision that identifies four types of activities as not being "research" as defined in the Rule. In other words, the revised Common Rule does not apply to the following types of activities because they do not meet the regulatory definition of research:

- Certain scholarly and journalistic activities,
- Certain public health surveillance activities,
- Collection and analysis of information, specimens, or records, by or for a criminal justice agency for certain criminal justice or investigative purposes, and
- Certain authorized operational activities for national security purposes

Human Subject: The regulatory definition of **human subject** remains substantively unchanged in the revised Common Rule. The definition has not been expanded. However, there have been clarifications to the wording that make explicit OHRP's current interpretation of the definition included in the pre-2018 Common Rule. The pre-2018 Common Rule referred to "data" obtained by an Investigator through intervention or interaction with the individual, but in the revised Common Rule "data" is replaced with "information or biospecimens" for clarity. In addition, language has been added related to "using, studying, or analyzing individuals' information or biospecimens or generating identifiable private information or identifiable biospecimens" to clarify OHRP's understanding of the meaning of "obtaining" in the pre-2018 Common Rule's definition of human subjects. The definition also now specifies what is meant by an identifiable biospecimen and includes a requirement for Common Rule departments and agencies to reexamine the meaning of "identifiable private information" and "identifiable biospecimen". In addition, the revised definition includes a provision requiring the Common Rule

departments and agencies to assess whether there are analytic technologies that should be considered by Investigators to generate "identifiable private information."

10.0 PRINCIPAL INVESTIGATOR

The purpose of this document is to define which individuals are qualified to serve as a Principal Investigator (PI) for nonexempt human subject's research conducted at Saint Luke's Health System (SLHS). The guidance seeks to implement a mechanism of accountability and continuity for human subject protections and is not intended to restrict productivity and leadership. Individuals who do not meet the criteria to be a PI may still participate as a Co-Investigator.

All human subjects research studies conducted at SLHS must designate an individual, qualified by training and experience, to serve as the PI they must have sufficient authority, relevant scientific knowledge, and the requisite training to personally carry out or supervise all aspects of the project. The individual is responsible for all aspects of the protocol, as approved by the IRB.

Principal Investigator:

The Principal Investigator (PI) is the individual responsible for ensuring that the research is conducted in accordance with the human subject federal and state laws and regulations, IRB policies and procedures, the Department of Health and Human Services (DHHS) Federal Policy Regulations, the Food and Drug Administration (FDA) regulations, the oversight of the research study and the informed consent process. The PI is responsible for ensuring that all requirements established by the study sponsor or the funding agency for the proper programmatic, scientific, and technical conduct of the project are met, and the research is conducted in compliance with the terms and conditions of the award and relevant SLHS and sponsor policies. In addition, the PI is responsible for supervising and directing all members of the clinical research team. Although the PI may delegate tasks to members of his/her research team, he/she retains the ultimate responsibility for the conduct of the study.

Who May Serve as a Principal Investigator?

The responsibility of a Principal Investigator (PI) is significant because it involves direct interaction and supervision of the research team. The PI must be current staff or have credentials of the Saint Luke's Health System and who is operating within their health system's role to oversee the conduct of the study.

To serve as a Principal Investigator an individual must be qualified under the following eligibility requirements:

Physician, Dentist, Psychologist, Psychiatrist, Registered Nurse, PhD, Audiologist, Respiratory Therapist, and Pharmacist and other employees of the health care system that are credentialed at Saint Luke's Health System (SLHS).

Individuals NOT qualified to serve as Principal Investigator:

Individuals who are trainees, including Fellows, Residents, Masters, or Doctoral Candidates, Postdoctoral Researchers, or any other patient services professional.

11.0 PRINCIPAL INVESTIGATOR DEPARTURE FROM INSTITUTION

The purpose of this document is to describe available options and next steps when a Principal Investigator (PI) of SLHS IRB approved human subjects research study departs from SLHS.

When a PI departs from SLHS or one of its affiliated institutions, they are responsible for ensuring the disposition of their studies prior to their departure. Likewise, department administrators have a responsibility to ensure these duties are carried out before the PI departs.

Below are the procedures to be followed. Please consider the status of the study as well as the PI's future plans related to the study when reading the instructions.

- Study Closure
- Active Study, but Principal Investigator will no longer be involved
- Active Study, but Principal Investigator will continue to be involved in study
- Transfer of Research Data/Specimens to a New Institution
- IRB Reliance Options
- Other Institutional Considerations

Study Closure:

If all research study activities have ceased, including data analysis, the Principal Investigator (PI) will not have access to identifiable data, and no research data or specimens will be transferred to a new institution, then the study can be closed at SLHS. The research records should be retained for as long as the applicable regulations require. The Principal Investigator is still responsible for:

- Continuing to maintain confidentiality protections of the data.
- Destroying all subject identifiers connect with the research if the study was approved with a HIPAA Authorization Waiver.
- Submitting for IRB Review and approval a modification requesting transfer of the study to another eligible Principal Investigator, if applicable.

Active Study:

(Principal Investigator will no longer be involved)

If the study will remain active at SLHS or one of its affiliated institutions and the departing Principal Investigator (PI) will have no further involvement with the study, a "Request to Remove or Add Study Personnel" form must be submitted to the IRB".

- Assign a qualified individual as the new Principal Investigator;
- Revise the appropriate study documents (e.g., consent forms, recruitment materials, etc.) to list the new PI's name and contact information;
- Confirm that all study records including data and specimens have been deposited with the new PI.

A PI change should be submitted within 14 days of the departure of the former PI to obtain review and approval by the IRB prior to the new PI assuming oversight of the study. In the event a PI departs from SLHS or one of its affiliated institutions before a "Request to Remove or Add Study Personnel" form is submitted, the Department Chair/Head may assign a qualified individual as the new PI and provide signature for transfer.

Prompt reporting of PI changes is required to ensure adequate oversight is in place for the conduct of the protocol and the protection of human subjects.

Active Study:

(Principal Investigator will continue to be involved)

If the study will remain active at SLHS or one of its affiliated institutions and the departing Principal Investigator (PI) will continue as part of the research team, a “Request to Remove or Add Study Personnel” form must be submitted to the IRB”.

- Assign a qualified individual as the new Principal Investigator;
- Revise the appropriate study documents (e.g., consent forms, recruitment materials, etc.) to list the new PI’s name and contact information;
- Explain the departing PI’s new role, including description of any continued access to research data and/or specimens;
- Confirm that all study records including data and specimens have been deposited with the new PI, or explain any alternate arrangements;
- Submit a copy of the departing PI’s IRB approval from his/her new institution, or if appropriate, execute an IRB Authorization Agreement or Individual Investigator Agreement.

Transfer of Research Data/Specimens to a New Institution:

Any departing Investigator wanting to transfer research records including data and specimens (tissue, blood, fluids, waster, and any cells or DNA) to a new institution must contact the IRB and the Office of Research Services (ORS) to determine next steps.

(Note: the IRB is obligated to ensure protections promised to research participants are maintained.)

If study activities are not complete but the Principal Investigator (PI) will be continuing his or her work at the new institution, then the IRB at the new institution will need to approve the study. Depending on the institutional requirements, the study consent forms, recruitment materials, etc. may need to be altered before receiving approval.

Once the new institution has approved the study, then the PI should ensure any appropriate agreement i.e., Data Use Agreement (DUA), Material Transfer Agreement (MTA), Business Association Agreement (BAA), etc., is in place. SLHS will likely facilitate the agreement(s) for the Investigator. The following will be taken into consideration in consultation with legal counsel:

- How were the data/specimens collected?
- What is the recipient doing with it?
- What does the informed consent form say, if applicable?
- HIPAA issues?
- Does the clinical trial agreement allow future uses, if applicable?
- Is the material export controlled?
- Is it going to a foreign country or foreign national?

Finally, the study will need to be closed out at SLHS.

IRB Reliance Options:

For studies that will remain open, the study team should consider whether an IRB reliance arrangement might be an option for streamlining the IRB process. An IRB reliance arrangement allows the SLHS to serve as the IRB of Record for another institution or vice versa. Such arrangements can be helpful in situations where the former SLHS Principal Investigator (PI) wishes to continue limited work on the study or limited study activities will be occurring at the SLHS and the study will be opened at the PI’s new institution.

Other Institutional Considerations:

In addition to the IRB the Principal Investigator (PI) will be responsible for following a closeout process through the Office of Research Services (ORS). This may include communication with the following:

- Department/Division Chair
- Sponsoring Agencies
- Budgets and Contracts Office
- Procurement Services
- Human Resources

12.0 STUDY TEAM MEMBERS

The following information is intended to provide guidance for Investigators to determine which study team member should be added to a study application in iMEDris.

For purposes of the application, study team members are individuals who:

- Interact with human subjects (e.g., informed consent process, manipulating subject's environment for research purposes, conduct invasive or non-invasive research procedures),
- Are involved with collecting, reporting, or analyzing identifiable subject data,
- Function outside or regular work practice (e.g., student administering research testing), or
- Are faculty advisors providing direct oversight of research involving human subjects, or human subjects' private information.

If an individual is functioning within his or her regular work practice (e.g., phlebotomist, x-ray technician) and involvement in the research is limited to only those work responsibilities without further contribution to the research, then such individuals do not need to be listed on the application. However, it is appropriate to describe their involvement in the protocol.

(Note: Funding agencies may have their own definition of study team members (i.e., "key personnel") as it applies to grant or other funding applications.)

Whom to include on the IRB Application:

- Individuals with the following roles must be included:
 - Principal Investigator
 - Co-Investigator
 - Sub-Investigator
 - Study Coordinator
- Individuals who meet the definition of study team members as stated above, *for example*:
 - *Staff obtaining consent for research participation*
 - *Staff collecting consent for research participation*
 - *Staff collecting, reporting, or analyzing identifiable subject data*
 - *Faculty advisors with direct oversight of the research*
- Individuals listed on a study plan, grant or budget who will have subject contact and/or access to identifiable subject data.

Listing External Unaffiliated Staff:

Whether to list study team members or collaborators not affiliated with Saint Luke’s Health System depends on if there is another IRB serving as the IRB of Record for these individuals.

- Do not list external study team members who will receive IRB approval from their own IRB as the IRB of Record. Involvement of these individuals should instead be described in the study protocol, as well as the consent if applicable.
- Do not list external study team members who are not engaged in human subject research (e.g., handing out recruitment brochures or flyers at an external facility, providing prospective subjects with information about contacting the Investigator or study team). Involvement of these individuals should instead be described in the study protocol, as well as the consent if applicable.
- When the SLHS will serve as the IRB of Record for an external site(s), the following should be followed:
 - The protocol should indicate that SLHS will be the IRB of Record for sites.
 - The application should indicate that this is a multi-site study and that the SLHS will act as the single IRB of Record for other participating sites.
 - Once the study is approved, participating sites and site PIs will be added to the iMEDris application by SLHS.
 - In the rare instances where External team members are listed in the iMEDris application, documentation of human subjects training must be uploaded.

Training Requirements:

All study team members are required to complete human subject protection training. Study team members listed in the application at the time of continuing review must have current training certification. Addition of new study team members will only be approved if the proposed individual(s) has completed the required training.

13.0 NON-HUMAN SUBJECT RESEARCH

The HRPP office has the sole authority to determine whether an activity meets the definition of “Human Subject Research”. When activities are conducted that might represent “Human Subject Research”, the activities must be submitted to the IRB for a determination. Investigators do not have the authority to make an independent determination and must submit a “Request for Determination of Non-Human Subject Research” to the IRB. An Investigator may request a determination that an activity is “Non-Human Subject Research,” but the final determination will be made by the IRB. The IRB will make a determination whether an activity is “Human Subject Research” by considering whether the activity either:

- Meets the regulatory definitions of “research” that involves “human subjects,”
- OR**
- Meets the regulatory definition of “clinical investigation”.

13.1 NON-RESEARCH

Activities are not research if they do not involve a systematic approach involving a predetermined method for studying a specific topic, answering a specific question, testing a specific hypothesis, or developing theory.

Examples of systematic investigations include, but are not limited to observational studies, interviews (including those that are open-ended) or survey studies, group comparison studies, test development; or program evaluation.

Examples of activities that would not normally be considered systematic investigations include, but are not limited to training activities (e.g., human subjects being trained to perform a certain technique or therapy such as art therapy, psychoanalysis, oral history techniques) and classroom exercises involving human participants or human participant data where the objective of the activity is to teach proficiency in performing certain tasks or using specific tools or methods.

Activities are not research if they do not contribute to generalizable knowledge or if the results (or conclusions) of an activity are not intended to be extended beyond a single individual or an internal program (e.g., publications or presentations). *Examples of activities that are typically not generalizable include: biographies and service or course evaluations, unless they can be generalized to other individuals; services, courses, or concepts where it is not the intention to share them beyond the SLHS community; classroom exercises solely to fulfill course requirements or to train students in the use of particular methods or devices; and quality assurance activities designed to continuously improve the quality or performance of a department or program where it is not the intention to share them beyond the SLHS community.* Thesis or dissertation projects conducted to meet the requirements of a graduate degree are usually considered generalizable and therefore, require IRB review and approval.

13.2 NON-HUMAN SUBJECT RESEARCH

Activities do not involve humans as participants if they do not involve the process of obtaining specimens or data through intervention or interaction with individual participants or identifiable private information. Information is considered “not identifiable” if it includes none of the following:

- Name;
- Any geographic subdivisions smaller than a state, including street address, city, country, precinct, ZIP code, and their equivalent geocodes, except for the initial three digits of a ZIP code;
- All elements of dates (except year) directly related to an individual (e.g., date of birth, admission);
- Telephone numbers;
- Fax numbers;
- Electronic mail addresses;
- Social Security numbers;
- Medical record numbers
- Health plan beneficiary numbers;
- Account numbers;
- Certificate/license numbers;
- Vehicle identifiers and serial numbers, including license plate numbers;
- Device identifiers and serial numbers;
- Web Universal Resource Locators (URLs);
- Internet Protocol (IP) address numbers;
- Biometric identifiers, including finger and voiceprints;
- Full-face photographic images and any comparable images; and
- Any other unique identifying number, characteristic, or code.

Specimens/data that are received by the Investigator as de-identified stripped of all HIPAA identifiers as noted above. When the Investigator receives the private information or specimens with no code or link that would allow an Investigator to establish identity, this would not involve human subjects. *For example, a publicly available, unidentifiable, non-linked cell line qualifies as not involving human subjects.* The Investigator may receive coded private information or specimens and qualify for non-human subject if the following conditions are met:

- The code is not derived or related to the HIPAA identifiers that must be stripped from the PHI (e.g., patient medical record # + last 4 digits of individuals Social Security Number);
- The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals;

AND

- The Investigator cannot readily ascertain the identity of the individuals to whom the coded private information or specimens pertain, because:
 - The key to decipher the code is destroyed before the research begins;
 - The Investigator and the holder of the key enter into an agreement prohibiting the release of the key to the Investigator under any circumstances, until the individuals are deceased;
 - The private information is received from an IRB-approved repository or data management center that includes written operating procedures that prohibit the release of the key to the Investigator under any circumstances, until the individuals are deceased; or
 - There are other legal requirements prohibiting the release of the key to the Investigator until the individuals are deceased.

13.3 QUALITY IMPROVEMENT VS RESEARCH

Generally, Quality Improvement (QI) projects do not require submission to the IRB. The HRPP office is willing to review submissions by medical students/trainees and faculty who are conducting quality improvement projects that request an authoritative determination of whether an activity does or does not meet the definition of research with humans. An authoritative determination might be required by a journal or conference prior to acceptance of a health care related manuscript for publication or presentation. When Investigators and staff are seeking an authoritative determination, these proposed QI activities must be submitted on a Non-Human Subjects Determination Form.

(Note: If you intend to submit for publication and/or present in a public forum HRPP office review is recommended. The HRPP office will provide a “determination letter” for your records. The HRPP office does not, and cannot, grant retroactive approval of an activity that is conducted as a QI project and is later determined to be human research.)

Saint Luke’s Health System Preparatory to Research:

For activities involved in preparing for research, covered entities may use Protected Health Information (PHI) or disclose PHI to a researcher without an individual’s Authorization, a waiver or alteration of Authorization, a data use agreement, or IRB Approval. The covered entity must obtain from the researcher presentations that:

- The use or disclosure is requested solely to review PHI as necessary to prepare a research protocol or for similar purposes preparatory to research;
- The PHI will not be removed from the covered entity in the course of review;
- The PHI for which use, or access is requested is necessary for the research.

(Note: SLHS HRPP does not, and cannot, grant retroactive approval for use of data that was collected for research purposes without IRB approval.)

Standard Guidance:

- Activities preparatory to research are activities conducted for the purpose of:
 - Preparing a research protocol;

- Developing a Hypothesis;
 - Writing a Grant Application; or
 - Identifying subjects or records of subjects who may be recruited for the research.
- Activities preparatory to research are not required to be submitted for review to the SLHS IRB, however the following must be certified;
 - The Use or Disclosure is requested solely to review PHI as necessary to prepare a research protocol or for similar purposes preparatory to research;
 - The PHI will not be removed from SLHS in the course of review; and
 - The PHI for which use, or access is requested is necessary for the research.
- When PHI will remain within SLHS, activities preparatory to research as allowed without an individual's Authorization, a waiver or an alternation of Authorization, or a data use agreement.
 - SLHS faculty are permitted, without IRB approval, to use PHI for all purposes preparatory to research.
 - Individuals from the outside the SLHS covered entity conduct limited activities preparatory to research. Such activity is limited to review of PHI and is considered a disclosure of PHI.
- Under the "preparatory to research" provision, no PHI may leave the covered entity. Anyone within SLHS sharing PHI with an outside researcher for the purpose of preparing a protocol must obtain documented proof that the SLHS IRB has approved the Waiver of Authorization or a Business Associates Agreement.

Case Report Guidance:

Federal regulations (45 CFR 46.102 (d) and 45 CFR 164.501) define research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

The review of medical records for publication of a single case report or a case series involving data from two or three patients is not considered by the SLHS HRPP office to be research involving human subjects, and therefore such a report of medical cases does not require IRB review and approval. This is because reporting such a small series of patients does not involve a systematic investigation, including defining a hypothesis that is then investigated prospectively and systematically, to develop or contribute to generalizable knowledge.

However, the HRPP office is willing to review submissions by medical students/trainees and faculty who are conducting case reports that request an authoritative determination of whether an activity does or does not meet the definition of research with humans.

When a larger series of patients is being prepared for presentation or publication, ordinarily a specific research question is posed, and then a systematic collection of data occurs. Such a systematic investigation more closely resembles prospectively designed clinical research. To distinguish non-research from research may be challenging, therefore useful guidance to those who would prepare case report for presentation or publication is helpful. The HRPP office regards such limited case report preparation as an educational activity, and thus it is permissible under the Privacy Rule (HIPAA) as a part of health care operations (45 CFR 164.501). However, from both the Common Rule and the Privacy Rule perspective, a case series involving more than 3 cases may meet the definition of research, and such submission to the HRPP office for an official determination is encouraged.

While HIPAA authorization may not always be required, there may be instances in which authorization from the patient may be needed to use their health information.

(Note: If you intend to submit for publication and/or present in a public forum HRPP office review is recommended. The HRPP office will provide a "determination letter" for your records. The HRPP office does not,

and cannot, grant retroactive approval of an activity that is conducted as a Case Study project and is later determined to be human research.)

Common Elements	
<i>Case Study</i>	<i>Research</i>
Report on 3 or fewer subjects	Report more than 3 subjects
Not meant to be a representative sample (not drawing conclusions)	Drawing conclusions about a broader population based on the reported cases (even if not statistically significant, e.g., pilot studies can be “research”)
Reported/Published without attempting to draw broader conclusions	Reported/Published in a way that suggests broad findings or recommendations

14.0 HUMAN SUBJECTS RESEARCH

All protocols must meet the criteria required under federal regulations [45 CFR 46.111](#). It is the IRB’s responsibility to assure that approved protocols meet these criteria. The submission of a new or continuing protocol or amendment to a protocol for IRB review requires the submission of a completed application or amendment form, all relevant consent/assent documents, and all other study documents via the IRB system.

Research Protocol:

The research protocol describes the study and is used by the IRB to assess the ethical merits of the proposed study. All of the following documents have to be submitted to the IRB via the Application System. Required information in the protocol includes:

- Protocol application
- Introduction/background
- Justification/rationale/significance of the study
- Purpose, including specific aims and/or hypotheses
- Study design including population to be studied, recruitment procedures and available resources
 - Upload and attach all study documents connected to the protocol (i.e., letter(s) of cooperation, data collection documents, data use agreements, etc.)
 - Upload and attach all recruitment documents (i.e., scripts, flyers, postcards, emails, etc.)
- Plan for obtaining informed consent, parental permission, and/or assent
 - Upload and attach all consent, parental permission, and/or assent documents
- Risks and discomforts to subjects and how they will be minimized
- Subject privacy and data confidentiality
- Data analysis plan
- If applicable:
 - Benefits to subjects
 - Costs to the subject
 - Payment to the subjects (include both reimbursement and incentives)
 - Alternative(s) to participation
 - Provisions for subjects from vulnerable populations

- References/Citations
- Plans, if any, for follow-up of the subjects at the end of the protocol
- An uploaded and attached copy of a federal grant application(s). Non-federal grant applications do not have to be uploaded and attached.

The IRB encourages the use of tables and flowcharts when they make the protocol easier to understand. The protocol should include a selective list of references that are related to the protocol. A lengthy list of references is not necessary.

Detailed Protocol Requirements:

Purpose, Including Specific Aims and/or Hypotheses:

State clearly what is hoped to be learned from the research. The purpose should be written at a level that to be understood by individuals with a general medical background.

Background and Significance:

Discuss the relationship of the research to previous studies in the field and include pertinent references. Describe relevant experimental or clinical findings which led to the plan for the project. This must be succinct and comprehensible without reference to other material. For studies designed to compare or evaluate therapies, there should be a statement of the relative advantages or disadvantages of alternative modes of therapy. A few pertinent references should be cited; however, exhaustive literature reviews are not necessary. If earlier studies have produced conflicting evidence, it is necessary to cite these studies and explain the rationale for the study design that was chosen.

The significance of the study for both for the individuals participating and for the advancement of knowledge should be stated. How significant is the new knowledge being sought in relation to the potential risks in carrying out the research?

Research Plan:

Inform the IRB of the specific nature of the procedures to be carried out on human subjects in sufficient detail to permit evaluation of the risks. This section should also provide information that will allow the IRB to confirm the claim that methods employed will enable the Investigator to evaluate the hypothesis posed and to collect valid data.

- Study Population

Protocols must be precise as well as concise in defining a study population and how the population will be contacted. Describe recruitment procedures, including how it will be ensured that subject selection is equitable and that all relevant demographic groups will have access to study participation ([45 CFR 46.111\(a\) \(3\)](#)). Part of subject selection includes ensuring that no person is unduly denied access to research from which they could potentially benefit, without good reason (*The Belmont Report*, ethical principle of Justice). *For example, to exclude non-English speaking individuals purely because it is inconvenient to have the consent form translated into an understandable language; or because the research staff does not speak the language, is not an acceptable reason for their exclusion.* The IRB would determine this to be unfair and an injustice to those individuals.

In describing the equitable selection of subjects, please ensure information is provided to justify the defined population(s) with regards to the following:

- The purposes of the research.
 - The setting in which the research would be conducted.
 - Whether prospective participants would be vulnerable to coercion or undue influence.
 - The inclusion/exclusion criteria.
 - Participant recruitment and enrollment procedures.
 - The amount and timing of payments to participants.
- Subject Privacy

Describe how you will protect the privacy of participants (i.e., what you will do to maintain individual's interest in being left alone and being treated in a way that is comfortable to the individual). Describe the procedures for identification of possible subjects and recruitment procedures.
- Inclusion and Exclusion

The inclusion and exclusion criteria for both subjects and, if appropriate, control subjects should be specifically stated. Assurance is required that there will be equitable selection of subjects. Limited participation or exclusion of populations (e.g., minorities or women) must be justified.

 - Patients identified from medical records must not be contacted without permission from the responsible health care provider. The lack of a response from the responsible institution cannot be construed as approval to contact the patient.
 - If patients are to be involved whose care is the responsibility of departments or special care areas other than that of the responsible Investigator, that department or special care area should be identified as having approved the recruitment process.
 - If children are included as research subjects the Investigator must provide an assessment of the level of pediatric risk ([45 CFR 46.404, 405, 406 or 407](#)) involved in the research. The final determination of risk level is made by the IRB.
- Study Design

If a study includes randomization, the procedure for randomization should be discussed.
- Assessment of Resources

Investigators must include information in the protocol to ensure:

 - access to a population that would allow recruitment of the required number of participants;
 - sufficient time to conduct and complete the research;
 - adequate facilities (i.e., private room for consent and interviews);
 - a process to ensure that persons assisting with the research were adequately informed about the protocol and their research-related duties and functions (i.e., verification of CITI certification); and
 - availability of medical or psychological services that participants might require as a consequence of the research, if applicable.
- Study Procedures

All specific procedures to be performed on human subjects for purposes of research should be detailed. It is important to distinguish between usual program implementation and/or class work and any experimental procedures. Include a description of the intended procedures as they directly affect the subjects. There need not be a detailed account of techniques that do not directly affect the human subject (e.g., details of laboratory methodology). Do include:

- The number and estimated length of study visits/interactions.
- The length of time for various procedures and frequency of repetition.
- Any manipulation that may cause discomfort or inconvenience.
- Plans for post-study follow-up, if applicable.

A general time schedule for various procedures should be provided, showing what a subject might expect regarding how long each aspect of the study will take; the frequency and timing of ancillary procedures; and the duration of discomfort. It would be helpful to present complicated studies with a simple flow chart to enhance the narrative description. The location of the study must be indicated.

- Federal Grant Applications

If an IRB protocol is based on a federal grant application, one copy of the complete grant application and attachments are to be uploaded and attached to the IRB application.

- Electronic Record System Use

If study procedures require the use of electronic documentation systems (i.e., electronic medical records, learning management systems, electronic data sets), the following information must be included in the research protocol:

- justification for use of the system and why this information cannot be obtained in another manner;
- what information will be collected from the system and the specific process for collection;
- how that information will be protected and secured including how long access to that information will be necessary through the electronic system;
- who will perform the data collection; and
- permission from the data source in the form of a letter of cooperation, IRB approval, and/or data use agreement.

Risks and Discomforts and How They will be Minimized:

Potential research risks include more than physical harm; risks may also include emotional or psychological harm, social risk of stigmatization, and economic or legal risk. There should be a description of all known or potential risks, discomforts, or inconveniences to the subject. This should include the Investigator's explanation of how he or she concluded that the risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result from the research. The description of risks may be extensive or may be brief, depending on the protocol. Risks related to the research need to be distinguished from risks that are part of standard program implementation.

Subjects should be told what will be done to minimize risks and which, if any, risks might be irreversible. Describe the procedures for protecting against or minimizing potential risks and assess their likely effectiveness. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects.

There are specific risks that may be present when genetic information is part of a protocol. The magnitude of the risks and a description of the risks should be given in both the protocol and the consent form. These risks may include:

- Future problems with access to or retention of benefits or entitlements (e.g., health insurance, life or disability insurance, educational opportunities, employment, etc.)

- Stigmatization: negative views of others, within or without the subject's family, about the subject; the possibility of altered family relationships and interactions.
- Psychological responses to information: altered self-concept; possible feelings of depression, guilt, anger, etc.
- Detection of previously unknown biological relationships within a family: paternity, maternity, and adoption.

Compensation for Injuries:

For any research involving more than minimal risk, federal regulations require an explanation as to whether any compensation and/or medical treatment is available if injury occurs and, if so, what it consists of, or where further information may be obtained. The Principal Investigator may need to distinguish between treatments for injuries related to the investigational intervention versus treatments for routine program implementation. If a study entails minimal risk and if, in the opinion of the Investigator, there is the potential for physical injury, an “in case of injury” section should be incorporated into the protocol and consent form.

“In case of injury” provisions should include:

- Where and from whom medical therapy may be obtained.
- What therapy will consist of and its duration.
- Who will pay for the therapy?
- Whom to contact in case of injury.
- What happens after the study ends or if the subject is dropped from the study?

The source of funds, if any, to cover the costs of medical therapy for injuries should be specified. If none is available, it is important that the subject understand what may be billed to him or her, or to a third-party payer. This includes routine medical care that is normally billed to the subject even when it is performed in conjunction with a research study.

Benefits to Subjects:

Describe the potential benefits to the individual subjects enrolled in the study. If there are no direct benefits, indicate there are none. Reimbursement or compensation is never a benefit. The potential benefits which may result for other individuals, general knowledge, etc., should also be discussed. For studies with greater than minimal risk, discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and in relation to the importance of the knowledge that may reasonably be expected to result.

Costs to Subjects:

Investigators must address any extra costs incurred because of the research project. If costs due to research are to be incurred by the subject, such costs must be stated on the consent form. Describe and justify any costs that the subject will incur as a result of participation; normally, subjects should not have to pay for research procedures that do not provide some direct benefit.

Alternative(s) To Participation:

Discuss the alternatives to participating in the study. Are some or all of the study components available without participating in the study? Can a former participant or someone who refuses to participate in the study remain in the program or class?

Payment to the Subjects:

(Recruitment Inducements/Reimbursement)

Describe any material inducements that will be offered to subjects in return for their participation: e.g., direct payment, food, test outcomes, etc. Discuss both reimbursement for expenses (e.g., parking and meals) and payments for time, effort, inconvenience, and discomfort. Describe the schedule of payment to subjects based on their complete or partial participation (prorating). Identify whether early withdrawal from the study will result in a reduced payment or whether it makes a difference if it is the subject or the Investigator who decides to terminate the subject's participation.

Plan for Obtaining Informed Consent

(Informed Consent Process)

Description of the Informed Consent Process:

The protocol must include a description of the informed consent process. Please consider the following points:

- The timing/waiting periods for participants to ensure that they are allowed adequate time to make an informed decision and to minimize the possibility of coercion or undue influence. Sufficient time must also be allowed for the participant to review and consider participating with the assistance of family members, research partners or representative if necessary. Other items to consider regarding time/waiting periods are: Is the potential participant given a copy of the consent form to read prior to the discussion of the study? Is the consent form presented in person or mailed to subjects (where they can review it in the privacy of their own home)? How much time elapses between the presentation of the study and informed consent form and the actual signing of the form?
- The steps taken to minimize the possibility of coercion or undue influence
- The language used by those obtaining consent
- The language understood by the prospective participant or the representative
- Who will be involved in obtaining consent?
- Who will be approached for consent/assent/permission (parental or guardian)?

Comprehension of informed consent:

In order for the IRB to evaluate issues of comprehension, the protocol needs to describe the steps taken to ensure that participants or their legal representative, and those who are involved in obtaining consent, understand the research. Once a potential participant is identified, what process is followed to inform the subject of the study prior to obtaining a signature on the informed consent form? Please consider the following points:

- Who introduces the study to the potential subject?
- Who reviews with the subject the informed consent document in depth?
- Do you require the potential participant to have another person present during the presentation of the study?
- Who answers the questions presented by the potential participant and/or family?
- What method is used to determine if the potential participant fully understands the study, what is required from them, risk and benefits, and their rights as a participant?
- Is the Principal Investigator usually present during the presentation of the informed consent?

Although written consent forms are generally required, in studies that present no more than minimal risk of harm to subjects and involve no procedures for which written consent is normally required, oral consent may be approved. Written consent may also be waived if the consent form is the only record linking the subject to research involving sensitive information and the primary risk of the research would be breach of confidentiality.

If the Investigator believes that oral consent is appropriate, the request for waiver of written documentation of consent must be justified in the protocol. If the IRB approves the waiver of written consent, i.e., verbal, or oral consent, an information sheet or a document that addresses the required elements of informed consent, may be required for subjects.

Provisions for Subjects from Vulnerable Populations address whether some or all subjects to be recruited will be vulnerable to coercion or undue influence. If they are, describe the additional protections provided to these subjects to protect their rights and welfare. Under *The Belmont report*, the ethical principle of Beneficence requires that risks to subjects are outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society (i.e., knowledge to be gained). In reviewing research involving vulnerable subjects, the IRB is required to determine whether the presented risks are fully justified; and the appropriateness of their inclusion has been demonstrated. *For example, if subjects who may not be competent to give consent are to be included, a description of how competency will be assessed needs to be included.* Vulnerable Populations include:

- Cognitively/Decisional-Impaired Persons (including dementia-affected people & the mentally ill)
- Minors
- Non-English-Speaking populations
- Physically Challenged Persons
- Pregnant Women, Fetuses and Neonates
- Prisoners
- University Employees
- University Students
- Wards of the State

Subject Privacy and Data Confidentiality:

Confidentiality Concerns Data and Privacy Concerns People:

Describe the provisions to protect a subject's privacy and the confidentiality of their data in connection with their participation in the research study. Ensure that you include a description of:

- how any identifiable information will be accessed;
- how the information obtained will remain confidential; how will you store and secure data;
- who will have access to said data;
- what will you do once you are done with research data; and
- (if applicable) that it will be disclosed only with the subject's permission or as required by U.S. or Missouri law.

Examples of information that are legally required to be disclosed include abuse of a child or elderly person, and certain reportable diseases.

Privacy of Participants:

Privacy refers to a person's desire to control access of themselves to others. Describe how you will protect the privacy of participants (i.e., what you will do to maintain individual's interest in being left alone and being treated in a way that is comfortable to the individual). Describe specifically, the procedures for identifying participants; how you will gather information from or about them; and how any invasion of privacy will be minimized. Please also consider the location where the information is to be gathered and whether the participants will be comfortable in the research setting being proposed.

Example:

People may be uncomfortable answering questions about their employer in an open cubicle, so Investigators may arrange for a more private interview location; or people may not want to be seen in a place that might be stigmatizing to them, such as a pregnancy counseling center, so Investigators may arrange for questionnaires to be mailed to subjects.

Confidentiality of Data:

Confidentiality refers to keeping data secret/protected within a small group of research staff; confidential data are not intended to be shared/disclosed publicly. Describe how research data will be stored and secured to ensure confidentiality. If data will be shared with other Investigators, explain why this is necessary and, if relevant, justify releasing data with identifiers that would permit the recipient Investigator to know or infer the identity of the subject ([45 CFR 46.111\(a\)\(7\)](#)). If highly sensitive information is to be gathered, such as information that would put the subject at risk of criminal or civil liability, either provide a Certificate of Confidentiality or explain why one was not requested. If audio or video tapes are made for research purposes describe how they will be kept secure and when they will be destroyed.

Further describe the disposition of information obtained during a study. When a study is of a diagnostic or therapeutic modality, information is very often entered in the subject's medical record, discussed with the subject, and transmitted to anyone else whom the subject designates.

When subjects will be tested for reportable diseases, such as HIV or hepatitis the protocol must clearly reflect these exceptions to confidentiality. Limits on confidentiality, such as inspection of records by the IRB should also be explained.

Data Analysis Plan:

Summarize the statistical/analytical methods to be used.

Plans for Subjects at the End of the Protocol:

Are there any post-research follow-up contacts? Do you want to hold on to contact information for future studies? If so, you must include this request in the consent process and documents.

When the Investigator is the Lead Investigator of a multi-site study:

The IRB evaluates whether the management of information that is relevant to the protection of subjects is adequate.

When the Investigator is the Lead Investigator of a multi-site study, applications include information about the management of information that is relevant to the protection of subjects, such as:

- Unanticipated problems involving risks to subjects or others.
- Interim results.

- Protocol modifications.

Amendments:

The IRB reviews and approves all amendment (i.e., revisions, modifications, or amendments) to an IRB approved research protocol prior to initiation of the amendment(s) except when necessary to eliminate apparent immediate hazards to the human subject.

(Note: Changes initiated without prior IRB approval in order to eliminate apparent immediate hazards to the human subject, must be reported to the IRB within 30 calendar days.)

Amendment to applications previously approved by a convened IRB may be reviewed using the expedited review process if they meet the following criteria:

- Do not pose an increased risk to subjects; and
- Constitute a minor change to previously approved research; and
- Any added research activity falls within categories 1-7 of the Health and Human Services (HHS) expedited review categories ([45 CFR 46.110](#) categories of research that may be reviewed by the IRB through an Expedited Review Procedure).
- Link to [45 CFR 46.110](#) for complete category details.

Amendment to applications previously approved by the expedited review process may be reviewed via expedited review if they meet the following criteria:

- The research continues to pose no more than minimal risk to subjects.
- Any added research activity falls within categories 1-7 of the HHS expedited review categories (45 CFR 46.110 – *Categories of Research That May Be Reviewed by the IRB through an Expedite Review Procedures*).
- Link to ([45 CFR 46.110](#)) for complete category details

Investigator Responsibilities:

- Promptly (within 30 calendar days) reports to the IRB any research activity amendments which were made in order to avoid apparent immediate hazards to a subject and were implemented prior to IRB approval.
- Evaluates each proposed amendment to the research activity to assess potential impact upon the risk/benefit ratio, severity, or frequency of the previously describe risk(s), safety, design, or execution of the research project.
- Revises research project documents accordingly. Describes each proposed amendment and the justification for the change in the IRB amendment application.
- Submits an IRB amendment application to the IRB and attaches a revised protocol, consent form (if applicable), and other documents associated with the requested change.
- Includes the justification for each amendment listed in the application.
- Re-consents or notifies subjects as directed by the IRB.
- Assures that any change to conflict of interest has been disclosed and reviewed by the Conflict-of-Interest Committee.

IRB Responsibilities:

- Determine whether the proposed amendment is a minor amendment or a major amendment and conducts its review accordingly.
- Reviews the proposed amendment(s) in accordance with approval criteria and determines whether amendment(s) are consistent with ensuring the subject's continued protection.
- Reviews amendments initiated without prior IRB approval that eliminate apparent immediate hazards to the human subjects and determines whether each change was consistent with ensuring the participant's continued welfare.
- Determines that any new significant findings arising from the review process, and possibly impacting the subject's willingness to continue participation are provided to the subject.
- Determines if any new information resulting from the amendment or from other sources necessitates an adjustment to the IRB's prior determination(s), such as inclusion of protected or vulnerable populations and findings regarding FDA-regulated products.
- Determines if the proposed amendments to the research require revision of the consent document(s). If so, the IRB will ensure that revised consent documents accurately reflect the amendments.
- Determines if the amendments warrant re-consenting of currently enrolled subjects or notification of subjects who have completed research interventions.
- Considers whether the interval for continuing review as last determined by the IRB should be adjusted based on the amendments.
- Notifies the Principal Investigator of IRB findings and determinations.
- Determines whether the amendments to the research activity may require verification from sources other than the Investigator that no material changes have occurred.

Minor Amendments:

An amendment may be considered minor if it meets the following criteria:

- Research that involves no more than minimal risk and meets the criteria for one of the Expedited Review Categories at 45 CFR 46.110;

AND

- Amendments that constitute a minor change to previously approved research and do not pose an increased risk to subjects.

Examples of minor amendments include (but are not limited to):

- *Administrative or clerical changes;*
- *Protocol revisions that entail no more than minimal risk;*
- *Decrease in the number and volume of sample collections as long as they do not negatively alter the risk/benefit ration of the research;*
- *Changes to the informed consent documents that do not affect the rights and welfare of research subjects, or do not involve increased risk to subjects, or significant changes in the research procedures;*
- *Minor changes to recruitment procedures, recruitment materials or submission of new recruitment materials to be used in accordance with approved recruitment methods;*
- *Minor changes to research project documents such as surveys, questionnaire, or brochures;*
- *New research project documents to be distributed to the subjects that are similar in substance to those previously approved; and*
- *Changes in payment to subjects that do not constitute undue influence or affect the risk/benefit ration of the research.*

Major Amendments:

Major amendments are changes to the research project that would materially affect the assessment of risks and benefits or may alter prior IRB decisions or determinations.

Examples of major amendments include (but are not limited to):

- *Changes in the Principal Investigator for research projects that have been deemed as greater than minimal risk;*
- *Changes in study design, population, or procedures that increase risk (e.g., revision of study purpose, broadening of eligibility criteria, addition of vulnerable populations, alteration of a data safety monitoring plan, change in drug dosage or frequency);*
- *Changes to the consent form(s) that have the potential to alter/affect the potential participant's understanding of the risk/benefit ration of the study, the study requirements, or his/her rights, e.g., new study procedures, new risks of increase in severity or frequency of known risks, changes to subject remuneration, reimbursement, or out of pocket expenses, extended duration of study participation, and/or changes to the HIPAA authorization); and*
- *Premature completion of the research project due to an unanticipated problem or determination by an oversight entity.*

Continuing Review/Annual Status Report Guidance:

The Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA) have specific regulations regarding IRB continuing review of ongoing research, to ensure that the rights and welfare of human subjects are protected.

The aims of continuing review are to reappraise the research to ensure:

- The risk/benefit ratio is still acceptable.
- The measures taken to safeguard subjects are adequate.
- The approved protocol is being followed.
- The protocol reflects changes in the regulations for human subjects' research that have been implemented since the last approval.
- To review the progress of the protocol since last review and the plans for the future based on the progress to date.
- Review adverse events, untoward reactions, or unanticipated problems that occurred since the last review.
- Evaluation of new significant findings that might relate to the participant's willingness to continue and which should be provided to participants.

Continuing Review submissions include general information about the study progress. Study teams will be asked to report enrollment numbers (which must not exceed the IRB approved enrollment numbers), any new financial interests, and protocol deviations. Please also select all applicable study milestones.

Continuing Review submissions must report details if any of the following occurred within the past year:

- Subjects experienced unexpected harm
- Anticipated adverse events have taken place with greater frequency or severity than expected
- Subjects withdrew from the study
- Unanticipated problems involving risks to subjects or others

- Complaints about the study
- Publications in the literature relevant to risks or potential benefits
- Interim findings
- Multi-center trial reports
- Data safety monitoring reports
- Regulatory actions that could affect safety and risk assessments
- Summary or log of protocol deviations
- Other relevant information regarding this study, especially information about risks

The study team must also confirm that:

- In the opinion of the Principal Investigator (PI), the risks and potential benefits are unchanged
- All modifications to the protocol have been submitted to the IRB
- All problems that require prompt reporting to the IRB have been submitted

Although continuing reviews are usually assigned an expiration date of 1 year, the Board may require certain projects, as determined by an evaluation of the risk-benefit ratio, to be reviewed more frequently than yearly. This can be either after a fixed period of time (such as at six months) or after a certain number of subjects have been enrolled.

Unless the SLHS IRB determines otherwise, continuing review of research approved under the 2018 Common Rule is *NOT* required for:

- Research eligible for expedited review
- Research reviewed by the IRB in accordance with limited IRB review;
- Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:
 - Data analysis, including analysis of identifiable private information or identifiable biospecimens,

OR

 - Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care

The SLHS IRB may determine that continuing review is required for any research protocol that falls within the above criteria. *For example*, the IRB may determine that continuing review is required when:

- *Required by other applicable regulations (e.g., FDA);*
- *The research involves topics, procedures, or data that may be considered sensitive or controversial;*
- *The research involves particularly vulnerable subjects or circumstances that increase subjects' vulnerability;*
- *An Investigator has minimal experience in research or the research type, topic, or procedures; and/or*
- *An Investigator has a history of noncompliance*

The expiration date (if any) for an IRB approved study is clearly indicated on the IRB approval or initial approval letter and is the last day that the study has IRB approval.

The Principal Investigator is responsible for ensuring that the research is submitted to the IRB for continuing review in an appropriate time frame, in order to avoid a lapse of IRB approval. The date by which a protocol must receive its continuing review is listed on the approval letter and indicates the date that the protocol is approved through. In order to avoid a lapse in approval, the Investigators must plan ahead to meet the required continuing

review dates specified by the IRB. The SLHS IRB recommends that a Continuing Review is submitted at least 6 weeks prior to the expiration of the study. The iMEDris system sends courtesy notices out at 30, 60, and 90 days.

(Note: When a continuing review application is submitted less than five (5) days before expiration to the IRB, the Principal Investigator, Co-Investigators, and study staff may be required to complete Continuing Review Education.)

If the continuing review involves modifications to previously approved research, submit those modifications as a combined Modification and Continuing Review in the electronic system. Please do not submit simultaneous but separate Modification and Continuing Review submissions (unless the Modification is only to change study personnel).

Addressing a Lapsed Study:

If the approval of human subject's research lapses, all human subjects research procedures related to the protocol under review must cease, including recruitment, advertisement, screening, enrollment, consent, interventions, interactions, and collection or analysis of private identifiable information. Continuing human subject's research procedures is a significant violation of policy. If current subjects will be harmed by stopping human subject's research procedures that are available outside the human subject's research context, provide these on a clinical basis as needed to protect current subjects. If current subjects will be harmed by stopping human subject's research procedures that are not available outside the human subject's research context, immediately contact the HRPP office and provide an explanation as to why they will be harmed by stopping human subject's research procedures.

If the Investigator continues to conduct the research after the study has expired (without prior approval from the IRB that it is in the best interest of the current subjects to continue activity), this becomes an issue of non-compliance and will be referred to the Research Compliance Business Partner.

If you fail to submit a continuing review form to close out human subject's research, you may be restricted from submitting new human subjects research until the completed application has been received.

If a continuing review submission is not reviewed and approved by the IRB before the study expires, the IRB will inform the Investigator that the study approval has expired and that no research activity, including data analysis may occur during the lapse in approval. Both automatic and manual notices will be sent via the electronic system. If a continuing review submission is not received for review within thirty (30) days of the expiration date, the HRPP office can administratively archive the study, and the study will be considered closed. All responses to IRB stipulations on an expired study must be received within 2 weeks, or the process for administratively archiving will continue. Once a study is closed in iMEDris it cannot be reopened. If the HRPP office archives a study with a greater than minimal risk designation, notification of that action will be sent to the Research Compliance Business Partner.

Study Administratively Discarded due to Lack of Response:

The study team has 60 days to respond to a request for modifications, clarifications, or deferral stipulations for a new study. The system will send out courtesy reminders every 15 days. If a meaningful response is not resubmitted within 60 days, HRPP staff may administratively discard the submission. At that point, a new study must be created if the study team wishes to move forward.

Study Closure:

Complete the Continuing Review in the electronic IRB system and attach all requested documents. Once completed, the Principal Investigator (PI) or PI Proxy will need to click “Submit” to send the submission to the IRB. Maintain electronic copies of all information submitted to the IRB in case revisions are required.

Please be mindful that certain sponsors, including the NIH, might have additional record retention policies. If your human subject’s research is sponsored, contact the sponsor before disposing of human subject’s research records.

After a protocol has been closed, the IRB does not accept further submissions unless they impact the rights and welfare of participants. The Investigator should keep all non-reported adverse events on file for review by regulatory agencies.

(IMPORTANT NOTE: Once a study closure has been submitted and processed by the IRB the study *CANNOT* be re-opened.)

Other IRB Submissions:

Please refer to subsequent chapters for more information regarding Reportable New Information (RNI) and reliant review submissions.

15.0 REGISTRY PROJECT

When is IRB approval needed?

If the plan is to develop a list or database of participants for research purposes and to grant access to that list of potential participants to multiple Principal Investigators and/or multiple projects, that is what the IRB refers to as a registry and some schools or departments refer to as a subject pool. For the purposes of this document, a registry.

A registry is an independent project that needs to be submitted to the IRB for review and approval. Because potential participants are specifically recruited to a registry with the expectation of that patient being eligible for certain kinds of research and because obtaining names and contact information from a registry for the purpose of recruitment is a step in the research process, oversight of the registry is within the scope and of the mission of the IRB. IRB approval is needed in accordance with the Federal guidelines and with regard to the Belmont principles around the protection of private identifiable information as it relates to voluntary participation and the right to be treated with dignity and respect.

A project needs to be submitted in the IRB and a protocol that describes a subject registry will include the following.

Introduction to the Registry should include:

- The purpose of the registry.
- Who is eligible to be recruited into the registry?
- What is the information that is kept in the registry about each participant and/or participant family unit? Attach to the protocol upload a copy of a blank data entry record or a codebook that describes the fields if they go beyond name, address, email, and phone number.

(Note: Typically, there would be no research data, no medical or diagnostic information kept in a registry unless there is a compelling reason.)

- How are the actual names entered into the registry (is it automatic from an online form or put in by hand or both?).

- What is the process for opting for inclusion to the registry and for opting out of the registry if someone changes his or her mind?

Description of Security for the Registry should include:

- Where and how for the physical storage of the registry, i.e., password-protected, secure Saint Luke's server, locked cabinet in the office of the Principal Investigator
- Access to the registry: describe how the information in the registry accessed and by whom. At a minimum, access to the contents of the registry should be governed by already having an IRB approved protocol that includes the option of access. In addition, explain how this will be monitored and/or verified. Include who will manage access and how with specific details with regard to role on the registry project, where passwords kept and how frequently changed.
- Specific information as to who is responsible for training and supervising individuals who may access the registry.
- Upload a blank copy of the letter of agreement that will be in place between the Principal Investigator (PI) managing the registry and the PI of projects that are requesting access to the registry. This letter should also include who from the lab is the designated person responsible for serving as administrator for their lab.

Description for Maintaining the Registry Information should include:

- A plan for how information in the registry will be accessed (directly or remotely) and what security is in place for maintaining real time recording of who is being contacted, when how and by whom. What is the agreement about who 'owns' the participant contact information once they come into one or more labs or studies? How will the registry monitor who is contacting whom if multiple projects are contacting the same families?
- A training plan for all individuals who will access the registry regarding the registry rules, policies and/or procedures for requesting access, obtaining access, and how to actually access the information. If there will be multiple research assistants accessing the registry, a manual may be more appropriate. Among other things, this training plan or manual should include a specific script that is standard language to be used by all projects when recruiting to and from the registry. Recruitment from the registry is different from recruitment to the registry and needs to be delineated that way.
- Include specific recruitment strategies that will be used to recruit participants to the registry. This could be traditional use of flyers, web site, ads online and so forth. If it is a student subject pool and all students enrolled in certain a class, program, or other academic entity are automatically included in the registry, include how they are informed and what options they have if they want to opt out.
- The text for recruitment material must include a brief description of the purpose of the registry, include the name of the registry and the study number. As part of any of the recruitment there must be a statement to the effect that if participants agree to inclusion to the registry this means they could potentially be contacted by different researchers.
- Include a description of how participants will be consented to the registry. This could be by registering through a web site using an online form that contains both recruitment and the consent information, it could be in person, by regular mail, email or it could be by phone. Regardless of the method used, there must be an approved consent that is completed to document a valid consent process. Consent to the registry is not done on the fly as someone is walking out the door. The participant must be able to have access to some sort of consent document that they can print, that they are handed, or receive by email. This consent document must include what they are agreeing to, who to contact if they have

questions contact information as well as information about how to stop being a part of the registry if they want to withdraw.

- Consent records: a field should be added to the registry to indicate that a participant has been duly consented to the registry, by whom, in what manner and if appropriate by what project so that if audited, it can be easily established which consents are in physical format and which are electronic.

In addition to the protocol, the submission to IRB should include the following documents:

- Copy of the agreement between the registry and the Principal Investigator (PI) or lab requesting access.
- Training plan for individual projects that will access the registry including how to use the registry, policies re; confidentiality and security of the registry.
- Sample copies of recruitment materials to recruit to the registry.
- Consent document language that will be used by anyone consenting participants to the registry.

16.0 CHART REVIEWS AND DISCARDED TISSUE

The SLHS HRPP permits separate submission requirements for research involving human participants that **only** include chart reviews of medical records and/or use discarded tissues that require IRB approval. In order for the IRB to approve the research, the Federal regulations for the protections of human participants (NIH and FDA agencies of the DHHS) must be met.

Research activities involving the use of chart reviews or discarded tissues must be reviewed and approved by the IRB prior to commencement. However, certain chart review/ discarded tissue studies may qualify for a Non-Human Subjects Determination or an IRB exemption.

If the research only includes chart reviews and/or discarded tissues, the protocol must be submitted via IRB application.

The study must only include SLHS charts/records and/or tissue from SLHS; the review must be limited to research involving materials (data, documents, records, or discarded tissue specimens) that have been collected or will be collected solely for non-research purposes; and the study must be no more than minimal risk to participants. For studies greater than minimal risk, the IRB new application including a protocol/research plan document; or the continuing review "CR" must be used.

Greater than minimal risk discarded tissue and/or chart review study applications must include a complete protocol/research plan. In addition, informed consent must be sought unless the regulatory criteria for waiving the consent process are met. If children are involved, parental permission and assent must also be obtained unless the criteria for waiving parental permission and waiving assent are met. Justification for all waiver(s) is required and must be approved by the IRB.

16.1 CHART REVIEW STUDIES

The SLHS IRB requires a protocol to be submitted for review for all Chart Review Studies. The IRB's main concern with chart reviews for research is the possible invasion of privacy and the use of confidential and privileged data or information. For any study to qualify as a chart review all the data accessed must have been collected (or will be collected) as part of routine clinical care. As with discarded tissue studies, informed consent must be obtained unless a waiver can be fully justified and meets the regulatory requirements. If an Investigator has support to obtain consent from a subject and if practicable according to applicable regulations, they must do so as usual

under the human subject protection regulations. The consent process and all requests for waivers must be addressed in the protocol/research plan.

Access to a Physician's own Records for Research:

With an IRB approved protocol, physicians may access their patients' existing medical records (or those of their group practice) for research, without obtaining patient consent. As part of the protocol application the Investigator must ensure that all collected data will be kept confidential and any study results will be presented in a way that preserves patient anonymity. If prospectively collected patient data are to be entered into a database with both clinical and research uses, then other rules apply.

Access to Another Physician's Records for Research:

If access to medical records (paper or electronic) of patients outside of a physician's practice is desired for research, then the protocol application submitted to the IRB must describe how patient privacy will be protected and how the confidentiality of the information will be maintained. The best way is for the patients' physician (or his or her staff) to extract the data from the charts or electronic records and de-identify it before giving it to the researcher. If this is not possible and a member of the research team must review the charts/electronic records, then only de-identified data may be taken from the physician's office and the person reviewing the charts/records must agree to keep all identifying data confidential. If identified data leaves the physician's office, then consent from the patient is usually required before they are included in the study. Due to HIPAA requirements, a telephone call or letter to the patients must come from their physician (or staff) and not be processed by the research staff.

Contact with Potential Participants from Chart Reviews:

Any investigational or research project involving use or review of medical records where contact will be made with patients or patients' families as a result of chart review requires approval by the IRB. The Investigator is required to submit a protocol application to the IRB indicating:

- Justification for contact of the patient\subject;
- Method of contact the patient\subject;
- Indication that prior approval will be obtained from the responsible physician of record to contact his/her patients.

No patient can be contacted to participate in research without the consent of the treating physician. If seeking approval from the physician via correspondence, the lack of reply from a physician can never be construed as approval to contact the patient.

16.2 DISCARDED TISSUE STUDIES

Discarded tissues obtained from surgeries, diagnostic procedures, and autopsies for research purposes are generally processed under the Pathology Department prior to distribution or transfer of the specimens to the Investigator.

The SLHS IRB requires that the protocol application/research plan for discarded tissue contain sufficient detail to fully describe the proposed research activities. Unless waived by the IRB, informed consent must be obtained from potential participants using a current approved SLHS research consent form. This clinical consent **cannot** be used as a substitute for the research consent process.

If it is deemed that informed consent does not need to be obtained, in order to use discarded specimens removed for diagnostic or therapeutic purposes for research, the following criteria must be met:

- No extra tissue will be taken;
- Any data collected about the subject are de-identified making the tissues unidentifiable back to the patients by the research Investigator and there is no commercial development from the tissues.

Discarded Tissue with Participants Identified:

If patient identifiers are kept with the research specimen, then consent from the patient will usually be required. If it would be extremely difficult, impractical, or impossible to obtain individual consent, or if the patient identifying data are very tightly controlled (as in a research tissue bank that releases specimens but does not release identifying data), the IRB will consider waiving consent if they determine the waiver meets the regulatory criteria.

Surgical Pathology Tissues:

Obtaining discarded tissue from surgical specimens requires release from the patient and protocol review and approval of the Department of Pathology before IRB submission. The tissue from each patient does not qualify as “discarded” until it has been released by the surgical pathologist.

Autopsy Tissues:

Since autopsy tissues are not from living human beings, IRB regulations do not apply. Unless the tissues are de-identified to the Investigator so he/she cannot identify the donors, HIPAA regulations may apply, and the Investigator may need to request a HIPAA waiver from the IRB. The HIPAA waiver request needs to be included in the application to the IRB.

17.0 INFORMED CONSENT

(The purpose of this policy is to provide a guidance to Investigators regarding the informed consent process for research subjects.)

It is the policy of SLHS for Human Research Protection IRB that Investigators will not involve human beings as subjects in research unless the Investigator has obtained the legally effective informed consent of the subject or the subject’s legally authorized representative. Exception to this policy requires that the IRB grant a waiver of the informed consent requirement.

Unless waived by the IRB, consent will be documented by the use of an approved, written consent form. The form will be signed and dated by the prospective subject or the prospective subject’s legally authorized representative.

The consent document will include the basic elements of informed consent as specified in 45 CFR 46.116.

An Investigator will seek informed consent only under circumstances that provide the prospective subject or, when approved by the IRB, the subject’s legally authorized representative sufficient opportunity to understand and consider whether or not to participate and that minimize the possibility of coercion or undue influence.

The information that is given to the subject or the representative will be in language understandable to the subject or the representative.

No informed consent, whether oral or written, will include any exculpatory language through which the subject or their legally authorized representative is made to waive or appear to waive any of the subject’s legal rights, or

releases or appears to release the Investigator, the sponsor, the institution, or its agents from liability for negligence.

17.1 WAIVER OR ALTERATION OF THE CONSENT PROCESS

(Note: The provisions for waiver of informed consent do not apply to FDA regulated research involving human subjects.)

An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

- The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs;

AND

- The research could not practicably be carried out without the waiver or alteration.

An IRB may approve a consent procedure which does not include, or which alters some or all of the elements of informed consent, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

- The research involves no more than minimal risk to the subjects;
- The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- The research could not be practicably carried out without the waiver or alteration; and
- Where appropriate, the subjects will be provided with additional pertinent information after participation. (45 CFR 46.116)

Waiver of Documentation of Consent:

(Note: The provisions for waiver of documentation of informed consent do not apply to FDA regulated research involving human subjects.)

The IRB will review the research proposal to determine if waiver of documentation of informed consent is appropriate. The IRB may waive the requirement for an Investigator to obtain a signed consent form for some or all subjects if it finds that either:

- The only record linking the subject and the research would be the consent form and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or
- That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.
- In cases in which the documentation requirement is waived, the IRB may require the Investigator to provide subjects with a written statement regarding the research.
- When the IRB considers waiving the requirement to obtain written documentation of consent, the IRB reviews a written description of the information that will be provided to subjects via an oral consent script, contact letter, phone script or similar document.

- If a waiver of written consent is granted by the IRB, the IRB will determine whether the Investigator must document the oral consent in research study files and/or the subject's medical record.

Consent Process Plan:

The Investigator will develop a detailed consent process plan for the initial research proposal submission to the IRB. The following factors should be assessed and used to develop the plan:

- Type of research project being conducted, *for example, biomedical research, behavioral/social science research, health services research.*
- Risk to subjects, including procedures, devices, drugs, or biologics.
- Vulnerable categories of subjects, *for example children; adults lacking decision-making capacity; prisoners; pregnant women and fetuses;*
- persons who are non-English speaking, economically or educationally disadvantaged, terminally ill, or students or employees of the organization.
- Characteristics of subjects such as age or health status that may influence health literacy and the consenting process.
- A plan for informing subjects of significant or incidental findings resulting from the research.

The plan must include a description of the following:

- Recruitment and advertising activities.
- Payment arrangement, if any.
- The method(s) for obtaining informed consent, including where or how communication will take place.
- The amount of time planned for the consent process.
- Method(s) for assessment of a subject's capacity to consent.
- The protections that are planned to reduce potential subject's vulnerability to coercion or undue influence during the consenting process.
- The waiting period between discussion, decision, and enrollment.
- Study team members who will meet with the prospective subject and obtain informed consent. These individuals must be sufficiently trained, knowledgeable about the research project in order to answer questions posed by the subject and must have IRB approval to obtain consent.
- If the Investigator has a preexisting relationship with a prospective subject, the responsibility for the consent process will be delegated to another qualified member of the study team to avoid the possibility of undue influence to participate in the research.

17.2 RECRUITMENT PLAN

The Investigator will:

- Provide a recruitment plan in the project proposal, including a description of the proposed recruitment method(s), advertisements, and if applicable, any payment arrangements.
- Specify the maximum number of contacts that will be attempted to contact a prospective subject (i.e., number of telephone calls, voicemail messages, emails, letters, etc.).
- Describe the extra protections for prospective subject populations that may be vulnerable to coercion or undue influence.
- Describe the source of prospective subjects.

- Ensure that recruitment methods, advertisements, payment arrangements are not misleading, inaccurate, exculpatory, or violate the equitable selection of subjects; and do not place prospective subjects at risk of coercion or undue influence.
- Ensure that subject privacy and confidentiality are protected.
- Consider a prospective subject's stress level or health status.
- Consider the timing of recruitment discussions with a prospective subject, *for example, in relation to a subject receiving a diagnosis and ensure the readiness of a prospective subject to understand information being discussed.*

The Investigator will submit copies of the following recruitment information, including advertisements or payment arrangements to the IRB for review:

- Printed materials, such as flyers, posters, brochures, postcards.
- Media advertisements such as newspapers, television, radio, and internet website postings.
- If advertisements will be taped for broadcast, Investigators should submit a copy of the audio/video tape or the text / script for review.
- If final copies of recruitment or advertising materials are not available at the time of initial IRB submission, draft versions may be submitted. When the final copy becomes available, it must be submitted to the IRB for review and approval to confirm the wording is appropriate and clearly reflects the intent of the research.
- Recruitment letters, phone, or e-mail scripts.
- Telephone call scripts.
- Direct advertising intended to be seen or heard by potential subjects.
- Payment arrangements, if applicable.

Required content of recruitment/advertisement materials:

- Name and address of the Investigator and research facility.
- The purpose of the research or the condition under study.
- A summary of the criteria that will be used to determine eligibility for the research project.
- The person or office to contact for further information.
- The voluntary nature of participation.

Optional content of recruitment/advertisement materials:

- A brief list of prospective benefits and risks to subjects, if any.
- The estimated time or other commitment required of the subject.
- A statement that remuneration will be provided, without emphasis on the payment or amount.

Recruitment/advertisement materials should not contain:

- Claims of safety, equivalence, or superiority to treatment.
- Phrases such as “new treatment”, “new medicine”, or “new drug”.
- The term “free” in reference to treatment procedures.
- Overestimations of benefits and underestimations of risks.
- Payment or the amount to be paid in large or bold type.

Recruitment Materials Posted on Websites:

- IRB review and approval of listings of clinical trials on the internet is not required when the system format limits the descriptive information provided to basic trial information, such as: the title; purpose of the

study; protocol summary; basic eligibility criteria; study site location(s); and how to contact the site for further information.

- **Examples** of clinical trial listing services that do not require prospective IRB approval include www.clinicaltrials.gov.
- Information exceeding the basic trial information, such as descriptions of clinical trial risks and potential benefits or solicitation of identifiable information, requires IRB review and approval before posting on websites.

Individual or Institutional Recruitment Incentives:

The following are prohibited:

- Payments to professionals in exchange for referrals of potential participants (“finder’s fees”).
- Payments designed to accelerate recruitment that are tied to the rate or timing of enrollment (“bonus payments”) unless they are judged not to interfere with providing prospective participants with sufficient opportunity to consider whether to participate and do not increase the possibility of coercion or undue influence on Investigators or participants.

Payment/Reimbursement of Research Subjects:

Research subjects may be paid; however, the payment of participation is not considered a benefit, but rather a reimbursement for time and effort. All payments to subjects in research must be fair and equitable. Participation in a clinical trial offered by a sponsor may not include a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

Principle of Reasonable Compensation:

The IRB will review and determine the amount is reasonable and not so large as to unduly induce participation. All information concerning payment, including the amount and schedule of payment, should be clearly stated in the application, and reflected in the consent documents. When the IRB evaluates the selection of subjects, it considers the influence of payments to subjects. While the federal regulations do not specifically state how much researchers should pay subjects or what that payment should look like, the IRB will apply a principle of reasonable compensation as it reviews subject payment for time, effort, and inconvenience.

Pro-Rated Payment and Bonuses:

Payment for participation in research should not be contingent upon the subject completing the entire study but rather be prorated as the study progresses to insure voluntary participation. While the entire payment should not be contingent upon completion of the entire study, payment of a small proportion as an incentive for completion of the study is acceptable providing that such an incentive is not coercive. If a bonus is given at the completion of the trial, it should not be more than one half of the total reimbursement.

Department of Defense- Recruitment and Payment:

When research involves U.S. military personnel, the additional protections to minimize undue influence for military research participants include:

- Officers are not permitted to influence the decisions of their subordinates.
- Officers and senior non-commissioned officers may not be present at the time of recruitment.
- Officers and senior non-commissioned officers have a separate opportunity to participate.

- When recruitment involves a percentage of a unit, an independent ombudsman is present.
- When research involves U.S. military personnel, the limitations on dual compensation prohibit an individual from receiving pay of compensation for research during duty hours. An individual may be compensated for research if the participant is involved in the research when not on duty. Individuals may be compensated for blood draws for research up to \$50 for each blood draw.

Use of Social Media for Recruitment:

SLHS Investigators using social media (e.g., Twitter, Facebook, YouTube, etc.) as a recruitment method must have the research reviewed and approved by the Saint Luke’s Health System marketing department.

- New projects proposing the use of social media as a recruitment method will contain a statement from the Principal Investigator (PI) in either the IRB application or the research project proposal that the use of social media for recruitment of research subjects has been reviewed and approved by the Saint Luke’s Health System marketing department.
- Investigators at institutions for which the Saint Luke’s Health System IRB is the IRB of record will include within the IRB application documentation of review and approval by the relying organization for the use of social media, or documentation that such review and approval is not required by the institution.

17.3 ENROLLMENT PLAN

When planning enrollment, the Investigator must address the following:

- Amount of time needed for reading or reviewing the consent document
- Amount of time needed for the prospective subject to make a decision
- The location or methods of communicating and the related privacy needs for the initial and on-going discussions (e.g., in-person, mail, telephone)
- The need for including a medical interpreter, Legally Authorized Representative, family member(s), witness, or advocate who may need to be present and observe the discussions within the informed consent process.

Non-English Speaking Prospective Subjects who are NOT Specifically Targeted for the Research Project:

If enrollment of a prospective non-English speaking subject is considered when a research project does not specifically target this population, the Investigator must:

- Have an independent medical interpreter provide an oral explanation (in person or by phone) of the entire content of the English version of the approved consent document to the prospective subject or the subject’s legally authorized representative.
- In conjunction with the oral presentation, Saint Luke’s Health System Investigators will use a written Short Form / Authorization to Use and Disclose Protected Health Information form, stating that the elements of informed consent have been presented orally. The short form must be translated into a language understandable to the subject. Translated short forms in several different languages can be found on the IRB home page under the Forms and Procedures tab, Forms and Templates.
- There must be a witness to the oral presentation. The witness must be conversant in both the English language and the language of the prospective subject. The interpreter may serve as the witness.
- Saint Luke’s Health System Investigators will assure that the prospective subject or their representative has signed the translated Short Form/Authorization to Use and Disclose Protected Health Information form.

- Saint Luke’s Health System Investigators will assure that the witness has signed both the translated Short Form and a copy of the English consent document.
- Assure that the person obtaining consent has signed a copy of the English consent document.
- Saint Luke’s Health System Investigators will provide a copy of the translated Short Form to the prospective subject or the prospective subject’s representative.
- A copy of the English consent document must be given to the prospective subject or the prospective subject's representative.

Non-English Speaking Prospective Subjects who are Specifically Targeted for the Research Project:

If a research project targets non-English speaking persons of a specific language, then all printed study materials that are provided to the subject must be translated in that language and approved by the IRB prior to enrolling potential subjects.

- Submit English versions of the documents to the IRB for review and approval.
- Saint Luke’s Health System Investigators will send the final English versions, which have been approved by the IRB, to an external translation vendor for translation for the intended targeted population.
- Investigators at institutions for which the Saint Luke’s Health System IRB is the IRB of record will ensure translation of the documents by either an external translator or by using the translation services available within the relying institution and per institutional policy. Submit the translated documents to the IRB with the *Certificate of Authenticity* provided by the translation service.

Guidelines for the Use of Interpreters:

- Saint Luke’s Health System Investigators will utilize an interpreter when obtaining informed consent for research from a non-English speaking prospective research subject or the subject has legally authorized representative.
- Investigators at institutions for which the Saint Luke’s Health System IRB is the IRB of record will utilize the translation services available within the relying institution and per institutional policy.

This will assure complete, accurate, impartial, and confidential communication. Study staff designated to obtain consent and fluent in the language of the prospective research subject may also serve as interpreters.

Telephone interpreting is permissible when an interpreter is unavailable for a face-to-face encounter, unable to arrive within a reasonable amount of time, or when institutional translation services do not have an interpreter on staff for a requested language. Telephone interpreting is used as a back-up, not as a replacement for an in-person interpreter.

At Saint Luke’s Health System, family members and friends may not serve as interpreters during the research consent process except in an emergency situation and only until an institutional or contracted telephone interpreter is available. However, adult family members or friends may serve as interpreters if the prospective research subject declines institutional interpreter services AND if the use of that person does not compromise the effectiveness of care or violate confidentiality. To ensure accuracy, the Investigator should request that an interpreter be present when a family member or friend is interpreting.

Minor children may not serve as interpreters for the research consent process.

An interpreter contracted by the Investigator for the purpose of a specific study may, with IRB approval, be utilized.

17.4 IRB SUBMISSION AND REVIEW

The IRB reviews the application and attaches documents including (but not limited to) the research protocol, consent forms, scripts and recruitment and advertising materials, and payment arrangements.

Role of the IRB:

- Determines whether the consent process is appropriate for the proposed research activities and if revisions to the consent process or document are necessary.
- Determines the amount of payment and the proposed method and timing of disbursement is neither coercive nor presents undue influence.
- Reviews the proposed research project and determines that the consent document accurately reflects the purpose, risks, benefits and procedures, and payments as outlined in the research protocol and contains all the required elements of consent disclosure.
- Determines whether documentation of informed consent is appropriate for the proposed research activities, the subject population, and the level of risk.
- Determines if revisions to the consent process or consent document are necessary.

The IRB will ensure that:

- The research project proposal and related materials (i.e., recruitment/advertisement materials, payments, consent documents, scripts) as submitted to the IRB are approvable.
- Recruitment sites, recruitment methods, advertising materials and payment arrangements do not place subjects at risk of coercion or undue influence or cause inequitable selection.
- The consent process minimizes the possibility of coercion or undue influence and maximizes continued legally effective informed consent. When prospective subjects are vulnerable to coercion or undue influence due to their status, condition or situational vulnerability, the IRB review will ensure that the informed consent *process* is appropriate for that population.
- The consent document has the requisite regulatory and institutional information and is written in language that is understandable to the research project population.
- The consent documents accurately describe the risks and benefits initially approved by the IRB and at the time of research project modifications, continuing review, submission of reportable events or other safety-related information.
- Significant new findings or alterations to the risks and benefits that may relate to the subject's willingness to continue participation will be provided to the subject.

17.5 INVESTIGATOR RESPONSIBILITIES AFTER IRB APPROVAL

Enrollment:

During the enrollment phase of a research project, the Investigator:

- Adheres to the IRB-approved research project and uses the current IRB-approved consent form and consent process plan as approved by the IRB
- Ensures that delegated activities are performed by authorized and qualified staff as listed in the IRB application
- Submits all proposed research project modifications and revised documents to the IRB for review and approval prior to use
- Documents and retains consent records as directed by the IRB

- Re-consents subjects as directed by the IRB
- Assesses a prospective subject's physical and emotional state to determine his/her capacity for decision making
- Stops or reschedules the enrollment process if a prospective subject is unable to engage in the discussion or comprehend the research project information due to their physical or emotional state or if they appear reluctant or decline participation. The Investigator (or their delegate) must never try to convince a prospective subject to participate in a research project
- Conducts the enrollment discussion with consideration given to the physical environment where enrollment activities will take place
- Privacy and confidentiality issues may arise when enrollment activities take place in areas that are not private
- Environments such as procedural rooms with multiple staff present or a waiting room lobby may introduce peer pressure, increase anxiety, foster intimidation, or present undue pressure to make an immediate decision
- Waiting rooms with other patients nearby, exam rooms after being gowned, or patients lying on a gurney in a hallway are environmental conditions that must be avoided
- Avoids having the enrollment discussion immediately before surgery or clinical procedures or when prospective subjects are deprived of their glasses, hearing aids, clothing, or have been pre-medicated for a procedure
- Conducts a conversation regarding the research and the consent document with the prospective subject. The Investigator (or their delegate) should:
 - Repeat important information to enhance subject recall
 - Use plain, nonmedical language whenever possible
 - Pause often for clarification, questions, and answers
 - Spend time listening to the prospective subject
- Verbally reminds the prospective subject that their decision to participate or not participate will not affect their clinical care
- Provides private and ample time for the subject, their family members and/or their LAR to assess, evaluate, and discuss the information they have been given before asking them for their decision.
- Discusses the research project in a way that is culturally and linguistically appropriate to the research project population
 - Depending on the subject population, enrollment requirements may include a medical interpreter, witness, advocate, parent(s), spouse, or a LAR to be present to support the subject, to communicate information, to ensure impartiality of the discussion, and to contribute to documentation of the prospective subject's decision
 - Non-English-speaking Prospective Subjects: An interpreter will be used for communication assistance whenever engaging a non-English speaking subject in the informed consent process, including the discussion and confirmation that the subject understands the consent document. See "Guidelines for the Use of Interpreters".
 - English-speaking, Illiterate Prospective Subjects: A person who speaks and understands English, but does not read and write, can be enrolled in a study by "making their mark" on the consent document. A person who can understand and comprehend spoken English, but is physically unable to talk or write, can be entered into a study if they are competent and able to indicate approval or disapproval by other means. If (1) the person retains the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained verbally (still

competent) and (2) is able to indicate approval or disapproval to study entry, they may be entered into the study. The consent form should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study. An impartial third party should witness the entire consent process and sign the consent document.

Participation:

During the participation phase of a research project, it is the responsibility of the Investigator (or their delegate) to:

- Take opportunities to increase or enhance a subject's understanding of the research project
- Provide opportunities for subjects to ask questions; confirm participation or withdraw from the research project
- Remind the subject that research project team contact information is provided in the consent document and may be used for research project related questions
- Provide the subject with a medical contact for clinical issues that may arise
- Keep research project team contact names and telephone numbers up to date and submit the updated consent to the IRB for review and approval
- Notify the IRB when there are significant changes in the research project and/or when information about the research project provided up to that point is no longer sufficient for maintaining legally effective informed consent. The IRB may determine that notification of subjects is necessary
- Verify the subject's willingness to continue in the research project
- Submit proposed changes to the consent process or consent document(s) to the IRB for review and approval prior to implementation

Study Completion and Last Contact:

The informed consent process ends at the point of last contact with the subject.

The Investigator will determine when the final communication with the subject is anticipated or scheduled. Final communication can occur at any time and includes, but is not limited to:

- The signing of the consent form
- After a single procedure
- As a planned oral expression of appreciation after multiple visits
- As follow-up mailings at the end of the research

17.6 DOCUMENTATION OF CONSENT

Most commonly, informed consent is documented by the use of a written consent document which has been approved by the Saint Luke's Health System IRB and signed by the subject and/or the subject's legally authorized representative (LAR). The subject's (and/or the LAR's) signature and date and time of their consent are required on the consent document to verify that consent has been obtained.

When a consent document incorporates the HIPAA (Privacy Rule) language, regulations require that the subject must be given a copy of the signed consent document.

Other signatures on the consent document may include (as appropriate):

- Individuals interacting with the subject to obtain consent (i.e., Investigator or research study staff identified on the research study application as approved to obtain consent).
- Legally Authorized Representative who may be consenting and signing for the child, relative, principal or ward of the state.
- Parents or guardians who may give permission and sign for the child or relative.
- Witnesses and/or advocates involved in the consent process.

If a subject is unable to physically sign the consent document but is capable of consenting to participate in the study, a witness will be present to observe the consent process. The witness should use the margin of the document to record a brief statement indicating the observation of the consent process and the subject's voluntary participation, and sign and date the note. The witness will then sign the written consent document on behalf of the subject and writes the subject's full name on the signature line.

- The date should include the month, day and year using the mm/dd/yyyy format.
- The time should include 'A.M.' or 'P.M.' or be in a 24-hour "military" format.
- If the IRB requires documentation of oral consent in the subject's medical record (also known as a 'Consent and Enrollment Note'), this will be specified in the IRB approval notification to the Principal Investigator (PI).
- The PI will maintain the original signed consent document in the study file. Documentation of oral consent will also be retained in the study file.

Consent Forms and the Subject's Medical Record:

Greater than Minimal Risk Research:

When a research subject is a patient or becomes a patient receiving medical care while participating in a greater than minimal risk research study, it is important that a copy of the consent form be made available to their health care providers.

For greater than minimal risk research conducted at Saint Luke's Health System, it is recommended that the consent document be scanned into the electronic medical record (EMR).

Investigators at institutions for which the Saint Luke's Health System IRB is the IRB of record will comply with the policies of the relying institution.

Minimal Risk Research:

For research conducted at Saint Luke's Health System, the IRB may recommend scanning of consent documents for a minimal risk study into the subject's EMR. If this is recommended, the IRB will specify this requirement in the IRB approval notification to the Principal Investigator.

Investigators at institutions for which the Saint Luke's Health System IRB is the IRB of record will comply with the policies of the relying institution.

When the IRB approves waiver of the requirement to obtain a signed written consent form, the Principal Investigator should consider including the following information in the research study files:

- Who was approached
- Name of project
- Who explained the project
- Brief summary of what was explained

- The subject expressed an understanding of the research project and willingness to participate
- Questions (if any) were answered to the subject's satisfaction
- Subject agreed to participate, and
- Written information about the project was given to the subject, if appropriate. This note should be signed and dated by the person obtaining consent.

Study Record Retention Requirement (Investigator):

- The Investigator will retain all written consent documents per federal regulations, Sponsor record retention requirements, and/or institutional policy.
- Study records related to research, including consent documents, must be retained for a minimum of 3 years after the completion of the research.
- FDA-regulated studies may require longer retention periods.
- The records must be accessible for inspection and copying by authorized representatives of regulatory entities such as the FDA and the Office of Human Research Protection (OHRP).

Subject Withdrawal and Data Retention:

- When a subject withdraws from a study, the data collected on the subject 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.
- An Investigator may ask a subject who is withdrawing whether the subject 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 subject distinguishes between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review and address the maintenance of privacy and confidentiality of the subject's information.
- The Investigator must obtain the subject's consent for this limited participation in the study (if such a situation was not described in the original consent document). The IRB must approve the consent document.
- If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the Investigator must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent. However, an Investigator may review study data related to the participant collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.

Re-consent Guidance:

Circumstances may arise when it is necessary to re-consent research participants who continue to undergo research related procedures. Although there may be various methods by which to provide this information to participants, the most common approach is to prepare a consent form addendum for participants to sign.

Federal regulations at 45 CFR 46.116 (b) (5) and 21 CFR 50.25 (b) (5) state that, when appropriate, the informed consent document include a statement that "significant new findings developed during the course of the research which may relate to the participant's willingness to continue participation will be provided to the participant." This is particularly true when a substantive change has been made to the study protocol/consent such as:

- new findings that change the risk/benefit profile including the identification of new risks, an increase in the magnitude of known or suspected risks, or a decrease in the expected benefit
- study procedures have been added, modified, or removed
- new alternative treatments become available

For research involving the participation of children:

Federal guidance states the following: “Unless the IRB determines that the requirements for obtaining informed consent can be waived, the Investigators should seek and obtain the legally effective informed consent, as described in 45 CFR 46.116, for the now-adult participants for any ongoing interactions or interventions with the participants.” Therefore, when a minor participant reaches the age of 18 and is still undergoing research procedures, re-consent is necessary. The same is true if previously collected samples are still being utilized, or if medical records will continue to be accessed/reviewed. In some circumstances, the IRB may approve a waiver of consent for these purposes if the Investigator can provide an appropriate justification.

For research involving adult participants with decisional impairment:

IRB Guidance and Procedures indicate that if the condition causing the participant’s decisional impairment is of an intermittent or temporary nature, the informed consent process should include a mechanism for obtaining the participant’s direct informed consent to participate in the research upon regaining decision-making capacity. If a participant regains decision-making capacity and declines to continue in the study, the decision must be respected.

The original consent was obtained improperly:

- Consent was obtained by an unauthorized individual. *For example, at Saint Luke’s Health System, a study that involves a drug, device, or surgical procedure requires that the consent be signed by a physician who is listed as an Investigator.*
- Consent was obtained utilizing the incorrect version of the document. This is only relevant if information in the consent document changed in the newer version. If the only difference between the consent documents is a change in the approval date, this can be handled by a note to file.
- Consent was obtained but the Investigator failed to include one of the research procedures or one of the common risks of the study intervention.

A change to consent form language is initiated by the IRB, sponsor, or other entity, which alters the information originally provided.

Consent is an ongoing process, and the Investigator should engage the participant in a discussion throughout the study. However, it is not necessary to require active participants to sign a new consent document on an annual basis.

The IRB would not necessarily require re-consent under the following circumstances:

- Changes to the study team unless this would be considered to be new information discussed under point #1 above.

An example of when re-consent might be required in this situation would be a new conflict of interest declaration by a newly named Principal Investigator.

- Typographical errors noted in the consent document unless the error significantly changes the intent of the sentence.

An example of when re-consent might be required in this situation would be a change from 5 tablespoons of blood to 50 tablespoons.

Methods for Re-consent/Notification:

When circumstances arise which necessitate that new information be provided to a research participant, the research team should take into consideration the subject population, the status of the participants, the information to be conveyed, and the length of the consent document. Forms of notification methods include:

- Consent Form Addendum – The IRB recommends use of a consent form addendum when new information needs to be communicated to already enrolled participants. The advantage of using this method of re-consent is that the document consists of three main sections (new information, right to withdraw, and the Investigator certification) with the new information being the focus of the document.
- Consent with a Revised Full Document – Some sponsors may require that the full consent document be revised and re-signed by enrolled participants. Although this may be easier for the Investigator, it may be less informative for the participants. If this method is utilized, the new information should be highlighted in some fashion.
- Letter - The letter should contain the three elements of consent (new information, right to withdraw, and voluntary consent). The nature of the new information dictates whether participants need to sign and return a copy to the study team. In this case, two copies of the letter should be included; one for the participant to keep and one to be returned with signature.
- Telephone call - The information provided to the participant should be documented in the research record. The documentation should include what information was provided, by whom, and date of the interaction.

Considerations for Notification of Subjects:

The table below lists questions and considerations to aid in determining notification requirements. Once the requirements are determined, recommended options for implementing the notification based on participant status may be found in the second table, Determining Methods of Notification.

<p><u><i>Who needs to be notified or re-consented?</i></u></p> <ul style="list-style-type: none"> • Subjects actively undergoing research intervention • All subjects • Subset of subjects 	<ul style="list-style-type: none"> • Does the change affect subject differently? • If yes, clearly define each subset affected differently by the change (i.e., males, females, specific age groups, subjects in active treatment, specific study arm, subjects off study, etc.)
<p><u><i>What is the change that requires communication?</i></u></p> <ul style="list-style-type: none"> • Additional risks or change in risk severity or frequency • Change in level of discomfort or other inconvenience • Procedural changes including change in remuneration or reimbursement • New treatment options available • Other 	<ul style="list-style-type: none"> • Could the change affect a subject’s decision to remain in the study? • Regulatory, ethical or policy requirements • New research findings at Saint Luke’s Health System or elsewhere • Will the change involve a different level of commitment from the subject?

<p><u>When must notification or re-consent occur to protect subject safety and rights (regardless of logistics)?</u></p> <ul style="list-style-type: none"> • Immediate (as soon as possible) • Before next study visit • Before specific study procedures • Within specified time period • Varies with affected participant 	<ul style="list-style-type: none"> • Are subjects coming in for visits or are study procedures done at home? • Are subjects impacted now or in the future? • Are subjects who have completed study procedures/visits affected? • Logistics (including any travel, expense, or inconvenience to subjects)
<p><u>Where and How should notification be implemented?</u></p> <ul style="list-style-type: none"> • In-person visit • Letter with phone follow-up • Revised consent form 	<ul style="list-style-type: none"> • Complexity and need for interactive explanation and discussion • Need for physical demonstration or other presentation of information best done in person • Timeline for next subject visit • Verification of subject identity if not consented in person • Any subject limitations such as age, disabilities, language, level of understanding, vulnerable population

Determining Methods of Notification-Based on Study Participant Status:

<p><u>Study Participant still Active in Study</u></p>	
<p>Participant Affected by Changes</p>	<p>Participant Not Affected by Changes</p>
<p><u>Examples:</u></p> <ul style="list-style-type: none"> • New risk or increase risk of drug • New risk or increased risk of procedure subject will undergo • Changes to remuneration 	<p><u>Examples:</u></p> <ul style="list-style-type: none"> • New procedure that the subject will not undergo (such as at baseline) • Arm/treatment not affected by change or risk (on a different treatment) • Subgroup not affected (women only - pregnancy testing)
<p><u>Method of Notification:</u></p> <ul style="list-style-type: none"> • Re-consent • If next study visit is greater than 3060 days, notify via phone/letter as • well, re-consent at next in-person visit 	<p><u>Method of Notification:</u></p> <ul style="list-style-type: none"> • Typically, no notification needed
<p><u>Study Participant has Completed Procedures and all Study Visits</u></p>	
<p>Participant Affected by Changes</p>	<p>Participant Not Affected by Changes</p>

<p>Examples:</p> <ul style="list-style-type: none"> Newly identified long term or late-occurring risk 	<p>Examples:</p> <ul style="list-style-type: none"> Changes to procedure or protocol Newly identified immediate, short-lasting risk
<p>Method of Notification:</p> <ul style="list-style-type: none"> Letter to notify of potential long term or late-occurring risk 	<p>Method of Notification:</p> <ul style="list-style-type: none"> Typically, no notification needed

If you have any questions about the information in this guidance, please contact the IRB at IRB@saint-lukes.org.

IRB Reliance Options:

For studies that will remain open, the study team should consider whether an IRB reliance arrangement might be an option for streamlining the IRB process. An IRB reliance arrangement allows the SLHS to serve as the IRB of Record for another institution or vice versa. Such arrangements can be helpful in situations where the former SLHS Principal Investigator (PI) wishes to continue limited work on the study or limited study activities will be occurring at the SLHS and the study will be opened at the PI’s new institution.

Other Institutional Considerations:

In addition to the IRB the PI will be responsible for following a closeout process through the Office of Research Services (ORS). This may include communication with the following:

- Department/Division Chair
- Sponsoring Agencies
- Budgets and Contracts Office
- Procurement Services
- Human Resources

18.0 TELEPHONE CONSENT

The purpose of this document is to describe the process of obtaining Consent/Assent for studies where written informed consent is required, however participants cannot be present in person during the consent process.

Verbal consent does not satisfy the federal requirements for written documentation of consent. Under rare circumstances the Participant/Legally Authorized Representative (LAR) may not be on site or able to come on site in order to conduct the consent process in person. In such rare cases, it is acceptable to utilize the telephone consent procedure. The study team must have prior IRB approval to utilize the telephone consent procedure as part of their study.

(Note: COVID-19 update. The IRB has temporarily removed the requirement of prior IRB approval in order to conduct the Consent/Assent process via Telephone platforms and the requirement for a witness for telephone consent.)

The general requirements for obtaining consent are outlined below:

- The Participant/LAR must be provided with a copy of the IRB-Approved Informed Consent/Assent before the discussion can take place. This can be accomplished via fax, mail, e-mail, through a family member, or an IRB-Approved eConsent process.

(Note: Communication via e-mail requires prior written approval from the potential Participant/LAR.)

- The person conducting the consent process will verify the Participant/LAR before beginning the discussion. How verification was conducted should be documented;
- The information in the Informed Consent/Assent must be discussed and reviewed as if the process were being conducted in person.

Waiver of Documentation of Consent/Assent:

If the IRB has approved a waiver of documentation of Consent/Assent, the remaining sections of this guidance do not apply.

Participant/LAR Signature:

- If the Participant/LAR gives their consent, he/she will be asked to sign and date the Informed Consent;
- When Assent is required, the study would be directly explained to the minor in simple terms that he/she will understand;
- A minor's mere failure to object should not, absent of affirmative agreement be considered assent. The minor will be asked to sign and date the form;
- When using paper form(s), once all Participant/LAR signatures are obtained, the Participant/LAR will be asked to return the form(s) as soon as possible to the person who conducted the consent process.

(Note: it is best practice to confirm the date with the individuals so that the form is dated correctly.)

Person Obtaining Consent Signature:

The person conducting the consent process will sign, date and time the Informed Consent he/she used for the conversation. They will also document the process used to obtain consent and the reason it could not be done in person.

When using paper form(s), once the signed Informed Consent is received from the Participant/LAR, it must be combined with the paper form signed by the person obtaining consent. A copy of the combined paper form with all signatures will be given to the Participant/LAR for their records.

No procedures can be performed until the signed and dated Informed Consent are received from the Participant/LAR or the eConsent Process has been completed. When using paper form(s), a faxed copy from the Participant/LAR is permissible.

19.0 EXPEDITED REVIEW

The SLHS IRB permits the use of expedited review procedures for eligible human subject research activities, as defined by federal regulations.

Eligibility for Expedited Review:

The IRB may use expedited review procedure to review either or both of the following:

- Research that involves no more than minimal risk and which appears on the following list of expedite review categories authorized by [45 CFR 46.110](#) and 21 CFR 56.110.
- Minor changes in previously approved research during the period for which approval is authorized.

Expedited Review:

- An expedited review will be performed by the IRB Chair or by an experienced IRB Member designated by the IRB Chair, i.e., a member with demonstrated knowledge and application of research ethics in human subject protections of at least one year.
- Reviewers receive and review the same materials that the convened IRB received for protocols reviewed by the convened IRB.
- The criteria for approval using the expedited procedures are the same as those for review by a convened IRB.
- The reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research.
- A research activity may be disapproved only after review in accordance with the non-expedited procedure.
- The reviewer will make one for the following determinations regarding the application:
 - Approved
 - Modifications to Secure Approval
 - Forward to Convened IRB
- Documentation of the review, action taken by the reviewer, and any specific findings required by federal regulations will be documented in the reviewer notes.
- In all cases the expedited reviewer reserves the authority to refer any study to a medical reviewer and/or to the Convened IRB review.
- Items approved using the expedited review procedure (initial review, modifications, and continuing review) are forwarded via the electronic IRB system to a convened IRB agenda review.

IRB Oversight of Expedited Review:

IRB Members are advised of research proposals, which has been reviewed by the expedited procedure with a listing provided with each convened meeting agenda. This information is also included in the meeting minute history. Any member can request to review the entire IRB record associated with items reviewed by the expedited review procedure.

Research may be reviewed by the IRB using an expedited review procedure, applicability:

- The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.
- The categories in this list apply regardless of the age of subjects, except as noted.
- The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
- The expedited review procedure may not be used for classified research involving human subjects.
- The standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of IRB review (expedited or convened).
- Categories 1 through 7 pertain to initial, modifications and continuing review.
- Categories 8 and 9 pertain to continuing review.

Expedited Review Categories:

- Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
 - a. Research on drugs for which an investigational new drug application (IND) is not required.

(Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
 - b. Research on medical devices for which (i) an investigational device exemption application (IDE) is not required; or (ii) the medical device is approved (cleared) for marketing and the medical device is being used in accordance with its approved (cleared) labeling.
- Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
 - Collected from healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
 - Collected from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8-week period and collection may not occur more frequently than 2 times per week.
- Prospective collection of biological specimens for research purposes by noninvasive means.

Examples:

- *Hair and nail clippings in a non-disfiguring manner*
- *Deciduous teeth if routine patient care indicates a need for extraction*
- *Permanent teeth if routine patient care indicates a need for extraction*
- *Excreta and external secretions (including sweat)*
- *Non cannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue*
- *Placenta removed at delivery*
- *Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor*
- *Supra- and sub gingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with acceptance prophylactic techniques*
- *Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings*
- *Sputum collected after saline mist nebulization.*
- Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples:

- *Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy*
- *Weighing or testing sensory acuity*
- *Magnetic resonance imaging*

- *Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography*
- *Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual*
- Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis).
- (Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101 (b) (4). This listing in this document refers only to research that is not exempt.)
- Collection of data from voice, video, digital, or image recordings made for research purposes.
- Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

(Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b) (2) and (b) (3). This listing in this document refers only to research that is not exempt.)

- Continuing review of research previously approved by the convened IRB as follows:
 - Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects;
 - OR**
 - Where no subjects have been enrolled and no additional risks have been identified;
 - OR**
 - Where the remaining research activities are limited to data analysis.
- Continuing review of research, not conducted under an investigational new drug application (IND) or investigational device exemption (IDE) where categories two (2) through eight (8) above do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

20.0 EXEMPT REVIEW

The SLHS IRB permits the use of exempt review as defined by federal regulations exemption criteria under 45 CFR 46.101 and 21 CFR 56.104.

Exempt research activities are subject to the same human subject protections and ethical standards as outlined in the Belmont Report. Exempt research activities offer no more than minimal risk to participants, selection of participants is equitable, and adequate provisions are in place to maintain the privacy interests of participants. If there is recording of identifiable information, there are adequate provisions to maintain confidentiality of the data. If there are interactions with participants, the IRB will determine whether there should be a consent process that will disclose such information as the activity involves research, a description of the procedures, that participation is voluntary, and the name and contact information for the researcher.

Only the IRB may determine which activities qualify for exempt status. Investigators do not have the authority to make an independent determination that research involving human subjects is exempt and must contact the IRB concerning the status of proposed research or changes in ongoing research.

Determination of exempt status is generally performed by a designated IRB Specialist with demonstrated knowledge of the application of research ethics in human subject protections. IRB Chair and designated IRB Members, Managers, and Administrators will review requests of exemption submitted by Investigators, when applicable.

IRB review, action taken by the reviewer and the permissible exempt category citation(s), if applicable, are documented in the IRB record.

When a research project has been determined by the IRB to be exempt from further IRB review, continuing review is not required.

Exemption Status and Research Project Modifications Certain project modifications may disqualify the research from exempt status. Therefore, any proposed modification to an exempt study must be submitted to the IRB for review and approval prior to implementation.

Investigator Responsibilities:

The Investigator will make a preliminary assessment that a proposal is eligible for exemption based on the regulatory criteria and submit an application for IRB review. The Investigator will not begin the project until the exempt status is confirmed by the IRB.

Criteria for Exemption:

Exempt Research under the Revised Common Rule:

As of January 19, 2018, the federal government changed the types of human subject's research that are considered "exempt." These projects will be exempt from annual IRB review and exempt from the informed consent requirements that apply to other types of research. However, some of the new categories will require prospective participant agreement and a limited form of IRB review.

Even when research is exempt from further requirements of federal regulations, basic ethical standards still apply:

- Except in the case of chart reviews or database research, potential subjects must be provided enough information to be able to choose whether or not to participate. The information would typically include the voluntariness of their participation, the purpose of the research, the nature of the subject's involvement, time commitments, and contact information for the Investigator.
- Research data must be handled and stored securely, in compliance with institutional policy.
- Access to research data must be limited to study team members and other authorized personnel.
- All members of the research team must be current on human subjects training and must have a current conflict of interest disclosure.

Under 45 CFR 46.101 (b) Department of Health and Human Services (DHHS) the IRB may determine a research activity to be exempt where the only involvement of human subjects will be in one or more of the following eight categories:

- (1) Research, conducted in established or commonly accepted educational settings that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most

research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

Most educational research on regular and special educational instructional strategies, and research on the effectiveness of, or comparison among, instructional techniques, curricula, or classroom management methods may be exempt under this category.

Changes to this exempt category include the caveat that there must not be any impact of subject's opportunity to learn or any negative impact if the research involves an evaluation of the instructors. If the research involves significant time and attention away from the delivery of regular curriculum or withholding of standard educational content, this exemption will not apply. Also, there must be protection against negative impact on employment if instructors are being evaluated. Research involving randomization to an unproven educational technique, or research conducted by supervisors involved in employment decisions may not be approvable under this exemption.

Applicability to vulnerable populations:

- Pregnant women may be included in this type of research.
- Research that targets a prisoner population is not eligible for this exemption. The exemption is allowable if the research is aimed at a broader population and only incidentally includes prisoners.
- Research involving children is eligible for this exemption.

(2) Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:

- (i) The information obtained is recorded by the Investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
- (ii) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
- (iii) The information obtained is recorded by the Investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review.

This exemption category involves several changes from pre-2018 rules. The wording of this exemption was changed to clarify that the category applies to research that only involves interactions. Additionally, the use of potentially sensitive information might be allowable if appropriate protections are in place and the IRB conducts a new process called 'limited IRB review.'

This category involves interactions (verbal and written responses) and data collection only. The data collection can include audio or video recordings. Research involving "interventions" would not be approvable under this category. Interventions include manipulation of the environment or physical procedures to collection information, such as a cheek swab.

Applicability to vulnerable populations:

- Pregnant women may be included in this type of research.

- Research that targets a prisoner population is not eligible for this exemption. The exemption is allowable if the research is aimed at a broader population and only incidentally includes prisoners.
 - Research involving children is eligible for this exemption only when it related to educational tests or observations in which the Investigators don't participate in the activities being observed. Additionally, children are not eligible for this exemption if the project requires limited IRB review.
- (3) Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:
- (i) The information obtained is recorded by the Investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
 - (ii) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
 - (iii) The information obtained is recorded by the Investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review.

For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the Investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, *examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.*

If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

This exempt category is completely new in the 2018 revisions to the federal regulations. There are limits on the interventions that are considered 'benign' and requirements on IRB review of this type of research.

Applicability to vulnerable populations:

- Pregnant women who are adults may be included in this type of research
 - Research that targets a prisoner population is not eligible for this exemption.
 - Research that could include children is not eligible for this exemption. The exemption is allowable if the research is aimed at a broader population and only incidentally includes prisoners.
 - Research involving decisional-impaired persons is not eligible for this exemption.
- (4) Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable bio-specimens, if at least one of the following criteria is met:
- (i) The identifiable private information or identifiable bio-specimens are publicly available;

- (ii) Information, which may include information about bio-specimens, is recorded by the Investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the Investigator does not contact the subjects, and the Investigator will not re-identify subjects;
- (iii) The research involves only information collection and analysis involving the Investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); or
- (iv) The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for non-research activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with applicable federal privacy standards found in the E-Government Act, Privacy Act, and the Paperwork Reduction Act.

The 2018 changes significantly broaden the type of secondary research that can be done under this exemption category:

- The requirement that all study data be existing at the time of IRB submission has been eliminated. Data under this exemption may be both retrospective and prospective.
- The requirement that the study involves data only has been eliminated. The research may also involve the use of specimens.
- Creating a de-identified dataset for analysis is still an approvable option and continues to be the most straight-forward approach.
- If Investigators need to retain data that contains any HIPAA elements or need to retain a linking list, then appropriate HIPAA protections could make the project approvable. Depending on the circumstances of the data, the HIPAA protections might include a Business Associate Agreement, a Data Use Agreement, or a waiver of HIPAA authorization with accounting of disclosures.
- Certain sources of publicly available data require the recipient to sign an agreement outlining restrictions on access, use, security, and transfer. Most often, those agreements will need review by the university's general counsel.

It is important to note the Exemption Category 4 only applies to the re-use of data and specimens that were or will be collected for non-research purposes or from research studies other than the proposed research study. The research materials typically will be publicly available materials, medical records, or existing repositories of clinical specimens. No contact between Investigator and subject is allowed. If an Investigator wants to collect information/specimens directly from research subjects, then another approval path would be required.

Applicability to vulnerable populations:

- Data/specimens from pregnant women would be allowed
- Data/specimens from prisoners could be allowed as long as the research wasn't designed to recruit prisoners and prisoners were only incidental subjects of the research.
- Data/specimens from children would be allowed
- Data/specimens from persons with decisional impairment would be allowed

- (5) Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended. Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal website or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.

The scope of this category has been broadened. Prior rules required that the Federal demonstration projects be conducted by the Federal agency. This category has been updated to allow projects that are simply funded by a Federal agency. The scope has been expanded to include purposes not only to study and evaluate but also to improve these programs.

(Note: that projects eligible for this exemption will be posted on a Federal website.)

- (6) Taste and food quality evaluation 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 Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. This exemption category was not changed in the revised Common Rule.

(Note: it is the only exemption that is allowable for FDA-regulated research.)

Applicability to vulnerable populations:

- Pregnant women may be included in this type of research.
 - Research that targets a prisoner population is not eligible for this exemption. The exemption is allowable if the research is aimed at a broader population and only incidentally includes prisoners.
 - Research involving children is eligible for this exemption.
 - Research involving decisional-impaired persons could be allowed if their inclusion was justified.
- (7) Storage or maintenance for secondary research for which broad consent is required: Storage or maintenance of identifiable private information or identifiable bio specimens for potential secondary research use if an IRB conducts a limited IRB review and makes the determinations required by 45 CFR 46.111(a)(8).

This exemption is new with the 2018 Common Rule. It will be implemented at SLHS when capacity to meet technical and regulatory requirements has been confirmed.

Research with vulnerable populations may be approvable with this exemption:

- Pregnant women may be included in this type of research.
 - Research that targets a prisoner population is not eligible for this exemption. The exemption is allowable if the research is aimed at a broader population and only incidentally includes prisoners.
 - Research involving children is eligible for this exemption.
- (8) Secondary research for which broad consent is required: Research involving the use of identifiable private information or identifiable bio-specimens for secondary research use, if the following criteria are met:
- (i) Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable bio-specimens was obtained in accordance with §__.116(a)(1) through (4), (a)(6), and (d);
 - (ii) Documentation of informed consent or waiver of documentation of consent was obtained in accordance with §__.117;
 - (iii) An IRB conducts a limited IRB review and makes the determination required by §__.111(a) (7) and makes the determination that the research to be conducted is within the scope of the broad consent referenced in paragraph (d)(8)(i) of this section; and 479 (iv) The Investigator does not include returning individual research results to subjects as part of the study plan. This provision does not prevent an Investigator from any legal requirements to return individual research results.

(Note: This exemption is new with the 2018 Common Rule.)

Research with vulnerable populations may be approvable with this exemption:

- Pregnant women may be included in this type of research.
- Research that targets a prisoner population is not eligible for this exemption. The exemption is allowable if the research is aimed at a broader population and only incidentally includes prisoners.
- Research involving children is eligible for this exemption.

FDA Exemption Criteria:

FDA Exemption Criteria under 21 CFR 56.104 (Food and Drug Administration), the following categories of clinical investigations are exempt:

- Any investigation which commenced before July 27, 1981 and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets FDA requirements in effect before July 27, 1981.
- Any investigation which commenced before July 27, 1981 and was not otherwise subject to requirements for IRB review under Food and Drug Administration regulations before that date.
- 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.
- 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 Food and Drug Administration or approved by the Environmental Protection Agency or the Food and Safety Inspection Service of the U.S. Department of Agriculture.

(Note: These exemptions do not apply to research involving prisoners.)

Research Involving Children:

- The exemptions specified in the above DHHS 45 CFR 46.101(b) exemption categories (1), (3), (4), (5), and (6) apply to research involving children.
- The exemption specified in the above DHHS 45 CFR 46.101(b) exemption category (2) only applies to research involving observation of public behavior when the Investigator does not participate in the activities being observed.
- The exemption does not apply where the research involves survey or interview procedures or any direct interaction with the subjects being observed.

21.0 CENTRAL AND EXTERNAL IRB REVIEW

Central and Commercial IRBs are external IRBs, often for-profit, providing IRB review services.

The SLHS may rely upon the IRB of another organization provided Investigators at SLHS are participating as Investigators on a research project and the IRB of the external organization is better prepared to review the research OR SLHS researchers receive a grant (or other federal funds).

When relying on an external IRB, whether it is for a single research project or a portion of the organization's research portfolio, the external IRB will meet Federal regulations for the conduct of research and IRB review. When SLHS relies on an external IRB to serve as the IRB of record, the external IRB will be evaluated by SLHS to determine if it meets specific criteria for the protection of human research subjects and, if so, written agreements outlining specific responsibilities of each party are executed.

There will be formal written authorization agreement between Saint Luke's Health System and the external IRB delineating the roles and responsibilities of each party.

Reliant Review:

Reliant Review engages reliance agreements to reduce duplicative IRB reviews, aiming to promote greater efficiency and consistency among IRB determinations for multisite research. Saint Luke's Health System is willing to enter into reliance agreements with external IRBs or serve as the Reviewing IRB for multisite research or an individual Investigator in order to better serve the research community and minimize redundant IRB reviews.

Reliance agreements outline the roles and responsibilities in the reliance relationship between IRBs; however, when using Reliant Review for a research study it is important for Investigators to recognize that SLHS still retain important institutional responsibilities for the oversight of the research study. The relying organization must ensure that local ancillary reviews required to conduct research at this site are completed and that local requirements and context unique to Saint Luke's Health System are communicated to the IRB of Record.

IRB Authorization Agreements (IAA):

IRB Authorization Agreements are agreements executed between, IRB of Record, and Relying IRB outlining the terms and responsibilities of each institution in the reliant relationship. IAA's will reviewed by the IRB Administration office and the SLHS Legal Department and signed by the SLHS Signatory Official. Authorization agreements can be executed for one single study or multiple studies. Investigators interested in collaborating with an institution where the above options are not applicable should contact the IRB for more information about executing an IAA.

Eligibility:

Types of Research that May Utilize External IRB Review.

(Note: Upon receipt of the reliance request, the SLHS HRPP office will review the request, will consider protocol specifics and local context, and will make a final determination regarding SLHS's willingness to rely on the external institution.)

SLHS will consider utilizing the services of a qualifying external IRB for review of research studies that meet ANY of the following criteria:

- An institutional or individual conflict with the research has been determined by the Saint Luke's Health System Conflict of Interest Committee, the Institutional Official (IO) or the convened SLHS IRB
- SLHS employees are engaged in multi-site research utilizing a central IRB
- SLHS employees are engaged in a study for which the Investigator provides sufficient rationale as to why external IRB review would be beneficial

NIH Mandate expects that all sites participating in multi-site studies, which involves non-exempt human subject's research funded by the NIH, will use a single IRB to conduct the ethical review required for the protection of human subjects.

Reliance Request and Acceptance:

The Investigator seeks approval from the SLHS HRPP to use an external IRB to serve as the IRB of Record and provide justification for reliance on the external IRB.

The SLHS HRPP assesses whether an external IRB is qualified to serve as the IRB of Record for SLHS human subject research project.

Once it is determined that an external IRB will be used for a study and/or there is an agreement to collaborate:

- Investigators assume responsibility for engaging research support offices/centers at SLHS with oversight responsibility for the implementation of research and provide any materials needed to those entities in order to grant approval. This includes but is not limited to, department review, radiation safety, electrical safety, research finance, grants, and contracts etc.
- SLHS HRPP office is responsible for confirming local context/ institutional issues, including: personnel qualification, expertise and education requirements, conflict of interest, department approval letter, required ancillary approval letters, the study protocol and consent documents. The SLHS HRPP office will also communicate with Research Business Operations regarding any additional requirements related to the study.

(Note: SLHS HRPP will manage all local personnel and site changes.)

- The SLHS Principal Investigator (PI) is ultimately responsible for ensuring that the IRB of Record has approved the study before beginning the study.

22.0 COMPASSIONATE USE

FDA regulations and guidance make provisions for access to investigational drugs and devices for treatment purposes through their Expanded Access Program (EAP). This access is commonly referred to as "compassionate use," however, Investigators should note that the term "compassionate use" does not appear in FDA regulations,

and its use is actively discouraged by the FDA Center for Drug Evaluation and Research (CDER). The term does appear in guidance issued by the FDA Center for Devices and Radiological Health (DCRH).

23.0 EMERGENCY USE

The FDA and other Federal agencies have strict regulations about the use of investigational agents in emergency situations. The regulations state “Nothing in this guidance is intended to limit the authority of a physician to provide emergency medical treatment for patients who need such care” ([45 CFR 46.116\(f\)](#)). These regulations mean that emergency medical care for patients may be provided without prior IRB review and approval when there is not adequate time to obtain IRB approval before administration/implementation.

DHHS regulations (45 CFR 46) do not permit DHHS-regulated research activities to be started, even in an emergency, without prior IRB Committee review and approval. When an investigational agent is used in emergency medical care without prior IRB Committee review and approval, the patient may not be considered a research subject as defined by DHHS regulations. However, the patient is a research subject under FDA regulations. Therefore, it is the SLHS IRB guidance that data obtained when an Investigator utilizes the emergency use provisions found in the FDA regulations for the administration of investigational, drugs, agents, biologics, or devices, the data may not be claimed as DHHS-regulated research, although the data must be claimed as FDA-regulated research. Data regarding such care may not be included in any report of a DHHS-regulated research activity but may be used in a report of an FDA-regulated research activity that is not DHHS-regulated.

The FDA regulations do NOT allow expedited IRB approval of research in emergency situations. Therefore, terms such as “interim approval,” “compassionate approval,” “temporary approval,” will not be utilized for requests for emergency use of FDA regulated products. The IRB must either grant approval at a convened full Committee meeting (may use the data for research), or if the conditions of [21 CFR 56.104\(c\)](#) are met and it is not possible to convene a quorum within the time available, the emergency use may proceed without prior IRB approval (may not use the data for research).

It is the guidance of the SLHS IRB to recognize the provisions found in the FDA regulations for the emergency use of investigational drugs, biologics, agents, or devices. The emergency use of investigational drugs, agents, biologics, or investigational (unapproved) medical devices, will be handled in accordance with FDA regulations and institutional policies and procedures. Although [21 CFR 56.104\(c\)](#) allows for an exemption from prior review and approval by the IRB for emergency use, the IRB requires prior notification of emergency use of investigational drugs, agents, biologics or investigational (unapproved) medical devices.

Emergency Use of Investigational Drug, Biologics, or Devices:

When the urgency of the patient’s treatment does not permit consideration at a convened IRB meeting, the emergency use of the test article may proceed. Emergency use of an investigational drug, biologics, or device may only occur if all FDA requirements ([21 CFR 56.104\(c\)](#)) for emergency use are met:

- The patient is in a life-threatening or severely debilitating situation.
- There is no standard acceptable treatment available.
- There is insufficient time to obtain approval from the IRB at a convened meeting. Any subsequent use will be reviewed by a convened IRB.

The emergency use provisions in the FDA regulations is an exemption from prior review and approval of the IRB. It allows for one emergency use of a test article without prospective IRB review. Any subsequent use of the investigational product at the institution must have prospective IRB review and approval.

It is the Investigator's responsibility to notify the IRB prior to emergency use of an investigational drug, agent, biologic, or device. This is done by contacting the IRB by telephone and completing the IRB Checklist, Emergency Use Involving Human Subjects determination form. When completing the checklist, the Investigator will need to decide if the patient's need for treatment is such that the emergency request can be considered at a convened IRB meeting before the treatment is administered. Since the IRB meets twice a month, it may not be feasible for the proposal to be added to the agenda of a scheduled meeting.

(Note: If the patient's condition allows waiting for review at an IRB meeting, then the FDA Emergency Use restrictions do not apply, the IRB approves the protocol, and the patient consents, and the Investigator may use the data for research purposes.)

When the Investigator notifies the IRB in advance of an emergency use, the IRB Chair (or in the Chair's absence, a designee) will review the circumstances of the use and ensure that FDA regulations [21 CFR 56.104\(c\)](#) and [21 CFR 50](#) will be followed. When an emergency use report is discussed at an IRB meeting, the minutes of the meeting must document that the IRB considers the use of the investigational agent to meet the requirements of [21 CFR 56.104\(c\)](#) and [21 CFR 50](#). If not, the matter will be handled as non-compliance.

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 potentially life-threatening situation requiring prompt intervention.

Informed Consent and Waiver of Informed Consent:

Even in an emergency situation, the Investigator is required to obtain written informed consent from the patient. Relevant items required in a research consent form should be present. The consent form is not approved or stamped by the IRB. The IRB is willing however to review the consent and offer suggestions. For those studies possessing the criteria for granting exceptions to the requirement of obtaining informed consent, and in turn wish to utilize this waiver, the Investigator is required to submit documentation supporting the waiver to the IRB within five days. For all protocols utilizing the exceptions to the requirement to obtain informed consent for emergency use of a test article, the IRB will review all submissions to determine whether the exception complied with regulatory requirements.

21 CFR 50.23 Exception from general requirements. An exception to the requirement for informed consent may be made if both the Investigator and physician who is not otherwise participating in the clinical investigation certify in the writing all of the following:

- The subject is confronted by a life-threatening (or severely debilitating) situation necessitating the use of the investigational drug or biologic;
- Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject;
- Time is not sufficient to obtain consent from the subject's legal representative; and
- No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the life of the subject.

If, in the Investigator's opinion, immediate use of the investigational drug or biological product 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 Investigator should make the determination and, within 5 working days after the use of the investigational drug or biological product have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

IRB Responsibilities:

The initial review is performed by the Chair or designee; and if they determine that the criteria have been met, the Chair or designee will communicate this in writing to the Investigator. The criteria for allowing emergency use of a test article in a life-threatening situation are listed on the “Emergency Use Involving Human Subjects” determination form.

The emergency use of FDA regulated products requires the involvement of an IRB Chair or his/her designee. The IRB Chair or his/her designee will be promptly notified of the Investigator’s intent for emergency use of an investigational drug, agent, biologic, or device. The IRB Chair or his/her designee will evaluate the Investigator’s notification and guide the Investigator in adherence to the FDA regulations and institutional policies and procedures. The IRB Chair or his/her designee may request:

- An authorization from the sponsor or manufacturer to allow the use by the Investigator for the test article;
- An approved IND/IDE or a letter explaining exemption from the FDA;
- An adequate description of the situation regarding the use of the test article with an independent physician’s certification, if applicable;
- The informed consent document or the certification for the exception from obtaining informed consent; and
- Any other materials that may aid in the evaluation of the request.

The full Board will be notified of the emergency use of an FDA regulated product and the IRB Chair or his/her designee will review the five (5) day follow-up report submitted by the Investigator with the full Board.

Some manufacturers or sponsor will agree to allow the use of the investigational agent, but their policy requires “an IRB approval letter” before the agent will be shipped. The manufacturer will be provided a written statement that the IRB is aware of the proposed use and based on the information it has been provided by the Investigator that the proposed use meets the requirements of [21 CFR 56.102\(d\)](#). If this acknowledgement is needed, it is requested on the Emergency Use Involving Human Subjects determination form. Although this is *NOT* an “IRB approval,” the acknowledgement letter is usually acceptable to the manufacturer and allows shipping the experimental agent to the Investigator.

The Investigator is required to submit a written follow-up report to the IRB within five working days of the emergency use of an investigational drug, agent, biologic, or device. This report should include the name of the investigational drug, agent, biologic, or device; a copy of the informed consent document (or justification for a waiver of informed consent); a description of the conditions, including date and time, under which the investigational drug, agent, biologic, or device was administered/utilized; measures taken to protect participants; adverse events or unanticipated problems to the recipient or others; and outcomes if known. The written follow-up report, protocol; and consent form (or justification for a waiver) is reviewed by the Board at the next convened meeting. The IRB will review the documents provided, together with the criteria to waive the requirements to obtain informed consent (if applicable) and determine whether the regulatory criteria for planned emergency research have been met and that the circumstances of the emergency use met the requirements of the FDA regulations. The criteria for allowing emergency use of a test article in a life-threatening situation are listed on the “Emergency Use Involving Human Subjects” determination form.

The Board’s determinations are communicated in writing to the Investigator.

Subsequent Use:

Investigators must understand that under no circumstances, can an emergency use procedure be done more than once for a single investigational drug, agent, biologic, or device. The Investigator is to evaluate the likelihood of a similar need for the drug, agent, biologic, or device occurring again, and if future use is likely, immediately initiate efforts to obtain IRB approval and an approved IND or IDE for subsequent use. If Investigators think they may need to use the investigational drug, agent, biologic, or device again, a complete IRB protocol must be submitted in time for full Board review. Since it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the protocol, it is permissible to treat a second patient prior to full IRB approval if the protocol has been submitted to the IRB and IRB review is in process.

FDA Requirement to Obtain and Emergency IND/IDE for Drug, Device or Biologics:

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 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. 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, the 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 312.36](#)).

If an IDE for the use of an investigational device does exist, the Investigator is to notify the sponsor of the emergency use, or if an IDE does not exist or if the need arises for an emergency use of an unapproved device before an IDE is approved,, the Investigator is to notify the FDA of the emergency use within 5 days through a submission of an IDE report and provide the FDA with a written summary of conditions constituting the emergency, subject protection measures, and results.

Criteria for the Emergency use of an unapproved medical device are as follows:

- Life-threatening or serious disease or condition
- No alternate
- No time to obtain FDA approval

24.0 EXPANDED ACCESS

Expanded access refers to the use of an investigational drug, device, or biologic when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition rather than to obtain the kind of information about the agent that is generally derived from clinical trials. FDA has a long history of facilitating expanded access to investigational agents for treatment use for patients with serious or immediately life- threatening diseases or conditions who lack therapeutic alternatives.

Under FDA's current regulations, there are three categories of Expanded Access:

- 1) Expanded access for individual patients, including for emergency use (21 CFR 312.310)
- 2) Expanded access 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) Expanded access for widespread treatment use through a treatment IND/IDE or treatment protocol (designed for use in larger patient populations) (21 CFR 312.320)

For FDA guidance on Expanded Access to investigational drugs for treatment use please visit:

<https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm351261.pdf>

For FDA guidance on Expanded Access to investigational devices for treatment use please visit:

<https://www.fda.gov/medical-devices/investigational-device-exemption-ide/expanded-access-medical-devices#:~:text=Expanded%20access%20to%20an%20investigational,procedures%20to%20obtain%20FDA%20approval>

25.0 HUMANITARIAN USE DEVICE

A device manufacturer's research and development costs could exceed its market returns for diseases or conditions affecting smaller patient populations. The FDA therefore, developed and published the Humanitarian Device Exemption (HDE) regulation (21 CFR 814.124) to provide an incentive for the development of Humanitarian Use Devices (HUDs) for use in the treatment or diagnosis of diseases affecting these populations. The regulation provides for the submission by a manufacturer of a HDE application. An HDE application is not required to contain the result of 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 risk of illness or injury, and that the probable benefit to health outweighs the risk of illness or injury from its use. Additionally, the manufacturer 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. FDA approval of a manufacturer's HDE application authorizes marketing of an HUD. However, an HUD may only be used in facilities that have established an IRB to approve the use of the device to treat or diagnose the specific disease.

The SLHS IRB reviews and approves HUDs for the treatment or diagnosis of a specific disease following the guidelines in the Code of Federal Regulations [21 CFR 814.124 \(Subpart H\)](#), Humanitarian Use Devices, IRB requirements.

Of note, the following does not apply to research protocols that include the investigation of a HUD. When a HUD is used for research purposes opposed to the treatment or diagnosis of a specific disease, the IRB follows regulations for the review of an investigational device.

IRB approval:

The HDE holder is responsible for ensuring that a HUD approved under this subpart is administered only in facilities having an IRB that can approve the original protocol and perform continuing reviews of use of the device. If, however, a physician in an emergency situation determines that approval from an IRB cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be administered without prior approval by the IRB. In such an emergency situation, the physician shall, within 5 days after the use of the device, provide written notification to the Chairman of the IRB of such use. Such written notification shall include the identification of the patient involved, the date on which the device was used, and the reason for the use.

Withdrawal of IRB approval:

A holder of an approval HDE shall notify FDA of any withdrawal of approval for the use of a HUD by a reviewing IRB within 5 working days after being notified of the withdrawal of approval.

The IRB requires the review and approval for the use of a HUD before the device is administered to patients of SLHS unless an emergency situation exists as defined above. The IRB full board will review and approve the use of the device for groups of patients meeting certain criteria or use of the device under a treatment protocol. The IRB

will review the HUD protocol for the patient's need for the device and the likelihood that the device is appropriate for the patient's condition or disease state as well as to determine if the risks to subjects are reasonable in relation to anticipated benefits.

For initial review of a HUD protocol, the IRB will perform a full board review. For continuing review, however, the IRB may vote during the initial review to use the expedited review procedures, unless the IRB determines that full board review should be performed.

For initial IRB approval of a HUD protocol, an Investigator must provide the following documentation:

- The HUD manufacturer's product labeling, clinical brochure, and/or other pertinent manufacturer information materials.
- A description of the device
- The patient information packet and/or consent form that may accompany the HUD.
- SLHS Department Review Committee approval to confirm that it has approved the HUD for clinical use.
- HUD protocol including a statement from the Investigator specifying a description of any screening procedures, the clinical indication, where and by who the HUD will be used, and any patient follow-up visits, tests or procedures within SLHS environments.

The HUD patient information packet or clinical consent form should be generally include the following:

- A statement reflecting the HUD status of the device.

Examples:

- *Your medical care will involve the use of (specify device), which has been approved by the U.S. Food and Drug Administration (FDA) as a HUD.*
- *A HUD is used to diagnose or treat a disease or condition that affects no more than 8,000 individuals in the US per year and for which no comparable device is available.*
- *The FDA approves the clinical use of a HUD based primarily on evidence that:*
 - *It does not pose a significant risk of injury to the patient,*
 - *That the potential benefit of the device to the health of the patient outweighs the risks if its use,*
 - *The effectiveness of the device for this use has not been demonstrated, and*
 - *Its use does not involve research.”)*
- A description of the HUD and how this device will be used in the clinical setting. Based on this description, it should be clear to the patient why they are a candidate for the use of this device.
- A discussion of the possible risks, side effects, and/or adverse events associated with the HUD and its proposed clinical use.
- A discussion of the possible benefit's associated with the clinical use of the HUD.
- A discussion of any alternative treatments or procedures (if any) that the patient may wish to consider in lieu of clinical application of the HUD.
- An explanation of cost associated with the device.

IRB approval is required for any modifications of the device and/or proposed clinical use of the device. An HDE holder may collect safety and effectiveness data to support a PMA under the approved HDE (i.e., no IDE is needed). If the HUD is the subject of a clinical investigation, (one in which safety and effectiveness data is being collected to support a PMA), SLHS IRB approval and informed consent are required.

The HDE holder is responsible for submitting updated information on a periodic basis to the IRB of record and the FDA demonstrating that the HUD designation is still valid.

Facilities that are using the device approved under an HUD are required to submit medical device report to the FDA, the IRB of record, and to the manufacturer whenever an HUD may have caused or contributed to a death or a serious injury.

HUDs may be used off-label in an emergency situation, but certain patient protection measures should be followed before the use occurs. Because SLHS IRB review and approval is required before a HUD is used within its approved labeling, a HUD should not be used outside of its approved labeling without similar restrictions. In an emergency situation, a HUD may be used off-label to save the life or protect the physical well-being of a patient, but the physician and HDE holder should follow the emergency use procedures governing such use of unapproved devices. According to this guidance, before the device is used, if possible, the physician should obtain SLHS IRB Chair's concurrence, informed consent from the patient or his/her legal representative, and an independent assessment by an uninvolved physician. In addition, authorization from the HDE holder would be needed before the emergency use of the HUD. After the emergency use occurs, the physician should submit a follow-up report on the patient's condition and information regarding the patient protection measures to the HDE holder and SLHS IRB.

A HUD may be used for compassionate use. As discussed for emergency use, the physician should ensure that the patient protection measures are addressed before the device is used. In addition to addressing the patient protection measures, prior FDA approval of the HUD for compassionate use is required just as it is for compassionate use of any unapproved device. According to the FDA's IDE policy on compassionate use, a physician who wishes to use a device for compassionate use should provide the IDE sponsor with a description of the patient's condition and the circumstances necessitating treatment with the device, a discussion of why alternative therapies are unsatisfactory, and information to address the patient protection. For compassionate use of a HUD, the physician should provide this information to the HDE holder, who would then submit it as an HDE amendment for FDA approval before the use occurs. FDA will review the information in an expeditious manner and issue its decision to the HDE holder.

If the request is approved, the physician should devise an appropriate schedule for monitoring the patient, taking into consideration the limited information available regarding the potential risks and benefits of the device and the specific needs of the patient. Further discussion of the post-approval procedures for compassionate use, including the submission of a follow-up report can be found at FDA, Guidance on IDE Policy and Procedures.

26.0 INVESTIGATIONAL MEDICAL DEVICE

A medical device is considered investigational if either condition applies:

- The device is not approved for marketing in the U.S.
- OR**
- The device is approved for marketing but is being *clinically* evaluated for a new indication.

The [Food and Drug Administration \(FDA\)](#) [3] regulates research involving medical devices ([see FDA definition](#) [4]), as well as all aspects of device manufacturing, marketing and distribution (*Code of Federal Regulations* Title 21, parts 800-1299). The FDA website contains several sets of useful and readable guidance documents about investigational devices, including mobile devices.

For many studies involving devices, an Investigator or sponsor must obtain an Investigational Device Exemption (IDE) from the FDA. See the [UCSF Investigator Checklist for IDE Exempt, Non-Significant, and Significant Risk Device Studies](#) [5] for a quick overview of when an IDE from the FDA is required or not required.

[FDA Regulatory Support at UCSF](#) [6] provides free consultations to the UCSF community on compliance with FDA regulations, including IDE requirements.

(Note: All device studies involving human subjects must be submitted to the IRB for review and approval before the investigation can begin.)

When Is an Investigational Device Exemption (IDE) Required?

There are two types of clinical studies involving medical devices that require than an Investigational Device Exemption (IDE) be obtained from the FDA in addition to IRB approval before a research study may commence.

- 1) A clinical study involving an unapproved device that poses significant risk to subjects

The majority of IDE studies are conducted to collect safety and effectiveness data used to support Premarket Approval (PMA) applications submitted to the FDA.

Example:

[Significant risk](#) [2] studies involve implantable devices such as cardiac pacemakers, orthopedic implants and stents. Significant risk studies can also involve products not introduced into the body, such as computer software used for prenatal risk evaluation. Each of these studies would require an IDE.

(Note: See UCSF guidance on [Significant and Non-Significant Risk Devices](#) [2] for more information.)

- 2) A clinical study involving an approved (legally marketed) device being tested for a new indication

This includes both a device being used or tested in a new way that significantly increases the risks associated with the device and/or significant risk studies testing an FDA-approved device.

Example:

A legally marketed coronary stent would be considered an investigational device and would require an IDE if used as part of a study to collect safety and effectiveness data for treating conditions involving other vascular sites.

When Is an IDE NOT Required?

There are four types of clinical studies involving medical devices that do not require that an IDE from the FDA be obtained be obtained. However, IRB approval is required before the study may commence.

- 1) Studies involving approved devices used with their approved labeling or devices that are [substantially equivalent](#) [7] (already granted an 510(k) by the FDA) to currently marketed devices
- 2) Studies involving approved devices that are determined by the IRB or the FDA to pose non-significant risks to the subjects.
 - IRB review and approval is required for all [non-significant risk device](#) [2] studies.
 - The FDA authorizes institutional review boards to conduct a risk assessment of all proposed non-significant risk studies. However, IRB cannot override NSR FDA determination if one has previously been made.
 - Study approval is dependent on the Investigator supplying the IRB with sufficient information, generally provided by the study sponsor, regarding the device and its intended use.
 - If the IRB determines that a proposed non-significant risk study is actually a significant risk study, the sponsor must submit a report to the FDA as [explained here](#) [2].

For more information, see UCSF guidance on [Significant and Non-Significant Risk Devices](#) [2].

Example:

Non-significant risk devices include daily wear contact lenses and associated care products; conventional gastroenterology and urology endoscopes; externally worn monitors for insulin reactions; and non-implantable electrical incontinence devices.

3) Practice of medicine

A physician can use a legally marketed device without IRB approval for any condition or disease within a “legitimate healthcare practitioner-patient relationship.” However, the results of an off-label use of a medical device cannot be presented as research.

4) Specific IDE-exempt studies, as described by FDA regulations

Review [21 CFR 812.2](#) [8] for a complete list of all types of investigations which are exempt from FDA IDE requirements. The more common IDE-exempt investigations submitted to the IRB meet the following criteria:

- Investigations conducted with legally marketed devices used according to labeling.
- Studies using in vitro diagnostics labeled for “research purpose only” as per regulations [21 CFR 809.10(c)] and if the testing:
 - is non-invasive;
 - does not require invasive sampling procedure that presents significant risk;
 - does not introduce energy into a subject; and
 - is not used as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure;

Additional FDA guidance on [studies using in vitro diagnostics](#) [9] is available. Also review the “[UCSF Investigator Checklist for IDE Exempt, Non-Significant, and Significant Risk Device Studies](#) [5]” for a quick overview of when an IDE from the FDA is required or not required.

26.1 IRB SUBMISSION AND REPORTING REQUIREMENTS

If your study involves a device, you must provide information about the device in the IRB Application and consent form [10] and submit other supporting documents.

IRB Application and Supporting Documentation Requirements:

For significant risk device studies:

- **IRB Application**
 - Indicate that the study involves a device in the "Initial Screening Questions" section.
 - Check the appropriate box in the "Drugs and Devices" section of the IRB Application.
- **An IDE number**
 - If the sponsor’s protocol does not list the IDE number, you must submit documentation from the sponsor or FDA identifying the IDE number for this study. The IRB will not issue final approval until the IDE number is reported to and verified by the IRB. However, the IRB will review the research before the IDE application is submitted to the FDA.
- **Investigator’s Brochure**

- **Directions for use**, typically provided by the manufacturer and device labeling consistent with federal regulations [[21 CFR 812.5](#) [11]]
- **Scientific/sponsor's protocol**
 - This document should describe the methodology to be used and offer an analysis that the study is scientifically sound.
- **An explanation of the device cost**
 - Determined by the [reimbursement category](#) [12] provided by FDA with each approved IDE. This information is needed for the consent form.
- **Clearance from the Radiation Safety Committee** [13] for radiation-emitting devices.

For non-significant risk device studies:

- **IRB Application**
 - Indicate that the study involves a device in the "Initial Screening Questions" section.
 - Check the appropriate box in the "Drugs and Devices" section of the IRB Application
 - Check Yes when asked if a Non-Significant Risk (NSR) determination is being requested for the investigational device. Then complete the "Non-Significant Risk Determination for an Investigational Device" section to provide the IRB with adequate justification why the use of the device in this study poses non-significant risk.
- **Detailed device information from the sponsor**
 - Such as a description of the device and how it is used.
- **Diagrams and/or *in situ* photographs of the device** are very useful (attach as "Other Study Documents").
- **Directions for use**, typically provided by the sponsor or manufacturer and **device labeling** consistent with federal regulations [21 CFR 812.5].
- **Scientific/Sponsor's Protocol**
 - This document should describe the methodology to be used and offer an analysis that the study is scientifically sound.
- **An explanation of the device cost**
 - Non-significant risk devices are placed in Category B and are most likely eligible for reimbursement. See the [reimbursement category](#) [12] overview provided by the FDA.

See our guidance on [Significant and Non-Significant Risk Devices](#) [2] for more info.

Consent Form Requirements:

All medical device studies involving human subjects require informed consent. Include the following key points within the [consent form template](#) [14] sections noted below:

Purpose and background:

- Must include a clear statement that the device is investigational and has not been approved by the FDA for clinical use or, if applicable, that the device has been approved for specific clinical indications but not for the use being studied.
- Should include a brief lay description of the device and what it is designed to do.
- Must not describe the issuance of an IDE as an approval or endorsement by the FDA.

Confidentiality:

Must state that the FDA may review research and subjects' medical records to verify study data.

Alternatives:

Must include a list of the various alternatives to participation in the study. This should name the standard therapies available with approved devices, as well as other experimental treatments with investigational devices.

Cost:

- Provide specific information regarding the participation in the device study. If applicable,
 - state if the sponsor is supplying the device at no charge.
 - state whether the subject or their insurance carrier will be billed for the device,
 - state that the cost may not be covered by insurance because the therapy is experimental,
 - provide a discussion of the cost of implanting and, if anticipated as part of the study, the cost of explanting the device.
- Describe how the subject can obtain more detailed information about the possible financial risks, if needed.

Adverse Event Reporting:

Adverse events associated with research participation must be reported expeditiously to both the [IRB](#) [15] and to the FDA (21 CFR 812.150).

Investigator's responsibilities:

- All Investigators have an obligation to [report certain adverse events](#) [15] directly to the IRB.
- Under IDE regulations, there are additional and separate federal requirements for reporting adverse events to the FDA. When the study sponsor holds the IDE, Investigators need to report all adverse events to the sponsor and the sponsor will submit appropriate reports to the FDA.

Investigator-sponsor responsibilities:

- Investigators who hold an IDE have responsibilities for reporting adverse events associated with the investigational device.
- In addition to [reporting to the IRB](#) [15], an Investigator-sponsor must report unanticipated adverse events investigated under a sponsor's monitoring requirements directly to FDA within 10 working days after the sponsor receives notice of the effect. See [FDA regulations](#) [16] and the [UCSF HUB](#) [17] for more info.

Types of IDE Applications:

Commercial IDE:

An IDE application submitted by a sponsor seeking FDA clearance to market a medical device.

Investigator-initiated IDE:

By submitting an IDE application to the FDA and conducting the clinical investigation, a physician takes on the responsibilities of both “sponsor” and “Investigator.”

Emergency Use IDE:

This is an exception to investigational device regulations permitting the *one-time treatment of one patient per institution* without prior FDA approval.

- Every effort must be made to obtain prior authorization from the IRB; at minimum at UCSF an IRB Chair must concur before treatment begins.
- Strict reporting requirements apply.
- The emergency use of an investigational device must meet all of the following criteria:
 - the patient has a life-threatening or severely debilitating condition, and
 - there are no other available treatments, and
 - there is not sufficient time for prior IRB review and approval.

(Note: Research may not be conducted under an emergency use IDE. Subsequent use(s) of the emergency use investigational device require prior IRB review and approval. For more information, please review the UCSF guidelines for [Emergency Use of Experimental Drugs and Devices](#) [18].)

26.2 EXPANDED ACCESS, HUMANITARIAN USE AND COMBINATION PRODUCTS

There are three regulatory mechanisms that allow expanded access to investigational medical devices while clinical studies and/or FDA review are on-going. Because FDA is primarily concerned with protecting public safety, the number of patients who can be treated under these special access mechanisms is limited and generally determined by the existence of sufficient safety and efficacy data. See [FDA Guidance on Expanded Access for Medical Devices](#) [19] or more details.

(IMPORTANT NOTE: Except for Emergency Use, both FDA and IRB review and approval is required before treatment can begin using these mechanisms. See guidance on [Emergency Use](#) [18] for requirements for details of that process.)

Expanded access programs are not considered research but rather treatment, and those enrolled in these programs should be referred to as “patients” and not “subjects.”

1. Emergency Use:

See discussion in section above.

2. Compassionate Use (or Individual Patient/Small Group Access):

Under an existing IDE, the FDA may allow treatment for an individual or a small number of seriously ill patients who have (a) a life-threatening disease or condition (b) with no other generally acceptable alternative treatment for the condition and (c) there is an existing concurrent clinical trial, but the patient(s) do not meet the inclusion criteria and (d) the treating physician believes the device may provide a benefit in treating and/or diagnosing their disease. The FDA requires the sponsor/Investigator either to supply a supplement to an existing IDE justifying the compassionate use or to request a new IDE.

(Note: Compassionate use requires FDA review and IRB approval before treatment can be initiated. The study involving the existing IDE must already be approved by the IRB. See the [Emergency Use and Compassionate Use of Experimental Drugs and Devices](#) [18] page for more info.)

3. Treatment Use:

If during the course of a clinical trial the data suggests that the device is effective, then the trial may be expanded to include additional patients with life-threatening or serious diseases for whom no comparable or satisfactory alternative is available. In addition, the sponsor of the controlled trial must be pursuing marketing approval/clearance of the device.

(Note: Treatment use may begin 30 days after the FDA has received the treatment IDE submission, or earlier if FDA notifies the sponsor in writing. Prior IRB review and approval are also required.)

Continued Access (Example of Treatment Use), a common type of treatment use occurs when after the completion of a controlled clinical trial, a supplement to an existing IDE is submitted and the FDA allows continued access to the device provided there are no safety concerns. The Continued Access Policy creates a bridge and allows access to promising devices while the marketing application is being prepared by the sponsor or reviewed by the FDA.

Drug-Device Combination Products:

The [Office of Combination Products \(OCP\)](#) [21] was created to facilitate the review process for combination products by coordinating interactions between reviewing branches. The OCP provides guidance documents for combination products.

Some recent combination product approvals [22] include drug-eluting coronary stents and antibiotic bone cement.

26.3 TIMING OF IDE SUBMISSION

Pre-IDE Process:

Applicants are encouraged to request feedback from the FDA regarding potential or planned IDE applications or other premarket submissions. For more info, review the [UCSF HUB's Pre-IDE Process](#) [17] page and [FDA's Pre-Submission Program guidance document](#) [23].

The IDE Submission:

The completed IDE submission to the FDA and the IRB Application should be initiated at the same time. However, because the IDE application process is more complicated than the IND process, inexperienced Investigators may wish to allow extra time to complete the paperwork for the FDA and complete this before preparing the IRB Application. The FDA has 30 days to review the completed IDE application. An Investigator cannot initiate a clinical study until the FDA and IRB have granted approval.

26.4 RESPONSIBILITIES OF INVESTIGATORS AND SPONSORS

While conducting significant risk and non-significant risk device studies, [Investigators and sponsors have many specific responsibilities](#) [24]. The obligations span a broad range, including FDA and IRB approvals, informed consent, study monitoring, and multiple reporting requirements. See the [FDA website](#) [24] for more info.

Control of investigational devices:

Investigators conducting studies in which an investigational device will be used must ensure adequate control of the device. Adequate control and handling of investigational devices include all of the following:

- The Investigator must ensure that the investigational device is used only in accordance with the IRB-approved protocol, the signed agreement, the investigational plan and applicable FDA regulations.
- The Investigator must administer the investigational device only to participants under the Investigator's direct personal supervision or under the supervision of a sub-Investigator directly responsible to the Investigator.
- The Investigator must not supply the investigational device to any person not authorized to receive it.
- The investigation must maintain the following accurate, complete, and current records relating to the Investigator's participation in an investigation.
 - Records of receipt, use or disposition of a device that relate to a) The type and quantity of the device, the dates of its receipt, and the batch number or code mark; b) the names of all persons who received, used, or disposed of each device; c) why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.
- If the investigation is terminated, suspended, discontinued, or completed, the Investigator must return any unused supplies of the investigational device to the study sponsor, or otherwise provide for disposition of the unused supplies as directed by the sponsor.

Here is a sample [Investigational Device Accountability Log](#) [25] you can use.

Import/export of investigational devices:

A complete overview of [medical device import/export regulations](#) [26] is provided by the CDRH. Clinical Investigators should be aware that FDA does not recognize regulatory approvals from other countries; therefore, an imported medical device must meet all FDA requirements. The IDE sponsor must be located in the United States. Anyone who intends to import an investigational device takes on the responsibilities of a sponsor.

Definitions and Resources:

Types of marketing applications:

[Premarket Notification \(510\(k\)\)](#) applies to Class I, Class II, and some Class III devices.

- A sponsor must demonstrate "substantial equivalence," meaning that a new device is as safe and effective as the predicate device(s).
- Guidelines describing [streamlined 510\(k\) options](#) [27] are available.
- Clinical studies using 510(k) devices may be subject to IDE regulations. Prior FDA and IRB approval are required.

[Premarket Approval \(PMA\)](#) [28] has more stringent requirements for high-risk Class II devices. In most cases an IDE is required to clinically evaluate devices subject to PMA regulations.

[Humanitarian Device Exemption \(HDE\)](#) [29] as discussed above, is aimed at encouraging device development for conditions with no more than 8000 patients.

[Device classification](#) is the level of regulatory controls placed on a medical device is determined by the risk classification. Most of the clinical studies at UCSF requiring IDEs from the FDA are significant risk, Class III devices.

The FDA provides an overview of the risk-based classification scheme. To help determine device classification, regulatory controls, and exemptions, the Center for Devices and Radiological Health (CDRH) maintains:

- A [searchable classification database](#) [30] containing information about all approved Class I, Class II, and Class III devices.
- A device listing categorized by [medical specialty](#) [31].
- A Listing of Class I and Class II devices deemed [exempt](#) [32] from Prepared Notification (510(k) regulations.
- Guidance for devices that [emit radiation](#) [33].

27.0 MOBILE APPS OR MOBILE MEDICAL APPS

The IRB recognizes that mobile apps may be valuable research tools and methodologies, yet their use presents special challenges to ensure that the research is conducted both legally and ethically.

The purpose for the guidance on the use of mobile apps or mobile medical apps is to provide researchers, HRPP staff, and IRB committee members with a common understanding of the following:

- Definition of mobile apps and mobile medical apps
- Regulatory requirements pertaining to mobile apps and mobile medical apps
- Points to consider when utilizing mobile apps or mobile medical apps in research

What are Mobile Apps and Mobile Medical Apps?

[Mobile Apps](#) are software applications downloaded to a mobile device, such as a cell phone or tablet, which provide the mobile device user with software that can be utilized on their mobile device in many different ways. For example, web browsing, social media connections, ridesharing applications, and many more. Many of these mobile apps also collect information about the user via the user's device.

[Mobile Medical Apps](#) as defined by the FDA, are medical devices that are mobile apps (see definition above), and also meet the definition of a medical device and are an accessory to a regulated medical device or transform a mobile platform into a regulated medical device.

For example, mobile apps that alter the function or settings of an infusion pump, such as turning the pump on or off; mobile apps that use a microphone or speaker within a mobile platform to serve as an audiometer to allow healthcare providers to determine hearing loss at different frequencies; mobile apps that use an attachment to the mobile platform to measure blood glucose levels; etc.

What are the Regulatory Requirements pertaining to Mobile Apps and Mobile Medical Apps?

[Mobile Apps](#):

There are no research-related regulatory requirements for mobile apps, in general, except for ensuring that the utilization of mobile apps adheres to the 45 CFR 46.111 criteria for IRB approval. However, many mobile apps have Terms of Service, User Agreements, etc. that researchers need to be aware of when utilizing mobile apps in a research study. Although not regulatory, ethical considerations, such as those described in [The Belmont Report](#), also need to be considered.

[Mobile Medical Apps](#):

Some mobile medical apps are subject to FDA regulations. The FDA is taking an approach that focuses on a small subset of mobile apps that meet the regulatory definition of "[device](#)" and are intended to be used as an accessory

to a regulated medical device, or transform a mobile platform into a regulated medical device. The FDA will apply the same risk-based approach the agency uses to assure safety and effectiveness for other medical devices. For more information about these types of apps, please see the [FDA's website](#).

There are many mobile apps that meet the regulatory definition of a medical device but pose minimal risk to patients and consumers; therefore, the FDA will exercise enforcement discretions and will not expect manufacturers to submit premarket review applications or to register and list their apps with the FDA.

For example, mobile apps that help patients/users self-manage their disease or condition without providing specific treatment suggestions; mobile apps that provide patients with simple tools to organize and track their health information; mobile apps that provide easy access to information related to health conditions or treatments; mobile apps that help patients document, show or communicate potential medical conditions to health care providers; mobile apps that automate simple tasks for health care providers; or mobile apps that enable patients or providers to interact with Personal Health Records (PHR) or Electronic Health Record (EHR) systems. For more information about these types of apps, please see the [FDA's website](#).

Points to consider and address in your IRB application (protocol) when utilizing Mobile Apps or Mobile Medical Apps in research:

Purpose of the app:

- What is the purpose of the app and how is it being utilized in the research?
 - To determine validity of the app to do something?
 - To collect information from participants and store it, such as through surveying?
 - To engage participants in activities, such as to send reminders, motivational messages, etc.?
- Is the app appropriate for the study population (e.g., content, age appropriateness, font size/color)?
 - If minors are involved, is the content appropriate for the age group?

App functionality:

- What is your plan to address issues related to the app not working?
- Will downloading or using the app cost the participant anything?
- Will the app only work on certain devices (e.g., iOS, Android)?
- Will participants use their own devices, or will the study provide them to participants?
 - If they use study devices, what are the requirements for returning the devices and are there consequences for not returning them?
- When a device's operating system is updated, how will the app's functionality be impacted?
- When the study is over or when a participant withdraws, how will you ensure the removal of the app from the participants' phones?

Participant/User support:

- How are participants being trained to use the app?
- How will participants get support if they need help with the app?
- How is the app being monitored to ensure it is working properly? How often and when?

Obtaining consent and the app's Terms of Service:

- How are you obtaining consent?
 - Written consent? Consent via the app?
 - If consenting via the app, what are the limitations to consenting using the app versus the standard written consent?
 - Waiver of Written Documentation of Consent? Waiver of Informed Consent?
- The app's Terms of Service will need to be uploaded in your IRB application.
- Is the consent form in-line with the Terms of Service for the app, if applicable?
 - Do the Terms of Service indicate data ownership?
 - Does the owner of the app own the data?
 - Does the researcher own the data?
 - Does the user own the data?
- How are the Terms of Service being explained to participants?
- Are the Terms of Service compliant with research regulations, local/state/federal law, etc.?
- What is your plan for monitoring the Terms of Service for updates or changes?

Privacy and confidentiality protections:

- What data will be collected?
 - Research data? Other data captured from the device the app is installed on?
- Will the data being captured be identifiable?
- How are you obtaining the data? Data sent from the app or device via the internet, or will it be a manual export of data?
- Where is the data being stored and how?
 - Is encryption utilized?
 - Are university devices, firewalls, etc. utilized?
- If the app is a commercial app, will the app have access to the research data?
- Do the apps require usernames and passwords?
 - Are they generated by the user or by the researcher?
 - What if a participant forgets their username and/or password?

Risks related to app use:

- What are the privacy and confidentiality risks?
- What if the app does not work as intended or malfunctions? Whom will participants contact?
- Who is monitoring the app for potential risks and how often (e.g., questions or functionality within the app that monitors for emotional distress, such as suicidality)?
- What about risks to third parties (e.g., social media engagement app that encourages communication between participants in the study and non-participants)?

Resources:

United States Food and Drug Administration (FDA) - [Mobile Medical Applications](#)

Federal Trade Commission (FTC) - [Understanding Mobile Apps](#)

28.0 DECEPTION IN RESEARCH

Studies may use deception if it is necessary to answer the research question.

Disclosure of Research Hypothesis:

If, in order to counter the demand effect, researchers cannot disclose their research hypotheses, the failure to disclose is not considered deception.

General statements about the purpose of the research, as well as a full description of the research tasks and activities, should be provided in the consent form.

Inappropriate Use of Deception:

The IRB discourages the use of deception when:

- Alternative methods can be used that will yield valid study results.
- The deception deprives participants of the opportunity to protect their own interests.
- The missing information affects the participants' ability to assess the risks of participation.

Justification for Using Deception:

If the subjects will be deceived, the ethical and regulatory requirement to fully inform subjects must be waived by the IRB.

There are three criteria that must be met in order for the waiver to be approved. In addition, it is usually necessary to debrief subject after the research.

- The risk must be no more than minimal.
 - *“Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”*
- The rights and welfare of the subjects will not be adversely affected.
- The research could not practicably be carried out without the waiver. This does not mean that it would be inconvenient to conduct the study without the waiver. It means that deception is necessary to accomplish the goals of the research.

Ameliorating Deception:

Protocols must include procedures for ameliorating possible negative effects of deception. In addition to thorough debriefing that explains the need for deception, emphasis should be placed on correcting any false feedback given to participants about their performance, competency, or other personal characteristics.

Participants whose behavior was recorded without their knowledge, such as during a fake “break” in study, should be given the opportunity to request that the recording be destroyed.

If a study was designed to provoke negative behaviors, participants should be told that most people react the way they reacted and that their behavior was a normal response.

Debriefing:

Debriefing for participants who were deceived includes a description of the deception and an explanation about why it was necessary. The discussion should be presented in lay language and should be sufficiently detailed those participants will understand how and why they were deceived. If the study included multiple deceptions, each should be addressed.

If participants were filmed without their knowledge, they must be given the option to ask that the researchers do not use the film.

Delayed Debriefing:

Delayed debriefing is an option if participants are part of a group that may share information about their experience in the research.

If researchers will use a delayed debriefing, the consent form must state additional information will be available at the study and participants' contact information should be collected. The contact information should not be linked to the study data.

Informed Consent:

Informed consent forms and scripts may never contain deception. Researchers may not make false statements during the consent process.

Review Type for Protocols Involving Deception:

Research involving deception cannot be screened for exemption.

Generally, research using the following deceptions may be reviewed using expedited procedures:

- Confederates: Attributing statements to or providing feedback from non-existent individuals or confederates in another room. Using actors in videos presented to participants.
- Giving people impersonal false information: Information about the performance of groups that participants will use to measure their own performance, *for example, "Most medical students can answer these questions in 3-7 minutes."*
- Priming designed to focus participants' attention or awareness, but not on a sensitive topic.
 - *For example, having participants complete sentence scramble tasks with words affiliated with different goals.*
- Presenting false scientific "facts," articles, or profiles of individuals or companies.
- Studies that activate stereotype threat.
- Experiments in which participants are told that two studies are unrelated when the first study is the manipulation, depending upon population and nature of manipulation.

Generally, research using the following deceptions will be reviewed by the full IRB:

- Any use of confederates in which the confederate engages in in-person dialog with a participant.
 - *For example, attempting to persuade a participant to make a certain decision or enter into a negotiation process.*
- Studies in which participants are given false feedback about their own attributes, performance or abilities, *for example, a manipulation in which medical students are told that their performance falls in the lowest quartile of UMKC students following the completion of a task.*
- Any study in which debriefing cannot be undertaken because to do so would cause more harm than good or when participants cannot be contacted, e.g., some types of Internet research.
- Any study involving subliminal priming.
- Covert observation and/or videotaping.
- Mood manipulations designed to induce feelings of guilt, sadness, depression.

- Any study in which participants are given false information about themselves in phase one of a study that is not corrected until a later session.
- Any deception of minors.
- Any study in which the researcher assumes a false identity.
- Manipulations designed to elicit behaviors about which participants' may feel shame or other strong negative emotions.

29.0 CLOSURE AND FINAL REPORT

Investigators have the responsibility to formally close a study with current IRB approval once it is completed or discontinued. Notification must be sent to the HRPP office by completing the Closure checklist. Any previously unreported adverse events unanticipated problems, or protocol deviations should be reported at the time of the closure. If the project was discontinued by the Investigators, include an explanation of why the project was discontinued and statement of results, if any. Once a protocol is permanently closed all research activities must cease, including data analysis (unless the data is de-identified). If the Investigator wishes to continue data analysis with identifiable data, a continuing review should be submitted. A protocol that has been closed cannot be reopened. To resume research activities a new protocol must be approved by the IRB.

When all research-related interventions or interactions with human subjects have been completed, and all data collection and/or utilization/analysis of identifiable private information, for any purpose, have been concluded, then the research may be considered as completed and the application may be closed. The Principal Investigator should not close an IRB application as long as the Investigator is utilizing individually identifiable private information collected as part of the research.

The closure of an IRB application can be managed in one of the following ways:

- The Principal Investigator may allow the IRB approval to expire.
- The Principal Investigator may elect to submit a final report via the electronic system, such as when obligated under a specific regulatory (i.e., FDA) or sponsor requirement.

(Note: If after an IRB application is closed, the Investigator seeks to engage in an activity such that the criteria for closure listed below would no longer be met, the Principal Investigator must submit a new application for IRB review and approval for the use of the previously collected data.)

Criteria for Closure:

The Principal Investigator may allow the IRB approval to expire or may submit a final report when:

- The research was *NOT* conducted or was canceled

OR

- **ALL** of the following conditions are met:
 - All human subjects have been accrued and IRB approved research-related activities, interventions or interactions with human subjects have been completed.
 - All collection, use, and analysis of individually identifiable private information has been completed. No further collection of data/information from or about the individuals will be obtained;
 - The study sponsor (IND/IDE-holder, funding entity, etc., as applicable) agrees to or recommends closure; and

- All publications and presentations derived from

Investigator Responsibilities:

- Continue to maintain confidentiality protections of the data.
 - Destroy all subject identifiers connected with the research data, if the study was approved with a HIPAA Authorization Waiver and the Investigator indicated in the IRB application that all subject identifiers would be destroyed upon completion of the research.
 - Retain research records in accordance with Saint Luke’s Health System Policy.
 - Understand the specific regulatory and/or sponsor requirements, which may obligate him/her to submit a final report to the IRB.
 - Ensure that all research-related activities, interventions or interactions with human subjects have been completed at the site(s) approved under the Principal Investigator’s IRB application at the time a final report is submitted to the IRB or at the time of approval expiration, whichever occurs first.
 - If electing to submit a final report, submit the report through the IRB system prior to the expiration of IRB approval.
 - When a Principal Investigator terminates employment or other associations with SLHS(or another organization(s) relying on the SLHS IRB, he or she is obligated to either:
 - Submit for IRB review and approval a modification requesting transfer of the study to another eligible Principal Investigator
- OR**
- Submit a final report to the IRB.

IRB Responsibilities:

- Review any new information provided in the final report and determine whether any additional action is required on the part of the IRB or the Investigator.
- Upon receipt and review of a final report, ensure the status of the IRB application is “complete”.

30.0 VULNERABLE POPULATIONS

The IRB recognizes that additional safeguards need to be included for other categories of participants who are likely to be vulnerable to coercion or undue influence such as house staff/students, persons who do not speak English, illiterate persons, and other classes of potential participants. The following information will assist Investigators in addressing these issues within their context of the research.

Non-English Speaking Participants:

Research *actively* recruiting participants who are Non-English speakers:

An Investigator who intends to include non-English speaking individuals must provide sufficient detail in the research protocol regarding the plan for inclusion, including the plan for obtaining informed consent and HIPAA Authorization and any other additional provisions during the study.

If an Investigator intends to enroll participants who speak a language other than English, a translated version of the informed consent form and HIPAA authorization must be submitted to the IRB for approval prior to use. The principal Investigator must provide the qualifications of the individual or the service that was used to translate the

informed consent documents. The principal Investigator may wish to delay translating the consent documents until the IRB has granted approval for the English version to avoid extra translation costs.

Participants who do not speak English must be given an informed consent document written in a language understandable to them. A person who is fluent in both English and the participant's language must participate in the informed consent process. If the person authorized to obtain informed consent in the research protocol is not fluent in the participant's language, an interpreter or interpreter service may be obtained.

(Note: family members and friends of the potential participant may not act as the sole translation/interpretation source for enrollment and participation in a research protocol as they are not familiar with medical terminology; they may withhold information during the translation process or may change the meaning of what is said by the potential participant or research staff.)

Research **NOT actively** recruiting participants who are Non-English Speakers:

Many protocols include the provision to include individuals who do not speak English as they are often a part of the general participant population; however, they are not the targeted population. As non-English speaking individuals are not the targeted population, often informed consent and HIPAA Authorization documents are not yet translated into other languages as the needed language is not yet known. For participants who may be eligible to be enrolled in a research protocol where there may not be sufficient time to obtain a fully translated version of the written consent form and HIPAA Authorization in the participant's native language, a "short-form" informed consent may be approved for use by the IRB. A "short form" consent form is a document that contains a brief paragraph that affirms all the elements of informed consent (As required by the Federal Regulations) were reviewed with the participant in a language understandable to the participant. The "short form" must be in the participant's native language. Multiple versions of the "short form" consent are available and can be found on the IRB Administration Office website.

(Note: The short form can only be used once per language per protocol.)

Other study related documents that will be filled out by the participant (e.g., log sheets, data collection forms, self-assessment tools, etc.) must also be translated into the participant's native language. If the study involves more than one study visit, a plan must be developed to ensure that an appropriate party is available to conduct all study visits in the participant's native language.

(IMPORTANT NOTE: If the participant will spend the night in the hospital, there should be an appropriate round-the-clock plan for the duration of the planned hospitalization. The plan should take into account the risk level of the research protocol, and also the ability to plan in advance. For example, a participant in a Phase I clinical trial will need to have a very strong plan to report side effects that may not be anticipated, but the visits can probably be planned well in advance.)

Prior to the release of any information to non-SLHS personnel, the HIPAA Authorization must be translated and signed by the participant prior to the release of any information. In addition, when the short form is used, a fully translated (and IRB approved) consent document must be given to the participant as an information sheet.

Additional Guidance Regarding the Process and Documentation:

When informed consent is obtained from non-English speaking participants using a translated consent form (traditional long consent form) all the following must be done:

- The translated consent document must be approved by the IRB and be provided to participants in language understandable to them.

- A translator who is fluent in both English and the language of the participant must be present if the person obtaining consent does not speak the language of the participant.
- The consent document must be signed and dated by the participant or the participant's legally authorized representative (unless the IRB has waived written consent).
- The consent document must be signed and dated by the person obtaining consent and, if the person obtaining consent does not speak the participant's language, by the translator.
- The process must be documented via a narrative or checklist to describe how the process occurred and who was involved.

When informed consent is obtained from non-English speaking participants using a translated short consent form all the following must be done:

- A written summary (English consent form) of the oral informed consent process (information to be stated to the subject or the subject's legally authorized representative) must be approved by the IRB.
- A translator who is fluent in both English and the language of the participant must be present if the person obtaining consent does not speak the language of the participant.
- When the person obtaining consent is assisted by a translator, the translator may serve as the witness and the witness should be fluent in both English and the language of the subject.
- The translated short form must be signed and dated by the participant or the participant's legally authorized representative (unless the IRB has waived written consent).
- The translated short form and written summary of the informed consent process must be signed and dated by the translator.
- The person obtaining consent shall sign a copy of the written summary.
- A copy of the written summary and translated short form must be given to the participant or their representative.
- The informed consent process must be documented via a narrative or checklist to describe how the consent process occurred, and who was involved.

Students and Employees:

Justification of the intention to enroll SLHS employees, house staff, or students must be provided in the protocol. The actions to prevent coercion or undue influence must also be detailed in the protocol. Anyone with an employment or academic relationship to SLHS must be informed that their participation in a study, or refusal to do so, will in no way influence their grades, employment, or subsequent recommendations. Employees must never be made to feel that their job, promotion, salary, or status in any way depends on participation in research studies.

The involvement of students, house staff or employees in studies also requires a statement in the consent form acknowledging that refusal to participate will have no influence on grades, recommendations or job status.

The Principal Investigator or any co-Investigator may not be responsible for directly recruiting and/or obtaining informed consent from any person under his or her direct supervision. Direct recruitment of students and employees may be undertaken using IRB approved recruitment text via standard recruitment methods (e.g., IRB approved text in recruitment flyers placed in staff/student mailboxes). Verbal recruitment is not an acceptable method of recruitment.

A Principal Investigator may not enroll his or herself into his or her own research protocol unless provisions are made in the research protocol to allow for the enrollment. In these cases, the IRB may allow the inclusion if the study outcomes are objectively measured and provisions are there with respect to recruitment, consent, and affirmation of eligibility (e.g., by a study co-Investigator).

Research protocols that do not directly recruit SLHS employees, house staff or students (e.g., a clinical trial enrolling general population patient with arthritis) and whereby the Investigators would not have any knowledge of the person's affiliation with SLHS (e.g., the participant is not requested to disclose this information during the course of the research) do not need to include provisions in the protocol or consent form to address enrollment of this population.

Principal Investigator's Clinical Patient Population:

Many research protocols may involve recruitment from one's own clinical pool of patients. To avoid any potential for undue influence that may result from the doctor patient relationship, the informed consent process should not be conducted solely by the physician who has a clinical relationship to the patient that will be enrolled. (e.g., research study coordinator). An additional person should be available to confirm eligibility (e.g., co-Investigator) and cosign the checklist. If possible, someone who does not have a clinical relationship to the potential participant should act as the "person obtaining informed consent".

Family members of the study team:

A Principal Investigator or any other member of the study team may not recruit and enroll any direct familial relation. Provisions must be made in the IRB approved protocol to allow for study personnel with appropriate expertise to recruit and enroll another study team member's direct familial relation.

Illiterate/Impaired Participants:

The IRB allows for illiterate persons who understand English and individuals who are seeing-impaired to participate in research studies. In these situations, the consent document must be read to the participant and the process documented in the research file. For an illiterate participant, the consent document should be subsequently signed by the participant "making their mark" on the signature section of the consent document, in order to document their understanding. The IRB also requires an impartial third party to serve as

the witness to be present during the entire consent process. Both the witness and the person obtaining informed consent must sign and date the consent document. As such, there must be an additional signature line and date for the witness on the consent document.

Participants who are Mentally Capable of Consenting but are physically unable to sign the document:

The IRB allows participants that are mentally capable of consenting to research studies but are physically unable to sign the consent document to participate in research as long as a witness is present. The witness must verify that the informed consent process has taken place and sign and date the consent document. In addition, if participants are capable of doing so, they must place a mark or cross on the signature line of the consent document, to confirm their participation in the research study. This process must be documented in the research file. If the reason that prevented signing the consent form resolves, the participant should be asked to sign and date the consent form. Protocols actively enrolling individual participants who are physically unable to sign the consent document should include a witness line on the consent document.

Other Vulnerable Adult Populations:

The IRB recognizes that the ability of adult populations to give voluntary informed consent may be compromised by circumstances. Such circumstances can include economical disadvantages, educational disadvantages, and physical handicap. The IRB will review the potential risks and benefits of each proposed study on a case-by-case

basis to assure rights and welfare are protected, coercion is minimized, and the study is conducted with the utmost regards for ethical standards.

31.0 PREGANT WOMEN, HUMAN FETUSES AND NEONATES

The IRB recognizes the additional protections required under Federal law for pregnant women, human fetuses and neonates who participate in research ([45 CFR 46, Subpart B](#)).

A research protocol is considered to include pregnant women, human fetuses, and/or neonates when:

- Any of the above are the target population that will be recruited;
- OR**
- Pregnancy occurs during the course of a research study and information about the pregnancy, fetus and/or neonate will be obtained as part of the research study.

31.1 PREGNANT WOMEN AND FETUSES

In order to approve the inclusion of pregnant women in a research protocol, the following conditions listed in [45 CFR 46.204, Subpart B](#) must be met:

- Where scientifically appropriate, preclinical studies, including studies on pregnant animals and clinical studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.
- The risk to the fetus: is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.
- Any risk is the least possible for achieving the objectives of the research.
- The research must either: holds out the prospect of direct benefit to the pregnant woman, or the fetus; or both; or no greater than minimal risk to the pregnant woman or fetus, and have, as its purpose the development of important biomedical knowledge that cannot be obtained by any other means.

The pregnant woman's informed consent must be obtained in accord with the informed consent provisions of [45 CFR 46 Subpart A](#).

- If the research holds out the prospect of direct benefit solely to the fetus, then the consent of the pregnant woman and the father must be obtained in accord with the informed provisions of [45 CFR 46 Subpart A](#), except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
- Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.
- For children who are pregnant, assent must be obtained from the pregnant child and consent from her parent or legal guardian.
- No inducement, monetary or otherwise, will be offered to terminate a pregnancy.
- Individuals engaged in the research will have no part in determining the viability of the neonate.

The research protocol must address how these conditions are met and provide sufficient justification for inclusion of pregnant women.

31.2 NEONATES

The IRB may approve research that involves the following categories of neonates: neonates of uncertain viability, non-viable neonates, and viable neonates, if all of the following are met ([45 CFR 46.205, Subpart B](#)), as well as additional criteria listed for each special population below:

- Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing the potential risk to neonates.
- Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
- Individuals engaged in the research will have no part in determining the viability of a neonate.

Neonates of uncertain viability:

A neonate whose viability has not yet been ascertained may only be involved in research if all of the following additional conditions are met:

- The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective; or
- The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means, and there will be no added risk to the neonate resulting from the research; and
- The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of the unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

Nonviable neonate:

After delivery, a neonate that is living but is not considered viable may be involved in research if all of the following additional conditions are met:

- Vital functions of the neonate will not be artificially maintained.
- The research will not terminate the heartbeat or respiration of the neonate.
- There will be no added risk to the neonate resulting from the research.
- The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means.
- The legally effective informed consent of both parents of the neonate must be obtained. If either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements.

Viable neonates:

A neonate determined to be able to survive to the point of independently maintaining heartbeat and respiration ("viable") upon delivery may be included in research to the extent permitted by and in accordance with OHRP (including Subpart D) and FDA requirements.

Research use of dried blood spots obtained through newborn screening programs:

Any use of newborn dried blood spots collected clinically for Federally-funded research is considered “human subject research” regardless of whether the specimens are identifiable. This means that the research project must receive IRB review (expedited or full board) and approval prior to initiation. In addition, parental permission to use the dried blood clinical screening sample for research purposes must be obtained for Federally-funded research. Federal law no longer permits waiver of informed consent (parental permission) in these situations.

Research activities involving the use of newborn dried blood spots that are not Federally-funded are not subject to this requirement. These projects may be submitted to the IRB prior to initiation and reviewed under the current OHRP human subject protection regulatory framework. These non-Federally funded research projects may qualify as “non-human research” (NHR) or exempt research or may require expedited or full Board review and approval. In addition, the IRB has the ability to waive or alter the requirements for parental permission pertaining to the non-federally funded research use of the dried newborn blood spots for the specific project.

31.3 INCLUSION OF PREGNANT PARTICIPANTS AND PARTNERS

Inclusion of Participant who becomes Pregnant after Enrollment in the Study:

If a research protocol intends to allow participants who become pregnant during the course of the research study and/or collect pregnancy follow-up and outcome information from the participant who has become pregnant, the provisions as they pertain to the protection of pregnant women as outlined under OHRP and FDA regulations, including 45 CFR 46 Subpart B, are applicable and criteria for inclusion must be met. The protocol and consent form must address the following:

- Whether research procedures will be continued;
- If research procedures will be discontinued, how this will be done to ensure participant safety;
- What clinical information will be collected about the pregnant women and how long will the information be collected;
- What clinical information will be collected about the fetus/newborn and how long the information will be collected?

If the IRB did not previously make a determination regarding the inclusion of pregnant women in the currently approved research protocol, then an amendment to allow the inclusion must be reviewed and approved prior to inclusion.

When the Pregnant Subject is an Adult:

If a research protocol proposes to collect information from the pregnant partner of a research subject, the pregnant partner becomes a “research subject” and the provisions as they pertain to the protection of pregnant women as outlined under OHRP and FDA regulations, including 45 CFR 46 Subpart B, are applicable. This includes obtaining informed consent from the pregnant partner for participation. See section C. Inclusion of Participant Who Becomes Pregnant after Enrollment in the Study.

When the Pregnant Subject is a Minor:

In addition to the regulations outlined by OHRP and FDA, including 45 CFR 46 Subpart B, if the pregnant subject is also a minor, there are additional considerations that must be accounted for under 45 CFR 46 Subpart D, Additional Protections for Children Involved as Research Subjects.

According to Missouri statute, a minor may consent to treatment “in case of pregnancy, but excluding abortion; venereal disease, drug and substance abuse. Separate statutes define HIV testing and reporting. Testing information from a minor-requested test may not be released without the minor’s consent if the test result is negative. However, breach of confidentiality does not apply if the healthcare provider decides to inform a parent/legal guardian of positive test results.

This decision is a difficult one and is up to the individual health care professional. When making such decisions, it is important to keep in mind that doctor-patient trust and rapport may be affected by this decision. The decision must be in the best interest of the minor.

When a minor receives medical treatment as allowed for pregnancy, VD or drug and substance abuse, “the parent, parents, or conservator shall not be liable for payment for such care unless the parent, parents, or conservator has expressly agreed to pay for such care. Although an un-emancipated minor patient may not provide legally required consent, the minor should be involved to the extent appropriate given the patient’s age, understanding and treatment contemplated. This is considered assent.

According to Missouri State Law (Chapter 431, Section 431.061, pregnant minors and/or mothers who retain custody of their child (ren) are considered legally capable of providing consent.

Contraceptives and Minors:

Missouri law does not specifically require healthcare professionals to obtain parental consent before a minor receives family planning services or contraceptives, so healthcare professionals can and do provide these services to minor patients without parental consent. Federally funded Title X (ten) family planning clinics must provide confidential services to minors and may not require parental consent for minors to receive the services. For a complete listing of Title X family planning clinics in Missouri.

In an emergency situation, consent to healthcare is implied, even if the minor objects or in the absence of consent of a parent or guardian. An emergency situation is one in which it is imminently necessary to provide medical care, and any delay caused by an attempt to obtain consent would jeopardize the life, health, or limb of the minor patient.

32.0 CHILDREN IN RESEARCH

When children are involved in research, Federal regulations require the permission of the parent(s) or guardian before a child can be enrolled in research. While children may be legally incapable of giving informed consent, they nevertheless may possess the ability to assent, or refuse participation in a research study. Assent is a child's affirmative agreement to participate in research after an explanation of the study in language the child can understand. Failure to object to participation cannot be construed as assent. The following guidelines have been established by the IRB to assist Investigators who conduct research involving children.

Federal regulations require that assent must be sought from children unless the requirement is waived by the IRB or is not required under applicable regulations. Assent must be taken seriously by all Investigators who include children as subjects of research.

Research, including chart reviews that involves children, or the use of protected health information of children must meet the criteria for approval set forth in 45 CFR 46 Subparts A and D, unless the research has been determined to be exempt from IRB review. There are, however, restrictions for approving exempt research involving children.

It is a requirement that the Investigator propose an assent plan as part of a research protocol that includes children as subjects. If the Investigator believes that assent is not appropriate for the child population being studied, appropriate justification must be provided in the protocol. Requests for waivers of assent need to be specifically requested and subsequently approved by the IRB. The Investigator must also describe the additional safeguards in place to protect the rights and welfare of the children.

The IRB must determine that the proposed research meets all the requirements of [45 CFR 46, subpart A](#) including the provisions for obtaining and documenting assent are adequate ([45 CFR 46.408\(a\)\(e\)](#)). The child should be given an explanation of the proposed research procedures in a vocabulary and language that is appropriate to the child's age, experience, maturity, and medical condition. This explanation should include a discussion of any discomforts and inconveniences the child may experience if he or she agrees to participate in the study.

Parent(s) or a guardian is encouraged be present during the process of obtaining assent, but this is not required. Parent(s) or a guardian are encouraged to be present during the research procedures, especially if a young child will be exposed to significant discomfort or if the child will be required to spend time in an unfamiliar place.

The IRB must also determine that adequate provisions are made for soliciting the permission of each child's parent or guardian. When parental permission is to be obtained the regulations require in all cases that both parents provide permission, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. However, for certain categories of research (research involving minimal risk or greater than minimal risk with the prospect of direct benefit ([45 CFR 46.404](#)) or ([45 CFR 46.405, Subpart D](#)), the IRB may, when appropriate, determine that the permission of one parent is sufficient, even when the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.

When approving research involving children, the meeting minutes must document the determinations required by the regulations to approve the research along with protocol specific findings to justify each of the regulatory determinations in accordance with [45 CFR 46.404, 405 or 406 and 407](#) and [21 CFR 50, 51, 52, and 54](#) as applicable. The minutes must also document the assent process, including whether assent is required or a waiver of assent has been approved, in accordance with, as applicable, [45 CFR 46.408](#) and [21 CFR 50.55](#) and [45 CFR 46.116 Subpart A](#).

When the IRB approves research involving children in accordance with [45 CFR 46.407](#), the following requirements must be met and are irrespective of the funding of the research. The SLHS IRB follows the OHRP guidance for situations when research meets the fourth category of pediatric research.

- Assent of child and permission of both parents
- IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children
- The DHHS Secretary or the FDA Commissioner approves, after consultation with a panel of experts in pertinent disciplines (i.e., science, medicine, education, ethics, law) and following public comment

The IRB will submit the protocol and supporting documents to OHRP for DHHS consideration under the provisions of [45 CFR 46.407\(b\)](#). When the proposed research is being conducted or supported by DHHS, the DHHS will consult with a panel of experts.

If a study lasts for multiple years, assent may need to be re-assessed as the child's cognitive ability matures. Also, if a child enters a study at an age where assent is not required, but during the study the child attains the assent age where assent is required, assent must be obtained for the child to continue in the study.

32.1 ASSENT GUIDELINES

Age Guidelines for Assent:

The following guidelines, based on the child's age, are often followed by the IRB in determining assent requirements. Because of the many variables involved in research with children (age, maturity, cognitive ability, degree of study benefit to the child, health of the child, etc.), the guidelines listed below may not be applicable to a specific study and the Investigator may propose and justify a different plan. This may include more than one of the applicable categories listed below based on the Investigator's determination in specific cases (e.g., studies involving children of differing ages; and maturity of all children). The plan must be fully described in the protocol/research plan and be approved by the IRB prior to implementation. Also, the IRB has the option to require a different approach.

6 Years of Age or Younger, Verbal or Written Assent is Usually Not Required:

Consent is based on the permission of the parent or guardian, and no assent is required. A brief verbal explanation of the research procedures should be provided to the child. A verbal script is an option for explaining the research to the child and can be submitted to the IRB for review.

Between The Ages of 7 to 13, a separate Assent Form is Required:

In addition to the parents' consent form, a separate assent form is required for the child. It should be in language appropriate for children 7-13 years of age. The assent form should outline what is involved for the child and emphasize the voluntary nature of the study. Depending on the research study, it will usually be one to two pages in length. All assents must at a minimum involve communication of the information in the assent form to the child and obtaining the child's verbal agreement

to participate in the study. The plan to obtain and document the assent process must be fully described and justified in the protocol/research plan. The IRB will make the final determination of the assent process.

14 to 17 Years of Age, a Consent or Assent Form May Be Used:

Children 14 to 17 years old may give assent after the information in the assent form has been communicated to them; and the child's verbal agreement to participate in the study has been provided. The IRB may determine that the child sign the Informed Consent document that has been signed by the parent(s) or guardian. A separate assent form may also be provided to the child if the Investigator believes it would better describe the information provided to the child about the nature of the study. This would most likely apply to 14 or 15 year old subjects in very complex studies, or children with mild cognitive impairment. The plan to obtain and document the assent process must be fully described and justified in the protocol/research plan. The IRB will make the final determination of the assent process.

Verbal Assent:

To obtain verbal assent the Investigator must communicate the information in the approved assent form to the child. If the IRB determines that the communication of the assent process must be documented in writing, this can be achieved either by the child (preferred) or Investigator signing the paragraph below.

Sample wording that can be used is as follows:

I have discussed this clinical research study with the child, using language which is understandable and appropriate. I believe I have fully informed this subject of the nature of the study and its possible risks and benefits. I believe the subject understood this explanation and assented to participate in this study.

Request for Waiver of Assent:

There are circumstances in which the IRB may determine that assent is not a requirement for children to be enrolled in a research protocol. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. The Investigator must specifically justify why obtaining assent is not appropriate, in the protocol/research plan.

Below are the circumstances under which an IRB may determine that assent is not a requirement:

- If the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (*for example, neglected or abused children*), it may waive the consent requirements in [45 CFR 46.116, Subpart A](#) and paragraph (b) of this section, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal, state, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.
- In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate.
- If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary
- Condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with [45 CFR 46.116, Subpart A](#).

A determination that assent is not a requirement for protocols involving greater than minimal risk must be approved at a convened IRB meeting. The IRB's determinations and protocol-specific findings are documented in the IRB minutes. Waiver approvals are listed on the IRB approval letter.

32.2 ALTERATION AND WAIVER OF PARENTAL PERMISSION

Alteration of Parental Permission:

When parental permission is to be obtained the regulations require in all cases that both parents provide permission, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. However, for certain categories of research (research involving minimal risk or greater than minimal risk with the prospect of direct benefit ([45 CFR 46.404 or 405](#))), the IRB may, when appropriate, determine that the permission of one parent is sufficient, even when the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.

Waiver of Parental Permission:

Under the federal regulation [45 CFR 46.408\(c\)](#) for DHHS funded research, if the IRB determines that a research protocol is designed for conditions or for a child subject population in which parental or guardian permission is not a reasonable requirement to protect the child subjects (i.e.; neglected or abused children), the research is not subject to FDA regulations, and the waiver is not inconsistent with applicable federal, state or local laws, then the IRB may waive the consent requirements. However, the Investigator must provide an appropriate mechanism for protecting the children who will participate as subjects in the research as a substitute.

Under the FDA regulations ([21 CFR 50.55](#)) the FDA do not permit such a waiver of parental permission.

Other Circumstances:

Emancipated Minors:

Missouri Statue provides that persons under the legal age of consent achieve emancipation by court order, marriage or serving with the armed forces or National Guard of the United States. Documentation of emancipation by court order is required before a minor may be recognized as an emancipated minor in the research context.

Pregnant Minors:

In Missouri, parenthood does not emancipate a minor (although it does in some other states). Consent for treatment procedures on a child of an unwed minor must be obtained from the parent or guardian of the unwed parent.

When pregnancy testing is done for research purposes (e.g., to determine eligibility), parents are told the test results. Therefore, the SLHS IRB requires that both the study protocol and the document used to obtain informed consent/assent for research state clearly that results of a positive pregnancy test for a minor will be reported to the parents of the minor.

Parent Conflict of Interest:

Parental permission may sometimes be insufficient to proceed with the research. In cases involving transplants (e.g., of bone marrow or a kidney) between siblings the parents' concern for the afflicted child may interfere with their consideration of the best interests of the healthy donor. Therefore, the IRB may consider asking for additional protections for the healthy donor, such as the presence of an independent physician or a court appointed guardian, if applicable, to represent the healthy donor.

Waiver of Assent for Experimental therapies for Life-threatening Diseases:

When research involves the provision of experimental therapies for life-threatening diseases such as cancer, Investigators should be sensitive to the fact that parents may wish to try anything, even when the likelihood of success is marginal, and the probability of extreme discomfort is high. Should the child not wish to undertake such experimental therapy, difficult decisions may have to be made by the parents in conjunction with the Investigator, child's physician, and the child? If the child is a mature adolescent, waiver of assent is usually not appropriate.

Child Abuse or Neglect:

In research on child abuse or neglect, there may be serious doubt as to whether the parents' interests adequately reflect the child's interests. In these cases, there must be alternative procedures for protecting the rights and interests of the child asked to participate, including, perhaps, the court appointment of special guardians. The choice of an appropriate mechanism would depend upon the

nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

If Investigators are planning to enroll children who are Wards of the State:

The IRB must be informed as additional requirements apply. Children who are wards may be included in research involving greater than minimal risk without the prospect of direct benefit but likely to yield generalizable knowledge about the child's disorder or condition if the research is either:

- Related to their status as wards,
- OR**
- Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as participants are not wards.

In such cases, an advocate must be appointed for each child who is a ward to protect the child, to the extent possible, from exploitation, coercion, or undue influence. The following requirements apply to individuals serving as advocates:

- The advocate will serve in addition to any other individual acting on behalf of the child as a guardian or in place of the parents.
- An individual may serve as an advocate for more than one child.
- The advocate must be an individual who has the background/experience and agrees to act in the best interests of the child throughout the child's participation in the research. This includes:
 - Helping to ensure that the child understands what will be required of him/her during the research, and if capable, that the child provides assent to participate; and
 - Acting in the best interest of the child by evaluating the ongoing effect(s) of the research on the child.
- The advocate must not be associated in any way (except in the role as an advocate or IRB Member) with the research, Investigator(s), or guardian organization.

If the Investigator did not originally intend to involve children who are wards of the state in a study but decides to do so after the study has been approved, he/she must alert the IRB before enrolling the child into the research study. The IRB requires the Investigator to submit an amendment outlining his/her intent to involve a child who is a ward of state. Investigators should never enroll wards of state without prior IRB approval.

Minors in custody of the Missouri Department of Social Services (Wards of the State):

A child in the custody of the Children's Division is considered a minor until age 21 (Missouri State Statute 453.015(1)). Often times, the ward's Family Support Team, which includes the child's parents, parent attorney's if applicable, foster parents, juvenile officer, Children's Division staff, Guardian ad Litem appointed for the child, service providers, and other natural supports, must be included and aware of a specific child's participation in a study. The juvenile court with jurisdiction of the child may be involved as well. After discussion and collaboration, a member of the child's Family Support Team is likely to be the one authorized to provide consent.

Additionally, any research that will involve wards must be approved by the Children's Division, in addition to the SLHS IRB, prior to enrolling any wards. An Application to Conduct Research must be submitted to the Research Committee of the Missouri Department of Social Services, Children's Division prior to enrolling wards of the state. To submit:

- Complete the application available at: <http://dss.mo.gov/cd/info/forms/pdf/886-4454s.pdf>
- Include with your application to the Children’s Division:
 - SLHS IRB approval letter
 - A copy of your IRB approved and stamped Informed Consent Document
 - Children’s Division cover letter
- Send the application via e-mail to CD.ResearchCommittee@dss.mo.gov

Obtain concept approval to enroll Wards of State from the Missouri Children’s Division Research Committee and CD local office approval for each individual Ward of the State to be enrolled in the research study.

Carefully review any conditions of approval provided the Children’s Division. Submit an Amendment if there are updates needed to the SLU IRB Application, consent forms or protocol materials to make them consistent with CD requirements.

(Note: The Board meeting minutes must document that the research is in accordance with [45 CFR 46.409](#) and [21 CFR 50.56](#) and is appropriate for the inclusion of participants who are wards of the state.)

33.0 PRISONERS IN RESEARCH

The inclusion of individuals in a research protocol who are considered “prisoners” involves special ethical considerations and requires meeting additional regulatory requirements to safeguard prisoners’ interests and protect them from harm. Prisoners constitute a research population who are at risk for coercion due to their legal status or confinement. Prisoners may be under constraints because of their incarceration, which could affect the ability to make a truly voluntary decision with respect to participation as subjects in research.

A research protocol is considered to include prisoners when:

- Prisoners are the target population that will be recruited; or
- The subject is a prisoner at the time of enrollment; or
- A currently enrolled subject becomes incarcerated during the course of the trial.

Permitted research involving prisoners includes those studies that aim to examine conditions, practices and antecedents specifically relevant to prisoners, prisons and incarceration.

When a research protocol involves the inclusion of prisoners, the IRB will review the research in accordance with institutional policy, with OHRP and FDA regulations, and with respect to 45 CFR 46 Subpart C (additional protections pertaining to research involving prisoners). Additional rules as determined by Federal, state, county, and local regulations may also apply. If a prisoner is pregnant or a minor, IRB policy regarding these vulnerable populations (45 CFR 46 Subparts B and D respectively) also applies.

Although Federal regulations allow for certain categories of research involving prisoners to be reviewed via expedited review, protocols involving prisoners will be reviewed at a convened IRB meeting, unless otherwise designated for expedited review by the IRB Chair. If a protocol involving prisoners is designated for expedited review, the IRB prisoner representative member will be involved in the review as appropriate.

None of the exemption categories in the HHS regulations for research involving human subjects at 45 CFR 46.101(b) apply to research involving prisoners.

Additional Requirements for New Protocols Recruiting Prisoners as Subjects:

Research Protocol:

In addition to the standard research protocol requirements, a protocol involving prisoners must clearly articulate that it meets all applicable criteria under 45 CFR 46 Subpart C. The protocol must include the following:

- Clarification about how the proposed research represents at least one of the following categories of research permissible for inclusion of prisoners.
- A study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the participants.
- A study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the participants.
- Research on conditions particularly affecting prisoners as a class (e.g., vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary of DHHS (through OHRP) has consulted with appropriate experts including experts in penology, medicine, and ethics and published notice, in the FEDERAL REGISTER, of his intent to approve such research.
- Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary of DHHS (through OHRP) has consulted with appropriate experts including experts in penology, medicine, and ethics and published notice, in the FEDERAL REGISTER, of his intent to approve such research.

Discussion, which makes it clear that the protocol satisfies all additional criteria for research with prisoners as subjects, including:

- The Risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers.
- That any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that [the prisoner's] ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired.
- Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the Principal Investigator provides to the board justification in writing for following some other procedures, control subjects must be selected randomly from the population of available prisoners who meet the characteristics needed for that particular research project.
- Discussion of the process for obtaining informed consent and study procedures to ensure that the information is presented in language that is understandable to the subject population.
- Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole, and
- If there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing prisoners of this fact.

Informed Consent:

The informed consent document as well as any study materials must be presented in a language that is understandable to the subject population. The consent form must also clearly address any risks of participation, the voluntary nature of participation, and state that participation in the research will not have any effect on a prisoner's parole.

In certain limited circumstances, informed consent may be waived or altered by an IRB according to 45 CFR 46.116 and 117. However, even if informed consent is waived or altered, subpart C of 45 CFR part 46 still requires that the subjects be clearly informed in advance that participation in the research will have no effect on their parole if such notification is relevant.

(Note: that prisoners cannot be involved in emergency research where the requirement for informed consent has been waived by the Secretary under the authority of [45 CFR 46.101\(j\)](#) and [45 CFR 46.101\(i\)](#).)

Additional Requirements if a Research Subject becomes a Prisoner:

If a subject becomes a prisoner after enrolling in a research study, the Investigator is responsible for immediately reporting the event in writing to the IRB on an "Unanticipated Problem/Protocol Deviation" form.

(Note: This is not required if the study was previously approved by the IRB for prisoner participation.)

The Investigator should provide detail on the subject and the incarceration, as well as the extent of the subject's participation in the research trial up to becoming a prisoner, what remaining study activities the subject has to complete and the plan for either inclusion or exclusion of the subject from further research activities.

If the study was not previously reviewed and approved by the IRB in accordance with the requirements of 45 CFR 46 Subpart C, all research interactions and interventions with, and obtaining identifiable private information from the prisoner must cease until the requirements of Subpart C are satisfied. This is necessary because it is unlikely that initial IRB review of the research and the informed consent documents contemplated the constraints imposed by the possible future incarceration of the subject. If the Investigators would like the subject to continue in participation in the research protocol, an amendment must be submitted with revisions to the protocol and consent form to detail how continuation of the prisoner meets applicable criteria under 45 CFR 46 Subpart C.

The convened IRB will review the current research protocol in which the subject is enrolled, taking into special consideration the additional ethical and regulatory concerns for a prisoner involved in research.

In special circumstances in which the Investigator asserts that it is in the best interests of the subject to remain in the research study while incarcerated, the subject may continue to participate in the research until the requirements of subpart C are satisfied. The Investigator must promptly notify the IRB of this occurrence, so that the IRB can review the study.

(Note: that in these circumstances, some of the findings required by 45 CFR 46.305(a) may not be applicable; *for example, the finding required under 45 CFR 46.305(a)(4) regarding the selection of subjects within the prison may not be applicable, if the subject was recruited outside of an incarcerated context.* The IRB should document findings of non-applicability accordingly.)

If research interactions and interventions or obtaining identifiable private information will not occur during the incarceration, IRB review and approval under the prisoner rules is not required.

Additional IRB Requirements:

For all new protocols that proposed to recruit prisoners as research subjects, or propose to include individuals who subsequently become incarcerated during the course of an active research trial, the IRB will review the protocols to determine if the inclusion is appropriate in accordance with OHRP 45 CFR 46 Subpart C.

In order to review research involving prisoners, the IRB will note appropriate constitution ([45 CFR 46.304 \(a\) and \(b\)](#)) by affirming the following:

A majority of the IRB (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the IRB.

- a. At least one member of the IRB must be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that, where a particular research project is reviewed by more than one IRB, then only one IRB needs to satisfy this requirement. If a prisoner representative is selected to serve on the IRB, the person must have a close working knowledge, understanding and appreciation of prison conditions from the perspective of a prisoner. Suitable individuals could include present or former prisoners; prison chaplains; prison psychologists, prison social workers, or other prison service providers; persons who have conducted advocacy for the rights of prisoners; or any individuals who are qualified to represent the rights and welfare of prisoners by virtue of appropriate background and experience.

The IRB will meet the special composition requirements for all types of review for the protocol: initial review, continuing review, review of protocol amendments, review of reports of adverse events or unanticipated problems involving risk to participants or others, or in the event an individual becomes a prisoner while participating in a research protocol.

The IRB must also find that the proposed research meets the requirements of 45 CFR 46.305, including that the research represents one of the categories of permissible research under 45 CFR 46.306. OHRP notes that in order to make some of these seven findings and meet the requirements of subpart A of 45 CFR part 46, the IRB must be familiar with the specific conditions in the local prison(s) or jail site(s) that are pertinent to subject protections, before approving the proposal for the local site (45 CFR 46.107(a)).

In order to approve research involving prisoners, the IRB must find that the proposed research falls into one of the permissible categories of research ([45 CFR 46.306](#)), and make six other findings under [45 CFR 46.305](#). The meeting minutes must document the IRB's discussion of these elements and affirm that the research meets the regulatory criteria. Additionally, the minutes must reference that a majority of the IRB (exclusive of prisoner member/representative) has no association with the prison(s) involved and a qualified prisoner representative was present and voted on the protocol.

Prisoner Certification Letter to OHRP:

An institution that intends to conduct research supported by the U.S. Department of Health and Human Services that will involve prisoners as subjects must certify to the Secretary (through OHRP) that the IRB has made the seven findings required under [45 CFR 46.305\(a\)](#), including the finding that the proposed research represents one of the permissible categories of research under [45 CFR 46.306\(a\)\(2\)](#).

The institution must send OHRP a certification letter, to that effect, which should include the name and address of the institution and specific identification of the research protocol, including the relevant grant number.

The OHRP requires the responsible institution to submit a copy of the research proposal so OHRP can determine whether the proposed research involves one of the categories of research permissible under [45 CFR 46.306\(a\)\(2\)](#), and if so, which one. This will include:

- The IRB-approved protocol.
- Any relevant DHHS grant application or proposal.
- Any IRB application forms required by the IRB.
- Any other information requested or required by the IRB to be considered during initial IRB review.

The IRB will also include the following information in its certification letter to OHRP to facilitate processing:

- OHRP Assurance number.
- IRB registration number.
- Date(s) of IRB meeting(s) in which protocol was considered, including a brief chronology that encompasses the date of initial IRB review and date of Subpart C review.

Other Approvals that may be required:

There may be other approvals required depending on the policies and procedures for the correctional facility at which the research will take place (e.g., Federal Bureau of Prisons, Missouri Department of Rehabilitation and Corrections, County jail, etc.). It is the Investigator’s responsibility to determine what additional requirements must be met prior to conducting research that involves prisoners, and to provide any necessary letters of support with the initial submission to the IRB.

34.0 LEGALLY AUTHORIZED REPRESENTATIVE (LAR)

Kansas Regulations:

A Legally Authorized Representative (LAR) for research is defined by state law governing surrogate decision-makers for research. Kansas law defines the group of individuals who may act as surrogate decision-makers for participating in clinical research.

In the state of Kansas an LAR can only consent to research if an adult or emancipated minor is incapable of giving informed consent to an IRB-approved research protocol and is being treated by a person licensed to practice medicine and surgery and who has medical staff membership with medical care facility that has its own, or contracts with, an independent institutional review board.

If these two conditions are met, a hierarchy of preferred decision-makers may provide informed consent on behalf of the incapacitated individual.

However, if neither such role exists, or if the person acting in the capacity cannot be contacted using reasonably diligent efforts, informed consent for research participation may be granted by a family member in the following order:

- 1) The adult or emancipated minor’s spouse, unless they are legally separated;
- 2) An adult child;
- 3) A parent;
- 4) An adult relative by blood or marriage.

The law places a caveat on surrogate decision-making, in that no decision in favor of research participation may be made if the incapacitated person has previously expressed contrary wishes, either orally or in writing.

Missouri Regulations:

The State of Missouri has enacted legislation that outlines how research participants unable to consent for themselves may be enrolled in research studies. The state recognizes the spouse as the highest priority for providing consent on behalf of another and specifically list circumstances under which the spouse may be bypassed. The guidelines below are too used when consent of a legally authorized representative is used to enroll research participants.

Greater than Minimal Risk studies:

The Missouri statute lists the people who may give consent on behalf of a potential participant who is incapacitated. The order is as follows: Legal guardian, attorney-in fact, or family member in the following order of priority:

- 1) Spouse, unless the patient has no spouse, or is separated, or the spouse is physically or mentally incapable of giving consent, or the spouse's whereabouts is unknown, or the spouse is overseas;
- 2) Adult child;
- 3) Parent;
- 4) Brother or sister;
- 5) Relative by blood or marriage.

The priority order is to be followed without deviation; that is, if the potential participant has a spouse, the spouse must give consent (unless the spouse is unavailable as described above). Consent may only be sought from the adult child if there is (1) no spouse; or (2) the spouse is unavailable as described above.

Minimal Risk studies:

Since the statute describes situations of “experiential treatment, test or drug”, studies that are minimal risk in nature may use the LAR process in a more flexible manner. If the spouse is not generally available, upon documented attempts to contact, researchers may proceed down the list to obtain consent.

(Note: this scenario only applies to minimal risk studies.)

35.0 SELF-EXPERIMENTATION

SLHS is committed to the protection of rights and welfare of individuals participating in research activities that involve self-experimentation (including Investigator is collecting samples from themselves). When self-experimentation meets the definition of human subject research, review and approval by the IRB is required. The regulations do not regard research on oneself as different from research on others.

Faculty and staff members who wish to act as participants in their own research protocols should consider themselves human subjects. SLHS requires submission of a protocol or submission of an amendment to the IRB prior to self-enrollment in a project or initiation of the experimentation on oneself. The IRB is authorized to review and approve requests for self-experimentation.

Prior to commencing any research activity, that involves self-experimentation (e.g., blood draws, sample collection); the Investigator must obtain IRB approval. This may be in the form of an individual research protocol if the Investigator will be the only subject or as part of a protocol, that involves multiple subjects.

The IRB will review each protocol (or an amendment to add self-experimentation) and determine the appropriateness of the research. The committee will consider as part of its review the level of self-experimentation and the potential risks and benefits to the Investigator as a research subject. A main concern for the IRB when reviewing a protocol that involves self-experimentation is that the ideation of a novel concept may outweigh the

Investigator's concern for his/her own welfare. For this reason, the committee may institute additional safeguards for the research project.

The informed consent regulations are also important to consider when an Investigator proposed to participate as a research subject in their own protocol. A standard consent form must be developed and include all of the required elements. In addition, the following statements must be added to the consent or as an addendum to the consent for the Investigator to sign before participating.

Required Statement:

I am an Investigator or key personnel on the above-referenced research study and intend to conduct the procedures as described in the approved protocol and consent form on myself: I am aware that the procedures are considered to constitute research on human subjects. I am performing these procedures on myself voluntarily.

Signature and Date

36.0 DIVERSITY

This guidance was prepared by the Medical Policy in the Center for Drug Evaluation and Research in cooperation with the Food and Drug Administration (FDA). For FDA guidance on enhancing diversity in clinical trials please visit: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial>

In August 2017, the FDA signed into law an amendment to revise and extend the user-fee programs for drugs, medical devices, generic drugs, and biosimilar biological products, and for other purposes. Section 610 (a) (iii) of this act discusses the inclusion and exclusion criteria and barriers to participation in clinical trials. In effort to satisfy this mandate the following policy was prepared to address the following:

- Broadening eligibility criteria and avoiding unnecessary exclusions for clinical trials
- Developing eligibility criteria and improving trial recruitment so that the participants enrolled in trials will better reflect the population most likely to use the drug, if the drug is approved, while maintaining safety and effectiveness standards
- Applying the recommendations for broadening eligibility criteria to clinical trials for drugs intended to treat rare diseases or conditions.

(Note: FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidance describes the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.)

Broadening Eligibility Criteria to Increase Diversity in Enrollment:

In April 2018, the FDA held a public meeting to discuss topics related to eligibility criteria in clinical trials including:

- The rationale for, and potential barriers created by, inclusion and exclusion criteria;
- The benefit to appropriate study populations from trials with alternative designs;
- Barriers to clinical trial participation;
- Clinical trial designs that increase population diversity;
- How changes to trial inclusion and exclusion criteria could impact clinical trials;
- How changes to eligibility criteria may impact the complexity and length of clinical trials.

One objective of eligibility criteria is to help protect participants by excluding people for whom the risk of an adverse event from participation is not likely to be reasonable in relation to any potential benefit and the importance of the knowledge that may be expected to result.

For example, patients with decreased renal function or certain concomitant illnesses are often excluded because of concerns that they may be more susceptible to the adverse effects of an investigational drug because it is metabolized by the kidney or interacts with other medications the patient takes.

In addition, participants with multiple concomitant illnesses and those receiving other drugs are often excluded because of concerns that such conditions or other drugs could affect a determination of the investigational drug's safety or effectiveness.

Pregnant women are also frequently excluded out of concern for fetal health. In addition to protecting participant safety, the exclusion of certain patients on multiple medications or with multiple comorbidities is sometimes intended to avoid noise in the safety data. Medically complex patients often have adverse clinical events that are related to their underlying conditions, which may make it difficult to determine whether the adverse event is related to the investigational drug, to the medical condition, or to a concomitant treatment.

At the same time, certain populations are often excluded from trials without strong clinical or scientific justification (e.g., the elderly, those at the extremes of the weight range, individuals with organ dysfunction, those with malignancies or certain infections such as HIV, and children).

Additionally, failure to include complex participants in a development program may lead to a failure to discover important safety information about use of the investigational drug in patients who will take the drug after approval. Therefore, broadening eligibility criteria, when appropriate, maximizes the generalizability of trial results and the ability to understand the therapy's benefit-risk profile across the patient population likely to use the drug in clinical practice, without jeopardizing patient safety.

Broadening Eligibility Criteria in Enriched Clinical Trials:

Enrichment is a trial design strategy in which there is a targeted inclusion of certain populations, with the goal of more readily demonstrating the effect of the drug, if there is one. Enrichment may increase the trial's potential to show an effect, if one exists, by ensuring that participants have a particular severity of a disease, a particular subset of a disease, or particular genetic markers. Prognostic enrichment enrolls participants who are more likely to reach study endpoints (e.g., participants with risk factors for cardiovascular disease in a cardiovascular outcome trial) or to have a disease of greater severity, reducing the size of a trial necessary to show an effect. Predictive enrichment includes participants with a specific characteristic (e.g., genetic, pathophysiologic) who may be more likely to respond to an intervention. Enrichment does not usually exclude demographic groups.

The FDA encourages the use of enrichment strategies to increase the potential of a trial to detect an effect of the investigational drug, although it is often advisable to include a reasonable sample of participants who have the disease but do not meet the prognostic or predictive enrichment characteristics pre-specified in the clinical trial.

FDA Recommendations:

Inclusive Trial Practices:

Sponsors should adopt practices for determining eligibility criteria that will allow the clinical trial population to reflect the diversity of the patients who will be using the drug if the drug is approved. Although there are many approaches a sponsor can take to broaden eligibility criteria in clinical trials, FDA provides the following recommendations and encourages the use of others as appropriate:

- Examine each exclusion criterion to determine if it is needed to help assure the safety of trial participants or to achieve the study objectives when developing clinical trial protocols. If not, consider eliminating or modifying the criteria to expand the study population as well as tailoring the exclusion criteria as narrowly as possible to avoid unnecessary limits to the study population.

For example, if there are unreasonable risks to participants with advanced heart failure, but enrollment of those with milder disease would be appropriate, the exclusion criteria should specifically define the population of heart failure participants that should be excluded.

- Consider whether criteria from phase 2 studies —, which may be more restrictive and are often transferred to phase 3 protocols — can be eliminated or modified to avoid unnecessary limits on the study population. Although excluding certain participants may be scientifically or clinically justified under specific circumstances (e.g., certain drug-drug or drug-disease interactions or concerns regarding a population’s vulnerability to a particular toxicity), such criteria may be removed or modified during study conduct based upon data available from the completion of other relevant studies (e.g., drug-drug or drug-disease interaction studies). It may be possible in some cases to have the development program include specific studies in higher risk populations conducted at sites with expertise in working with such participants (although in such a case the consent form should identify this increased risk among certain participants).
- Base exclusions on an appropriate measure of organ dysfunction that does not lead to the unnecessary exclusion of certain populations when such exclusions are necessary because participants with impaired organ function would be placed at unreasonable risk.
- Consider including children (ages 2 to 11 years) and adolescents (ages 12 to 17 years) in confirmatory clinical trials involving adults when appropriate.

Trial Design and Methodological Approaches:

Sponsors may consider various trial design and methodological approaches to enrolling a broader population. The following are examples of potential approaches to consider:

- *Consider characterizing — in early clinical development — drug metabolism and clearance across populations that may metabolize or clear the drug differently (e.g., the elderly and patients with liver or kidney dysfunction). Early characterization of drug metabolism and clearance across groups will help avoid later exclusions. Alternatively, an expansion cohort may also allow dose modification and may be used to assess a reasonably safe dose in specific populations in which there may be significant differences in the systemic exposure to the investigational drug (e.g., pediatric or elderly participants or participants with organ impairment).*
- *Consider using adaptive clinical trials, which allow for pre-specified trial design changes during the trial, including altering the trial population. An adaptive design can start with a narrow population if there are concerns about safety and can expand to a broader population based on interim data from the trial as well as external data. Adaptive trials may also provide for broader enrollment when there is uncertainty regarding whether the drug will be effective in certain populations, with an interim analysis that will enable adjustment of future enrollment based on pre-specified criteria regarding response.*
- *Consider a pediatric development program early (although enrollment of children and adolescents in development programs is a complex subject that is beyond the scope of this guidance). For pediatric trials with potential safety concerns, consider staggering enrollment based on age (i.e., enrollment of older pediatric participants first, then younger pediatric participants). Because this approach may not always be*

warranted, such enrollment should be justified with a clear scientific rationale (e.g., juvenile toxicity studies have not yet been completed to support studies in younger pediatric participants).

- Consider including a broader participant group in the trial as part of the secondary efficacy and safety analyses, even when the primary analysis population is narrowed (e.g., when using enrichment designs). Consider enrolling participants across the full spectrum of disease severity, and structure eligibility criteria to include participants from all disease stages or syndrome presentations, while assessing efficacy and safety for the larger population, even if the primary endpoint is based on a population with a particular stage of the disease. This approach allows the study to utilize enrichment to help demonstrate effectiveness while also providing information on effectiveness and safety in a broader population and not decreasing the chances of achieving success on the primary clinical endpoint.
- Consider including pharmacokinetic sampling when appropriate and when it is possible for continued participation with sufficient assurances of safety during pregnancy to establish dosing in women who become pregnant during a trial and in whom the risks of continued trial participation are reasonable in relation to the anticipated benefits and the importance of the knowledge that may be expected to result. This may provide important information regarding drug metabolism during pregnancy and across the trimesters, a time when physiology can change significantly.

Other Study Design and Conduct Consideration for Improving Enrollment:

Beyond the limitations in participation imposed by narrow eligibility criteria, potential participants may face additional challenges to enrolling in clinical trials. A trial requiring participants to make frequent visits to specific sites may result in added burden for participants, especially the elderly, children, disabled and cognitively impaired individuals who require transportation or caregiver assistance, or participants who live far from research facilities, such as those in rural or remote locations. Burdensome financial costs (e.g., travel, missing work) may also impede participation, and study visits may interfere with jobs and/or family and community obligations. Moreover, for individuals under current clinical care on a regularly scheduled basis (e.g., individuals with multiple chronic conditions), additional clinical trial study visits may be burdensome and a disincentive for enrollment in clinical trials. A mistrust of clinical research among certain populations also impacts enrollment. FDA, the National Institutes of Health (NIH), and HHS have a number of resources that serve to further the goal of improving enrollment practices and broadening inclusion criteria.

As part of the overall study design, sponsors can improve the diversity of enrolled participants by accounting for logistical and other participant-related factors that could limit participation in clinical trials. *The following are a few examples of potential approaches, and FDA encourages the development of other approaches.*

Make Trial Participation Less Burdensome for Participants:

During the study design phase, consider the recruitment challenges that may occur because of the planned visit schedule: reduce the frequency of study visits to those needed to appropriately monitor safety and efficacy and consider whether flexibility in visit windows is possible and whether electronic communication (e.g., telephone/mobile telephone, secured electronic mail, social media platforms) or mobile technology tools can be used to replace site visits and provide Investigators with real-time data.

During recruitment, offer and make participants aware of financial reimbursements for expenses associated with costs incurred by participation in clinical trials (e.g., travel and lodging expenses). FDA does not consider reimbursement for reasonable travel expenses to and from the clinical trial site and associated costs such as airfare, parking, and lodging to raise issues regarding undue influence. Similarly, consideration may be given to paying participants in exchange for their participation in the research; however, FDA recognizes that payment for participation may raise difficult questions that should be addressed by the IRB, such as how much money

participants should receive, and for what should participants receive payment, such as their time, inconvenience, discomfort, or some other consideration.

Adopt Enrollment and Retention Practices That Enhance Inclusiveness:

Work directly with communities to address participant needs and to involve patients, patient advocates, and caregivers in the design of clinical trial protocols. Patients may provide valuable insight into challenges and burdens and may be more willing to accept risk for a potential benefit as long as the risks are clearly communicated in the informed consent and the research team explains the risks. Community-based participatory research promotes the design of clinical research with the assistance of community members and leaders to more effectively meet the needs of potential participants. Understanding how participants choose whether to participate in a clinical trial allows sponsors to more effectively recruit participants who may be reluctant to enroll.

Ensure that clinical trial sites include geographic locations with a higher concentration of racial and ethnic minority patients to recruit a more diverse study population. Consider diversity when selecting health care providers to assist with clinical trial recruitment because this may promote diversity among participants.

Incorporate strategies for public outreach and education. Industry, patient advocacy groups, medical associations, and other stakeholders can consider collaborating to educate participants about clinical trial participation.

Make recruitment events accessible by holding them often, as well as offering them during evening and weekend hours. Consider holding the events in non-clinical but trusted locations (such as houses of worship) and social commercial venues (such as barbershops and beauty salons) as a means of connecting with diverse populations.

Explore agreements to foster the exchange of medical records between clinical trial sites in order to promote participant retention by obtaining participant consent for clinical trial Investigators to transfer medical records, including electronic medical records, when participants move from one location to another, because participants often struggle to navigate the gathering and transfer of records between sites.

Expanded Access:

Despite efforts to broaden inclusion criteria, there may be patients who do not meet the eligibility criteria or for other reasons cannot participate in the clinical trial. FDA's expanded access regulations provide a pathway to potentially offer such patients, when they have a serious or immediately life-threatening disease or condition, treatment with an investigational drug, provided certain criteria are met, including that there is no comparable or satisfactory alternative therapy. Expanded access refers to the use of an investigational drug when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition rather than to obtain the kind of information about the drug that is generally derived from clinical trials. However, in certain limited circumstances, data from expanded access use may inform clinical development.

Broadening Eligibility Criteria and Encouraging Recruitment for Clinical Trials of Investigational Drugs Intended to Treat Rare Diseases or Conditions:

Clinical trials of investigational drugs intended to treat rare diseases or conditions present a unique set of challenges. Because of limited numbers of patients, maximum participation in clinical trials is essential for successful trial completion and interpretation. Subsets of potential participants are sometimes excluded from clinical trials because of narrow eligibility criteria, including (1) those with advanced disease or without narrowly defined symptoms in a heterogeneous disorder, (2) age, (3) duration of disease, (4) severity of symptoms, (5) concomitant medication, or (6) disability. Because rare diseases often affect small, geographically dispersed patient populations with disease-related travel limitations, special efforts may be necessary to enroll and retain these participants to ensure that a broad spectrum of the patient population is represented.

Although certain strategies, including predictive and prognostic enrichment, are used to increase the efficiency of clinical trials for rare diseases, the effects in the broader population remain of interest.

Sponsors should therefore consider the following approaches (and others as appropriate) to broadening clinical trial eligibility criteria for clinical trials of investigational drugs intended to treat rare diseases and improve the enrollment and retention of participants with rare diseases:

- Engage early in the drug development process with patient advocacy groups that are strongly committed to finding new therapies, to elicit their suggestions for the design of trials, including trial protocols that participants will be willing to enroll in and support. For a number of rare diseases, there are active patient advocacy groups that are strongly committed to finding new therapies and supporting clinical trials.
- Plan to re-enroll participants from early-phase trials into later-phase trials when studying the effectiveness of treatments for rare diseases — in limited circumstances, if medically appropriate, and if there is no unreasonable anticipated safety issue. Traditionally, participants are often ineligible for a phase 3 trial if they had been previously exposed to the drug in an earlier-phase trial; however, with so few participants in rare disease trials, re-enrolling participants may facilitate the analysis of safety and efficacy in the broadest possible population. Caution should be exercised to avoid selection bias, as the participants who better tolerated the drug and experienced more effectiveness in early phases may be disproportionately selected for a phase 3 trial, which may contribute to efficacy findings that are not representative of the larger population that will use the drug if the drug is approved.
- Make available an open-label extension study after early-phase studies to encourage participation by ensuring that all study participants, including those who received placebo, will ultimately have access to the investigational treatment.

Conclusion:

Broadening eligibility criteria and adopting more inclusive enrollment practices will open clinical trials to a diverse participant population reflective of the population that will use the drug if the drug is approved. To avoid unnecessary exclusions and obtain critical safety and effectiveness data applicable to a more representative patient population, sponsors should consider the recommendations in this guidance when designing and conducting clinical trials. FDA also encourages sponsors to consider and develop other approaches as appropriate.

Appendix A: Current Efforts to Broaden Eligibility Criteria in Clinical Trials:

The Food and Drug Administration (FDA) and the International Conference on Harmonization (ICH) have issued a number of population-specific guidance to address the need to include a broad population in clinical trials and avoid unnecessary exclusions.

- Inclusion of Clinically Relevant Populations:
 - In 2013, FDA broadly addressed inclusion criteria with its good review practice document titled *Good Review Practice: Clinical Review of Investigational New Drug Applications* that guides its clinical reviewers to examine investigational new drug protocols for unwarranted exclusions.
 - In 2014, FDA published an action plan titled *FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data* (FDASIA Action Plan) in response to the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA). The FDASIA Action Plan proposes strategies to encourage greater clinical trial participation, including collaborating with industry, other federal agencies, and interested stakeholders to improve clinical trial diversity.
 - In 2016, prompted by the FDASIA Action Plan, FDA published the guidance titled *Collection of Race and Ethnicity Data in Clinical Trials*, which encourages sponsors to enroll participants who reflect the demographics of clinically relevant populations with regard to age, gender, race, and ethnicity, and

recommends that sponsors submit a plan to address the inclusion of clinically relevant populations to the Agency.

- Inclusion of Elderly Populations:
 - In November 1989, FDA articulated its support for the inclusion of elderly participants in clinical trials with the release of a guidance for industry titled *Guideline for the Study of Drugs Likely to be used in the Elderly*.
 - In June 1993, within the global pharmaceutical regulatory community, ICH (of which FDA is a member) issued a guideline titled *Studies in Support of Special Populations: Geriatrics E7*, which discourages arbitrary maximum age requirements in clinical trial protocols and encourages the inclusion of participants with concomitant illness and those receiving concomitant medications, many of whom are often elderly.
 - In February 2012, an ICH guidance for industry, adopted by FDA, clarifies ICH E7 and emphasizes the importance of including elderly patients in clinical trials, especially patients 75 years or older.
 - In 2014 in the FDASIA Action Plan, FDA reiterated support for efforts to include elderly patients in clinical trials.
- Inclusion of Women:
 - In July 1993, FDA issued a guidance titled *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs*, which discourages unjustified exclusion based on gender in clinical trials. FDA encourages the inclusion of women in clinical trials and the analysis of clinical trial data by gender, which reflects good drug development practice and provides better health information for both genders across demographic groups.
 - In 2016, Section 204110 of the 21st Century Cures Act required the establishment of a Task Force on Research Specific to Pregnant Women and Lactating Women. The task force was charged with providing advice and guidance to the Secretary of Health and Human Services on Federal activities related to identifying and addressing gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women. The task force convened from August 2017 to May 2018 and developed recommendations to address areas such as building research infrastructure and networks and overcoming participation barriers for pregnant women and lactating women.
 - In April 2018, FDA published a draft guidance for industry on scientific and ethical considerations for inclusion of pregnant women in clinical trials.
 - In May 2019, FDA issued two draft guidance providing trial design recommendations for post-approval pregnancy safety studies and for clinical lactation studies.

Although the terms sex and gender have sometimes been used interchangeably in scientific literature and health policy, FDA guidance and regulations address the reporting and analysis of clinical trial data by gender.

FDA also supports the analyses of data by sex, with sex defined as a biological construct and gender as a social construct in accordance with the 2001 Institute of Medicine (IOM) report.

Analyzing data by sex allows researchers to determine if there are any sex differences impacting health conditions and treatment options across the continuum of life stages and can provide insight into the scientific basis for individual therapy differences.

Appendix B: Current Efforts to Improve Enrollment in Clinical Trials:

The following is a sampling of efforts by the Food and Drug Administration (FDA), the Department of Health and Human Services, and the National Institutes of Health (NIH) to improve enrollment practices in clinical trials:

- FDA maintains a Consumer Update web page that provides general information on clinical trials for consumers, including information on clinical trial participation and informed consent.
- FDA's Office of Minority Health provides a web page for minority consumers that contains a clinical trial diversity tool kit, a webinar, multilingual fact sheets, videos, and links to relevant resources.
- The HHS Office for Human Research Protections provides resources and information for the public on clinical trial participation, including informational videos and links to other federal websites and media articles.
- NIH informs the public about the availability of clinical trials and how to enroll through its website "NIH Clinical Research Trials and You."
- The website clinicaltrials.gov maintained by the NIH National Library of Medicine, provides a database with information on publicly and privately supported clinical studies that is accessible to the public and health care providers.
- Research Match, a public clinical research registry partially funded by NIH's National Center for Advancing Translational Sciences, connects researchers with people who are interested in participating in clinical trials

37.0 REPORTABLE EVENTS

The IRB must comply with all applicable local, state, and federal regulations in the conduct of research studies. Federal regulations [45 CFR 46.108\(a\)\(4\)](#) and [21 CFR 56.108\(b\)\(1\)](#) require IRBs to have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the federal department or agency head of any unanticipated problems involving risks to subjects or others, or any serious or continuing noncompliance with the regulations or the requirements of the IRB.

An unanticipated problem is any incident, experience, or outcome that meets all of the following criteria:

- Unexpected, in terms of frequency or severity
- Related or Possibly Related to participation in the research
- Suggests that the research places subjects or others at a greater risk of harm

Noncompliance occurs when any action or activity associated with the conduct or oversight of research involving human subjects that fails to comply with federal regulations, SLHS institutional policies, or the requirements or determinations of the IRB.

The SLHS IRB will review the reports and fulfill reporting requirements to the appropriate institutional officials and federal departments or agencies.

In order to approve research, the SLHS IRB must ensure that risks to subjects are minimized, and the risks are reasonable in relation to the anticipated benefits. They are also responsible for conducting continuing review of research to review reports of unanticipated problems, adverse events, protocol deviations, and other risks. The risks may involve physical, emotional, financial, social, psychological, or legal harm to the subject (or to others). The IRB has the authority to suspend or terminate approval that has been associated with unexpected serious harm to subjects or others.

Reporting Criteria:

In keeping with the regulations cited above, Investigators are required to promptly report to the IRB any (a) unanticipated problems involving risks to subjects or others or (b) noncompliance with the regulations or the requirements of the IRB.

Examples of incidents, events or outcomes that require reporting:

- *Adverse events that meet all three criteria of an unanticipated problem*
- *Protocol deviations or noncompliance attributable to the study team or sponsor*
- *Protocol deviations or noncompliance attributable to a participant **only if results in safety issue or increased risk of harm** (e.g., missed safety labs, incorrect self-administered dose of study drug, participant or partner becomes pregnant when study involves potential risks to fetus)*
- *Participant complaints*
- *Breaches of confidentiality*
- *Suspension or termination of study procedures by the Investigator, sponsor, or regulatory agency*
- *Audit, inspection, or monitoring reports*
- *Data Safety Monitoring Board (DSMC)/Data Monitoring Committee (DMC) reports*
- *Incarceration of a participant in a study not IRB-approved to involve prisoners*
- *Any new information that potentially impacts the welfare or increases the risk to current, former, or future participants in the research*

Examples of incidents, events or outcomes that DO NOT require reporting:

- *Adverse events that DO NOT meet all three criteria of an unanticipated problem*
- *Protocol deviation or noncompliance attributable to a participant **that do NOT result in a safety issue or increased risk of harm** (e.g., nonconsequential out of window visit)*

Adverse events in clinical trials must be reported to the sponsor in compliance with FDA regulations and sponsor requirements. Unless specifically required by the IRB, the SLHS IRB does not accept reports of adverse events that do not meet the definition of an unanticipated problem. If Investigators are uncertain but believe that the event might qualify as an unanticipated problem, a report should be submitted.

Reporting Timeframes:

Within 24 hours:

- Fatal or life-threatening event involving a SLHS participant
- Breach of confidentiality
- Suspension or termination of a study by the Investigator or sponsor

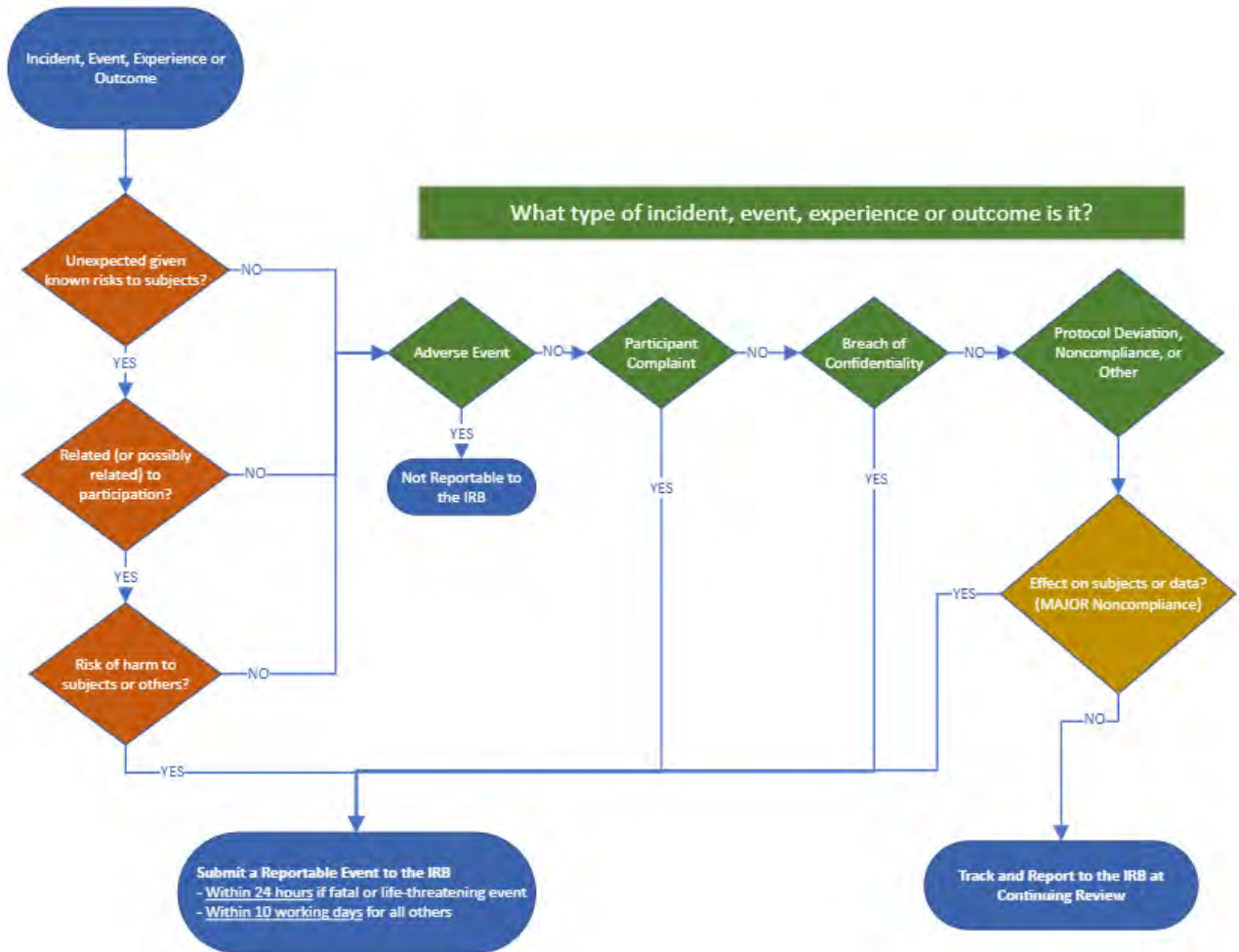
Within 10 working days:

- All other reportable events excluding minor noncompliance (protocol deviation/noncompliance that does not affect subject safety or data)

At the next Continuing Review:

- Minor noncompliance

For guidance on reporting timeframe, please reference the Reportable Event graph shown below:



Submission of Reports:

Investigators or the study team must submit Reportable Events via the IRB submission system. The report should contain the following:

- Detailed information about the event or issue, including relevant dates.
- Any corrective and preventative actions planned or already taken, to ensure that the issue or problem is corrected and will not occur again.
- An assessment of whether any subjects or others were placed at risk as a result of the event or suffered any harm (e.g., physical, social, financial, legal or psychological) and any plan to address these consequences.
- If a report from a sponsor is the basis for the report of a possible unanticipated problem involving risks to subjects or others, or a sponsor has requested the submission to the IRB, the report should be accompanied by an analysis from the sponsor detailing (1) how the event or problem satisfies the definition of a UAP, (2) proposed study-wide corrective actions or modifications to the research along

with a timeline for anticipated completion of the actions, and (3) whether or not the problem has been reported as a UAP to any relevant federal agencies.

- If a sponsor or Lead Investigator or coordinating center suspends or terminates some or all research activities, the report should be accompanied by information from the sponsor detailing (1) why the suspension or termination was enacted, (2) if it was due to a possible UAP (in which case the information in “d” above must be included), (3) any impact on subjects or actions to be taken to protect subjects, (4) any plan to inform subjects of the suspension or termination and other pertinent information, and (5) whether the suspension or termination has been reported to any relevant federal agencies.
- Any other relevant information.
- Any other information requested by the HRPP office.

38.0 IRB REVIEW OF UNANTICIPATED PROBLEMS

Saint Luke’s Health System complies with DHHS and FDA regulations which require organizations to have written policies on reporting unanticipated problems (UPs) to the IRB, organizational officials and relevant federal agencies and departments.

The following procedures describe how UPs are handled by the HRPP office and IRB:

- Upon receipt of a potential UP, the HRPP staff checks the form for completeness. If any applicable sections of the form are incomplete or have been answered unsatisfactorily, the HRPP staff will contact the Investigator or the designated contact person to obtain additional information.
- Once all the required information is received, HRPP staff determine whether the incident, event or outcome meets the reporting criteria for an UP.
- If HRPP staff determine that the report does NOT meet all the criteria for an UP, the report will be administratively acknowledged. This administrative action acknowledges receipt of the submission and informs the Investigator that the report did not meet reporting criteria.
- If HRPP staff determine that that all reporting criteria for an UP have been met, the Reportable Event will be assigned to a convened meeting of the IRB for review.
- At the convened meeting, the IRB will make a final determination as to whether the event constitutes an UP.
- Additional actions the IRB may take include:
 - Request additional information
 - Require changes to the protocol or consent form to protect participants
 - Suspend research to ensure protection of the rights and welfare of participants

Any suspension or termination of research by the IRB must be promptly reported to the IO and relevant federal regulatory agencies through the IO. This should be done in writing.

39.0 IRB REVIEW OF NONCOMPLIANCE

The following describes the process that the HRPP office will follow to manage noncompliance with human subject protection regulations and subsequent review by the SLHS IRB.

Noncompliance occurs when any action or activity associated with the conduct or oversight of research involving human subjects fails to comply with federal regulations, SLHS institutional policies, or the requirements or determinations of the IRB. Noncompliance with respect to human research participant protection violates SLHS

[Federalwide Assurance Registration](#) (FWA). Even in the absence of intent, an unapproved or otherwise noncompliant research activity may place a research participant at unnecessary risk.

The following procedures describe how reports of noncompliance are handled by the HRPP office and IRB:

- Upon receipt of a report of noncompliance, the HRPP staff checks the form for completeness. If any applicable sections of the form are incomplete or have been answered unsatisfactorily, the HRPP staff will contact the Investigator or the designated contact person to obtain additional information.
- Once all the required information is received, HRPP staff determine whether the incident constitutes minor or major noncompliance.
 - [Minor Noncompliance](#) occurs when noncompliance does not have an effect on subject safety or data integrity.
 - [Major Noncompliance](#) is a more serious incident involving noncompliance with the protocol usually involving critical study parameters. Major noncompliance generally affects the subject's rights, safety, or welfare, or the integrity of the study data.
- If HRPP staff determine that the report does NOT constitute noncompliance, the report will be administratively acknowledged. This administrative action acknowledges receipt of the submission and informs the Investigator that the report did not meet the definition of noncompliance requiring IRB review.
- If HRPP staff determine that the report constitutes minor noncompliance, the report will be forwarded to a designated member for expedited review. Logs of minor noncompliance submitted in tandem with a Continuing Review submission will be paired with the Continuing Review for review by the IRB.
- If HRPP staff determine that the report constitutes major noncompliance, the report will be assigned to a convened meeting of the IRB for review.
- At the convened meeting, the IRB will make a final determination as to whether the event constitutes noncompliance and what (if any) corrective actions are required in order to protect participants. Additional actions the IRB may take include requesting additional information, suspending research to ensure protection of the rights and welfare of participants, or determine that an investigation is warranted.
- Additional actions the IRB may take include:
 - Request additional information
 - Suspend research to ensure protection of the rights and welfare of participants
 - Conduct an investigation
- Once the IRB has made a final determination in regards to the noncompliance, the IRB must also determine whether the report constitute serious and/or continuing noncompliance.

IRB determination of Serious or Continuing Noncompliance:

Federal regulations [45 CFR 46.108\(a\)\(4\)](#) and [21 CFR 56.108\(b\)\(1\)](#) require IRBs to have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the federal department or agency head of any serious or continuing noncompliance with the regulations or the requirements of the IRB.

[Serious Noncompliance](#) occurs when an action or omission in the conduct or oversight of research involving human subjects that affects the rights and welfare of research participants, increases risks to research participants, decreases potential benefits or compromises the integrity or validity of the research.

Examples of serious noncompliance include but are not limited to:

- [Conduct of human subjects research without prior IRB approval.](#)

- *Modifications to human subjects research without prior IRB approval.*
- *Failure to obtain legally effective informed consent when required by the IRB.*
- *Any incident which:*
 - *Affects the rights, welfare or safety of subjects*
 - *Increases risk of harm to subjects*
 - *Decreases potential benefits of study participation*
 - *Compromises the integrity/validity of the study data*

Continuing Noncompliance occurs when a pattern of noncompliance or unrectified instance of noncompliance, if left unaddressed, is likely to increase risks to research participants, adversely affect the rights, welfare, or safety of research participants, or affect the scientific integrity of the study or the continued violation of SLHS policies, state or local laws, or federal regulations.

Examples of continuing noncompliance include but are not limited to:

- *An Investigator makes the mistake constituting noncompliance repeatedly, particularly after the IRB has addressed the issues.*
- *An Investigator has multiple problems with noncompliance over a long period.*
- *An Investigator has problems with noncompliance over multiple projects.*

Determinations of serious or continuing noncompliance can only be made by the convened IRB.

Suspension or Termination:

If reported noncompliance may expose research subjects to immediate harm or seriously compromise the integrity of the study data, the convened IRB, the IRB Chair or the Institutional Official (IO) may suspend or terminate research activities as appropriate.

Suspension or termination of IRB approval of research will be reported to the appropriate regulatory agencies and institutional officials.

40.0 APPEALING AN IRB DETERMINATION

Determinations made by the IRB may not be reversed by any SLHS official, any state or federal agency, or another IRB. However, an Investigator may appeal to the IRB to formally re-review a decision if the Investigator believes that the IRB's decision is due to inadequate or inaccurate information, a misunderstanding, or IRB non-compliance with SLHS policy, state law, or federal regulations.

To appeal an IRB determination, the Investigator must submit a detailed rationale as well as any additional information they believe to be pertinent to the IRB's determination. The Investigator's rationale and any additional information provided will be sent to the IRB for consideration. The decision of the IRB will be provided to the Investigator in writing.

41.0 IRB RECORDS AND RETENTION GUIDANCE

(This guidance describes the essential records prepared and maintained by the SLHS HRPP.)

This guideline details the IRB's recommendations for document retention and destruction. The Health System, its faculty, and its trainees have a common interest and a shared responsibility to ensure that research is appropriately recorded, shared, and retained. Consequently, researchers have a responsibility to retain original

research results, in whatever form they may take, for a reasonable length of time to protect intellectual property rights, support scholarly collaboration and publication, and answer any questions that may arise about the conduct of the research. Likewise, the Health System has an interest in, and shared responsibility for, ensuring that research is appropriately recorded, archived, and available for review under appropriate circumstances.

Federal regulations require research records to be retained for at least three (3) years after the completion of the research (45 CFR 46). Additional standards from your discipline may also be applicable to your data storage plan. Research that

involves identifiable health information is subject to Health Insurance Portability and Accountability Act (HIPAA) regulations, which require records to be retained for at least six (6) years after a participant has signed an authorization.

(Note: Research sponsors may require longer retention periods.)

41.1 FEDERAL REGULATIONS

All IRB files and documents that relate to the protection of human research participants are retained for at least 6 years following completion of the study. Study records involving pediatric research participants must be maintained until the youngest child on study is 21 years old, or for 6 years following completion of the study, whichever is longer. If a protocol is cancelled without participant enrollment, IRB records are maintained for at least 6 years after cancellation. Such files and documents include, but are not limited to:

Per 45 CFR 46.115:

- Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by Investigators, and reports of injuries to subjects.
- Minutes of IRB meetings, which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution. Any findings required under the regulations.
- Records of continuing review activities, including the rationale for conducting continuing review of research that otherwise would not require continuing review as described in §46.109(f)(1)..
- Copies of all correspondence between the IRB and the Investigators.
- A list of IRB Members in the same detail as described in § 46.108(a)(23).
- Written procedures for the IRB in the same detail as described in § 46.108(a)(3) and § 46.108(a)(4).
- Statements of significant new findings provided to subjects, as required by § 46.116(c)(5).
- The rationale for an expedited reviewer's determination under §46.110(b)(1)(i) that research appearing on the expedited review list described in §46.110(a) is more than minimal risk.
- Documentation specifying the responsibilities that an institution [relying on another IRB] and an organization operating an IRB [the IRB of record] each will undertake to ensure compliance with the requirements of this policy, as described in §46.103(e).

Per 21 CFR 56.115:

- Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by Investigators, and reports of injuries to subjects.

- Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.
- Records of continuing review activities.
- Copies of all correspondence between the IRB and the Investigators.
- A list of IRB Members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; *for example*:
 - *Full-time employee, part-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.*
 - *Written procedures for the IRB as required by 56.108 (a) and (b).*
 - *Statements of significant new findings provided to subjects, as required by 50.25.*

41.2 SLHS HRPP REQUIREMENTS AND PROCESS

In order to allow a reconstruction of a complete history of IRB actions related to the review and approval of the protocol, the IRB records include copies of the following, as applicable:

- Investigator brochure.
- Recruitment materials.
- Data and safety monitoring reports.
- Unanticipated problems involving risks to participants or others.
- Documentation of non-compliance.

IRB records for Initial and Continuing review of research by the expedited procedure include:

- The justification for using the expedited procedure.
- Justification that the criteria for approval are met.
- Actions taken by the reviewer. Justification for conducting continuing review of research that otherwise would not require continuing review as described in §46.109(f)(1).
- Rationale for an expedited reviewer's determination under §46.110(b)(1)(i) that research appearing on the expedited review list described in §46.110(a) is more than minimal risk.
- Any findings required by laws, regulations, codes, and guidance to be documented.

SLHS HRPP Record Retention:

- IRB records document the justification for Exempt determinations, as well as assessment of submitted proposals as Not Research or Not Human Subjects Research.
- Saint Luke's Health System IRB records, such as IRB rosters, may also be stored on the IRB department server or in paper form.
- New research applications that are in the pre-submission state, or are withdrawn, with no IRB review history or activity for one year or more will be deleted from iMEDris.
- All electronic or paper correspondence unrelated to a specific research protocol or study but of importance in documenting IRB policy development or the evolution of the IRB's assessment of a topic of importance is retained indefinitely.

- All electronic or paper correspondence related to FDA or OHRP regulatory matters (even if not considered a study record required to be maintained by the IRB) will be brought by HRPP staff to the attention of the Institutional Official (IO), HRPP Manager and IRB Chairperson(s) for proper handling and disposition. A copy of all such correspondence will be retained by the Institutional Official indefinitely.
- Paper records on site are maintained in a locked file room or locked offices within the main HRPP office and are available only to HRPP staff. All paper records previously scanned and stored in the software Iron Mountain are accessible through Iron Mountain. The HRPP staff have access to documents kept with Iron Mountain.
- Paper files of studies that have been officially closed via IRB approval of the Final Closure Report are physically maintained in storage in the IRB Main Office or at a secure external site through a contract agreement with Recall, Iron Mountain. These paper files may be recalled, if needed, within three to five business days via notice to Iron Mountain.
- Electronic IRB Record System (iMEDris) are maintained and accessible by HRPP staff. These files are backed up approximately 3 times per hour in iMEDris. "iMEDris" is used to prepare, document, maintain and store records related to IRB activities, including, but not limited to, designated expedited reviewer and individual convened IRB Member review notes, and minutes of IRB meetings documenting protocol-specific determinations and summarizing discussion of controverted issues and their resolution.
- All records are accessible for inspection by authorized representatives of the OHRP, FDA, sponsors, and other authorized entities at reasonable times and in a reasonable manner.
- When the retention period for a paper record expires, and a decision is made by the HRPP Manager or designee in conjunction with the Institutional Official (IO) to no longer retain the record, the record will be shredded or otherwise destroyed. In such an instance the HRPP staff member who works with the Principal Investigator's department or division will advise the Principal Investigator to inform the sponsor that study records will be destroyed on a specific date so that the sponsor may discuss any concerns with the IRB before the action is taken. The IRB anticipates maintaining its electronic records indefinitely.
- A signed and dated consent form (on paper with original signature) must be maintained by the Investigator at SLHS for as long as the research records are retained or completed. This can be satisfied by placing the signed consent form in the medical record or by keeping it in the study's research files.

Principal Investigator Record Retention:

The Principal Investigator (PI) of a study approved by the SLHS IRB is required to retain records associated with a human subjects research project. The recordkeeping requirements vary depending on whether federal funding was provided for the project, whether there is funding from industry with contractual provisions governing data retention, or whether the study was conducted under FDA regulations.

SLHS Organization Requirements:

Original data must be retained for at least 5 years from the date of publication. Beyond that, where questions have been raised regarding the validity of the published data, Investigators must preserve the original data until such questions have been resolved to the satisfaction of the Organization and any involved government agencies. The director or Chair of each department or research unit must decide whether to preserve original data for a given number of additional years or for the life of the unit.

For research involving children, the Organization requires that records must be retained (at a minimum) until the pediatric subject reaches the age of 23.

HIPAA:

Under the HIPAA Privacy Rule, subjects have the right to ask SLHS for an accounting of certain disclosures of their identifiable health information for a period dating 6 years from the date of the last covered disclosure. To ensure that SLHS can meet this accounting requirement, Investigators must retain study records, along with records of all disclosures of study information, for at least 7 years after either of the following (whichever is later):

- The last subject has completed his or her participation in the study;
- OR**
- The date of the last disclosure of identifiable health information from study records if disclosures continue after all subjects have completed the study. [45 CFR 164.528]

This requirement to retain study records and to account for disclosures also applies to research that involves the secondary use of medical records or other identifiable health information.

41.3 FEDERALLY FUNDED, FDA-REGULATED AND PRIVATE SPONSOR REQUIREMENTS

Federally Funded Research and FDA-Regulated Research:

DHHS regulations require that, “records relating to research which is conducted shall be retained for at least 3 years after completion of the research.” [45 CFR 46.115(b)]

For Investigational New Drug (IND) research, the FDA requires that sponsors and Investigators retain “records and reports required by this part for 2 years after a marketing application is approved for the drug; or if an application is not approved for drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA so notified.”

For Investigational Device Exemption (IDE) research, the FDA requires the Investigator or sponsor to maintain the records “for a period of 2 years after the latter of the following two dates: The date on which the investigation 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.”

Private Sponsors:

For research sponsored by corporations or private foundations, the Principal Investigator (PI) should maintain the records for either the length of time required by the corporate sponsor, or the time required by DHHS rules, or Organization policy, whichever is longer.

OHRP Requirements:

45 CFR 46 requires research records to be retained for at least three years after the completion of the research.

HIPAA Requirements:

Any research that involved collecting identifiable health information is subject to HIPAA requirements. As a result, records must be retained for a minimum of six years after each subject signed an authorization.

FDA Requirements:

Any research that involved drugs, devices, or biologics being tested in humans must have records retained for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified.

(Note: that it is recommended that you receive written confirmation from the sponsor and / or FDA granting permission to destroy the records (21 CFR 312.62.c).)

Sponsor Requirements – contract:

If your study is sponsored you must ensure that you comply with any terms for record retention detailed in the contract with the sponsor. *For example, a sponsor may require you to retain your research related documents for 20 years.* Prior to agreeing to a contract that specifies how long records will be maintained you should ensure you will receive adequate funding to pay for the storage.

Questions of data validity:

If there are questions or allegations about the validity of the data or appropriate conduct of the research, you must retain all of the original research data until such questions or allegations have been completely resolved.

42.0 ADMINISTRATIVE HOLD, SUSPENSION OR TERMINATION

The IRB conducts administrative holds, suspensions, and terminations in accordance with [45 CFR 46.113](#) and [21 CFR 56.113](#).

The IRB has the authority and responsibility to suspend or terminate approval of research that is not being conducted in accordance with the IRB policies and procedures, or that has been associated with unexpected harm to participants or others. The IRB has the ability to temporarily or permanently suspend or terminate approval for some or all research activities. Depending on the circumstances surrounding the suspension or termination action, the Investigator may be required to submit a report to the IRB, detailing any adverse events and/or study outcomes that were previously unreported to the IRB for consideration. Any letter of suspension or termination of approval to an Investigator must include a statement of the reasons for the action by the IRB ([45 CFR 46.113](#) and [21 CFR 56.113](#)).

The IRB Chair or the Saint Luke's Health (SLH) Institutional Official (IO), is authorized to suspend or terminate the enrollment of subjects; and the ongoing involvement of subjects in research, as it deems necessary to protect the rights and welfare of participants. This also includes compelling and urgent instances when subject safety is of concern. The IRB will review such suspensions and terminations at a subsequent convened meeting. A plan will be developed that takes into account the rights and welfare of currently enrolled subjects and those subjects who may need to be withdrawn from the study. If the agreed upon plan of action involves withdrawal of enrolled participants, the IRB will take into account their rights and welfare (e.g., arranging for medical care outside of a research study, transfer to another researcher, and continuation in the research under independent monitoring). If the IRB determines that a suspension or termination of the research will place subjects at risk of harm, the Investigator will be requested to submit a proposed script or letter for participants for IRB review and approval. The IRB determines the information that is to be provided to subjects and the method of their notification e.g., in writing or by telephone. This includes appropriate subject follow-up and notification of the reasons for the action. All protocol suspensions or terminations are reviewed at a subsequent IRB meeting.

Depending on the reasons for the suspension or termination and the design of the protocol, the IRB may require that the following subjects be notified of the suspension or termination:

- All subjects who have been or are enrolled
- Subjects currently on protocol; or
- Subjects who participated in a certain aspect of the protocol

The IRB will ensure prompt reporting to the following:

Notification of the IRB Members:

As required in [45 CFR 46.110\(c\)](#), the SLH Institutional Official (IO) will keep all IRB Members advised of activities occurring outside of the full board meetings including protocols that have been suspended or terminated. The IRB Members are advised of activities occurring outside of the full board meetings in a monthly written report, which is presented at a convened meeting.

During an investigation for human subjects' non-compliance, the IRB Chair will notify the principal Investigator of such terminations or suspensions by letter and will include a statement of the reasons for the IRB's actions. The Investigator will be provided with the opportunity to respond in person or in writing. The IRB Chair reviews and signs the letter. The letter includes:

- The nature of the event
- Name of the institution conducting the research
- Title of the research project and/or grant proposal
- Name of the principal Investigator on the protocol
- A detailed description of the problem including the findings of the organization and the reasons for the IRB's decision.
- The activities to be stopped
- Actions to be taken by the Investigator; including those to protect the rights and welfare of currently enrolled subjects.
- A request to immediately notify the IRB Chair with a list of names of participants who might be harmed by stopping research procedures and a rationale why they might be harmed.
- In the case of a suspension or termination of IRB approval by an IRB designee, the date and time of the IRB meeting at which the suspension or termination will be reviewed by the convened IRB; and the actions required to protect the rights and welfare of currently enrolled participants.
- An offer for the Investigator to respond to the convened IRB in writing

The IRB may find it in the best interest of the enrolled subjects to allow continued participation in the research interventions or interactions, but enrollment of new subjects cannot occur during IRB suspension. The convened IRB will determine the appropriate actions and if a study is to be terminated, or may continue with enrollment at the completion of the human subjects non-compliance investigation.

Reporting to Regulatory Agencies, Department Heads and Institutional Officials:

The IRB will report events of suspensions or terminations of IRB approval to Regulatory Agencies, Department Heads and Institutional Officials.

Lapse in Continuing Review:

The IRB and Investigators must plan ahead to meet required continuing review dates specified by the IRB. The IRB has an established Continuing Review Notice system which reminds the IRB and its Investigators when an approved IRB research protocol is due to expire. The notices are sent eight and six weeks in advance of IRB expiration. A notice is also issued the week of IRB protocol expiration, which notifies the principal Investigator that the protocol will expire and once expired, all research activities including enrollment of new subjects must cease.

In certain circumstances, the IRB has the authority to allow the continued participation of subjects in research in which IRB approval has lapsed while the continuing review process occurs, if there are overriding clinical or safety concerns or ethical issues that indicate it is in the best interest of the participants to continue.

The Federal regulations do not allow for the conduct of human subject research without IRB approval. Any report of continuation of study activities after IRB expiration (outside of the above noted exception) will be investigated

as an matter of potential non- compliance and may be reportable to the [Office for Human Research Protections](#) (OHRP), the Food and Drug Administration (FDA), the SLH Compliance Officer, and Department Heads and other Institutional Officials, in addition to other applicable governing Federal Agencies.

43.0 REPORTING TO REGULATORY AGENCIES

It is the responsibility of the SLHS HRPP office to assure reporting occurs according to the Federal regulations, institutional policy and SLHS IRB standard guidance.

This standard guidance establishes guidelines to ensure prompt reporting by the SLHS HRPP office in response to findings of the SLHS IRB of those events listed in Federal regulations. These regulatory requirements may be found in [45 CFR 46.103\(b\) \(5\)\(i\)](#) and [21 CFR 56.108\(b\)\(1\)](#).

If the IRB determines that an event represents:

- An unanticipated problem involving risks to subjects or others;
- A serious or continuing non-compliance with research regulations or determinations of the IRB; or
- A suspension or termination of IRB approval.

In these instances, HRPP staff will prepare a draft report within fifteen (5) working days after the IRB meeting at which the determination occurred or after which time an appropriate administrative action was taken outside of a full Board meeting of the IRB.

Any concerns regarding data integrity outside of the jurisdiction of the SLHS IRB will be referred to SLHS the Institutional Official (IO).

The contents of the required reporting will include:

- The nature of the event (unanticipated problem involving risks to participants or others, serious or continuing noncompliance, suspension or termination of approval of research);
- Name of the institution conducting the research and the awardee institution as applicable;
- Protocol title;
- Name of the Principal Investigator;
- IRB number and identification numbers of any applicable Federal or non-Federal award(s) (grant, contract, or cooperative agreement, etc.);
- A detailed description of the issue including the findings of the institutions involved and the reasons for the investigation and the IRB's decision;
- Actions the institution or the IRB is taking or plans to take to address the problem (e.g., revise the protocol, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring of subjects, etc.); and plans, if any, to send a follow-up or final report by the earlier of: a specific date, when an investigation has been completed or a corrective action plan has been implemented.

HRPP staff in consultation with the IRB Chair and the SLHS Institutional Officer (IO) will review and finalize the report within fifteen (10) working days after the IRB meeting at which the final determination occurred. Once finalized, the report will submitted to the applicable agency immediately.

44.0 DEFINITIONS

Administrative Hold is a voluntary action by an Investigator to temporarily or permanently stop some or all research activities as a modification to approved research. Although the Investigator may discuss this action beforehand, the hold must be initiated voluntarily by the Investigator and must not be used to avoid IRB mandated suspension or termination or reporting requirements. During an administrative hold the research remains subject to continuing review and requirements for reporting non-compliance and unanticipated problems involving risks to subjects or others. Administrative holds must not be used to avoid reporting deficiencies or circumstances that otherwise require reporting by federal agencies. Administrative holds are not considered suspensions or terminations, and do not meet reporting requirements to OHRP, FDA and other federal agencies.

Adult is a person who has attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. Who is an adult may vary depending on the specific treatments or procedures involved in the research and on the jurisdiction in which the research will be conducted.

Adverse Event for the purposes of these policies and procedures, an adverse event (AE) is any untoward or unfavorable occurrence in a human subject, including any abnormal sign (*for example, abnormal physical exam or laboratory finding*), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events are a subset of UAPs.

Assent means a child's affirmative agreement to participate in research. Failure of a child to object to participation cannot be construed as assent. Assent is a process involving communication with the child. A signature on an assent document is not, by itself, assent.

Chair/Director an appointed Lead Member of a clinical organizational unit/department at Saint Luke's Health System

Child is a person, who has not attained the legal age for consent to treatments or procedures involved in research, under the applicable law of the jurisdiction in which the research will be conducted.

- For purposes of this policy, individuals under 18 years of age are considered Minors in Missouri and Illinois unless they meet the definition of Emancipated Minors, with the following exceptions:
- In Missouri, a Minor may consent to medical treatment if married or in the case of pregnancy (excluding abortion), sexually transmitted infections, or substance abuse.

Clinical Investigation use of a drug or medical device other than the use of an approved drug or medical device in the course of medical practice, when data will be gathered, submitted to, or held for inspection by the FDA in support of an FDA marketing permit for a food, including a dietary supplement that bears a nutrient content claim or a health claim, and infant formula, a food or color additive, a drug for human use, a medical device for human use, a biological product for human use, or an electronic product.

Closure/Final Report a report the Principal Investigator may elect to submit to the IRB to serve as a final record of any pertinent activity since the last continuing review report and to record research project completion.

Commercial/Central IRB an independent organization that provides IRB review services.

Common Rule refers to the "Federal Policy for the Protection of Human Subjects" adopted by a number of federal agencies. Although the Common Rule is codified by each agency separately, the text is identical to DHHS regulations in

45 CFR 46 Subpart A. For the purposes of this document, references to the Common Rule will cite the DHHS regulations.

[Comparable Device](#) is considered one where the indication for use and technological characteristics are similar, one where the patient population to be treated or diagnosed with the device is similar and one where the device meets the needs of the identified patient population.

[Compassionate Use](#) of an unapproved device may occur when a device that is being tested in a clinical trial is the only option available for a patient faced with a serious condition. Such uses require prior FDA approval of a protocol deviation under 21 CFR 812.35(a). Prior FDA approval for compassionate use should be obtained before the device is used. On occasion, compassionate use may occur even if there is no IDE for the device. Under this situation, the physician would submit the compassionate use request directly to FDA.

Compassionate use of an unapproved device also requires as many of the following patient protections as possible: (i) informed consent; (ii) clearance from the institution; (iii) concurrence of the IRB Chairperson (this concurrence does not constitute IRB approval); (iv) an independent assessment of an uninvolved physician; and (v) authorization from the IDE sponsor. Follow-up reports should be provided to the Sponsor. Such use may involve an individual patient or a small group of patients. The compassionate use of an investigational device may take place only where the FDA has specifically approved the use. IRB approval and the informed consent of the patient-subject must be obtained prior to the use unless the criteria for emergency use of devices described above have been satisfied.

[Confidentiality](#) refers to how the participant's identifiable private information (data) will be handled, managed and disseminated. This is not to be confused with anonymity, which is the quality or state of data that does not include names or other identifiers that could be linked to a subject's identity.

[Consent Document](#) is a structured, written description in understandable terms of relevant research project information. The written consent document is not consent itself; it is the record of what has been communicated to a potential participant. It is the document that ensures all regulatory elements are present and communicated to a potential participant. When signed by the potential participant, the consent document is a record of the receipt of research-related information by the participant. It also serves as reference material for the participant as the research project progresses. It is not a contract and is not legally binding, and the participant may choose to withdraw consent at any time.

[Continuing Noncompliance](#) occurs when a pattern of noncompliance or unrectified instance of noncompliance, if left unaddressed, is likely to increase risks to research participants, adversely affect the rights, welfare, or safety of research participants, or affect the scientific integrity of the study or the continued violation of SLHS policies, state or local laws, or federal regulations.

[Continuing Review](#) is periodic review of research activities necessary to evaluate the progress of the study and to determine whether the risk/benefit ratio has changed, whether there are unanticipated findings involving risks to participants or others, and whether any new information regarding the risks and benefits should be disclosed to participants.

[Covered Entity](#) a health plan, a health care clearinghouse, or a health care provider who transmits health information in electronic form in connection with a transaction for which HHS has adopted a standard.

[De-Identified](#) is information that does not identify an individual and with respect to which there is no reasonable basis to believe that the information can be used to identify an individual. This includes that there is no means to re-identify individuals after the data have been de-identified (e.g., using a code or other means of record identification).

[Department of Health and Human Services \(DHHS\)](#) is the United States government's agency for protecting the health of all Americans and providing essential human services, especially for those who are least able to help themselves.

[Department Research Review Committee](#) two or more members of the clinical units/departments who are appointed to this function by the Chair/Director at Saint Luke's Health System. For the purpose of this standard guidance this includes the Nursing Research Council.

[Documentation](#) of informed consent includes use of a written IRB-approved consent document, signed and dated by the prospective subject or the prospective subject's legally authorized representative.

[Electronic Informed Consent](#) refers to the use of electronic systems and processes that may employ multiple electronic media, including text, graphics, audio, video, podcasts, passive and interactive Web sites, biological recognition devices, and card readers, to convey information related to the study and to obtain and document informed consent.

[Emancipated Minor](#) is a person under the legal age who, because of a special situation, has the legal rights of an adult. Situations that qualify a person as an emancipated minor vary from state to state. In Missouri a person under the age of eighteen years of age in an Emancipated Minor if any of the following conditions are met:

1. He/She enters into a valid marriage, whether or not the marriage is subsequently dissolved;
2. He/She has served or is currently serving with the armed forces or National Guard of the United States; or
3. He/She receives a judgement of emancipation pursuant to sections 2 to 4 of the Missouri [Emancipation of Minors Act](#).

[Emergency Use](#) is the use of an investigational drug, agent, device 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.

[Enrollment](#) occurs when an eligible, informed, potential participant undergoes the initial informed consent process and voluntarily agrees to participate in a research project. *For example, you enroll 100 to accrue 25. See also Accrual.*

[Exempt Research](#) qualifies for exemption from the requirements of federal regulations [45 CFR 46.101](#) or [21 CFR 56.104](#), including continuing review by the IRB, and that meets the criteria within one or more of the six exempt categories designated in the federal regulations (45 CFR 46.101(b)).

[Expedited Review](#) is review of research involving human subjects by the IRB Chairperson or by one or more experienced reviewers designated by the Chairperson from among members of the IRB in accordance with the requirements set forth in [45 CFR 46.110](#).

[Expiration Date](#) is the last day that a protocol maintains IRB approval. *For example, an IRB approval letter that indicates that a protocol expires on "2/1/2018" is active through midnight on 2/1/2018 and no longer has IRB approval on 2/2/2018 if the continuing review has not yet been reviewed and approved.*

[Expired Study](#) is when continuing review of the research does not occur prior to the end of the approval period specified by the IRB, IRB approval expired automatically. No activities can occur after the expiration date.

[Evidence](#) means any document, tangible item, or testimony offered or obtained during a research misconduct proceeding that tends to prove or disprove the existence of an alleged fact.

[Federalwide Assurance \(FWA\)](#) is a written agreement that establishes standards for human subjects' research as approved by the Office for Human Research Protections and is executed by the Institutional Official (IO).

Fetus(es) means the product of conception from implantation until delivery ([45 CFR 46.202, Subpart B](#)).

Full Board Review is review of research involving human subjects conducted by the full IRB Board at a convened meeting where quorum is present and is in accordance with the requirements set forth in [45 CFR 46.108](#).

Generalizable Knowledge is information that expands the knowledge base of a scientific discipline or other scholarly field of study.

Guardian is an individual, who is legally authorized under applicable state or local law, to consent on behalf of a child to general medical care.

Health Information is any information, whether oral or recorded in any form or medium, that (1) is created or received by a health care provider, health plan, public health authority, employer, life insurer, school or university, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual.

Humanitarian Use Device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 8,000 individuals in the United States per year. FDA developed this regulation to provide an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting these populations. The HUD regulation provides for Humanitarian Device Exemption (HDE) applications.

Humanitarian Device Exemption (HDE) 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. 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.

An approved HDE authorizes marketing of the HUD. However, a HUD may only be used after the institution's convened (full) IRB has approved the use of the device at the institution. The IRB's responsibility in this case is to conduct a special limited review simply to verify that the proposed (non-research) use of the device is consistent with the HDE's FDA-approved indication. (21 CFR 814.124(a)). After granting initial approval, the IRB may use expedited procedures for conducting subsequent continuing reviews, which must be performed at least annually. Informed consent of patients is not required because the use of the HUD in a manner consistent with its marketing approval under the HDE does not constitute research.

Human Subject/Participant as defined by DHHS: a human subject is a living individual about whom an Investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information ([45 CFR 46.102\(f\)](#)). If the research involves a medical device, individuals are considered "subjects" when they participate in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control ([21 CFR 812.3\(p\)](#)).

Research activities involving human subjects either (1) meet the DHHS definition of "research" and involve "human subjects" as defined by DHHS OR (2) meet the FDA definition of "research" and involve "human subjects" as defined by FDA. The definition of research and human subjects must consistently reference the same set of regulations (i.e., DHHS or FDA) and cannot reference the definition of research from one set of regulations, and the definition of a human subject from the other. Anyone who plans to engage in an activity that qualifies as "research involving human subjects" requires IRB review and approval prior to commencement of the research.

Identifiable the identity of the individual subject is or may readily be ascertained by the Investigator or may be associated with the information.

Identifiable Health Information that is a subset of health information, including demographic information collected from an individual, and (1) is created or received by a health care provider, health plan, employer, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual; and (a) that identifies the individual; or (b) with respect to which there is a reasonable basis to believe the information can be used to identify the individual.

Information Sheet is a simplified explanation of the major points of the research. An information sheet is not signed by the child nor used to obtain verbal assent. An appropriate information sheet may be used when assent has been waived by the IRB and the child would benefit from being informed about the study.

Informed Consent is an individual's voluntary agreement, based upon adequate knowledge and understanding of the relevant information, to participate in research either for themselves or for a child for whom they are the parent or guardian (defined as an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care).

IRB is an administrative body established by a local institution to protect the rights and welfare of human subjects recruited to participate in research activities conducted under the auspices of the institution.

Interaction includes communication or interpersonal contact between an Investigator and his/her research staff and the research participant or their private identifiable information.

Intervention includes both physical procedures by which data are gathered (e.g., venipuncture) and manipulations of the subjects' environment that are performed for research purposes.

Investigation means the formal development of a factual record and the examination of that record leading to a decision not to make a finding of research misconduct or to a recommendation for a finding of research misconduct which may include a recommendation for other appropriate actions, including administrative actions. The purpose of the Investigation is to develop a factual record by exploring the allegations in detail and examining the evidence in depth, leading to recommended findings on whether research misconduct has been committed, by whom, and to what extent.

IRB Authorization Agreement/Reliance Agreement is a formal, written agreement which documents respective authorities, roles, responsibilities, and communication between an organization providing the ethical review and a participating organization relying on a reviewing IRB.

IRB of Record/Reviewing IRB is a term utilized when an institution assumes the IRB responsibilities for a human subject research protocol conducted at another institution. An IRB Authorization Agreement signed by institutional officials at both institutions is required.

Lead Investigator is a principal Investigator at the coordinating study site.

Legally Authorized Representative (LAR) is an individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. The State of Missouri has enacted legislation that outlines how research participants unable to consent for themselves may be enrolled in research studies. For more information on the use of a Legally Authorized Representative, see "Guidelines for Use of Legally Authorized Representatives."

Legally Effective Informed Consent occurs when a potential participant has been provided enough information to make a decision; the potential participant has the capacity to make a decision; the potential participant

understands the consequences of his or her decision; and the potential participant can communicate that decision.

[Major Protocol Deviation](#) is a more serious incident involving noncompliance with the protocol usually involving critical study parameters. Major protocol deviations generally affect the subject's rights, safety, or welfare, or the integrity of the study data. A major protocol deviation can also be called a protocol violation.

[Medical Device](#) is a device is "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."

[Minimal Risk](#) means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests ([45 CFR 46.102 \(j\)](#)).

[Minimal Risk for Prisoners](#) is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examinations of healthy persons (46.303, HHS definition).

[Minor Noncompliance](#) occurs when noncompliance is neither serious nor continuing. An example of minor noncompliance includes failure to comply with IRB policies that are administrative in nature (*for example, events submitted outside of the reporting window*).

[Mobile Medical Apps](#) are software programs that run on smartphones and other mobile communication devices. They can also be accessories that attach to a smartphone or other mobile communication devices, or a combination of accessories and software. Mobile medical apps are medical devices that are mobile apps, meet the definition of a [medical device](#) and are an accessory to a regulated medical device or transform a mobile platform into a regulated medical device.

[Neonate\(s\)](#) means a newborn ([45 CFR 46.202, Subpart B](#)). The accepted medical definition of neonate refers to the period between birth and 28 days of life.

[Noncompliance](#) occurs when any action or activity associated with the conduct or oversight of research involving human subjects that fails to comply with federal regulations or the requirements or determinations of the IRB. Noncompliance actions may range from minor to serious, be unintentional or willful, and may occur once or more than once. **Examples** of noncompliance include, but are not limited to:

- *conducting human subject's research without IRB approval (e.g., before approval; after expiration of approval and in the absence of a continuing renewal submitted to the IRB; during a suspension of IRB approval; after termination of IRB approval);*
- *inadequate or nonexistent procedures for the informed consent process as well as disregarding or otherwise violating IRB approved informed consent procedures (e.g., failing to obtain consent/assent, using unapproved or outdated consent, assent, and information sheets);*
- *inadequate supervision;*
- *failure to follow recommendations made by the IRB;*
- *failure to report adverse events, unanticipated problems, study changes and/or protocol deviations.*

[Oral Consent](#) refers to a spoken presentation of the elements of informed consent to the prospective subject or their legally authorized representative. The presentation may be based on information contained within an oral consent script or the written consent document. Oral consent is often associated with waiving the documentation of consent. Oral consent is usually recorded in the research project files.

[Parent](#) generally means a child's biological or adoptive parent. Foster parents are not authorized to give research consent.

[Permission](#) means the agreement of the parent(s) or legally authorized guardian to the participation of a child in research. This term is often used to emphasize that the parent is not the subject of the research. In this context permission has the same meaning as consent.

[Pregnancy](#) includes the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery ([45 CFR 46.202, Subpart B](#)).

[Preparatory to Research](#) activities involved in preparing for research such as identify prospective research participants, reviewing records to determine whether there is a sufficient number or type of records to conduct the research, or under certain circumstances contracting potential participants for recruitment.

[Prisoner](#) is any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial or sentencing.

(46.303, HHS definition) Internment in a facility for psychiatric illness or substance abuse is considered to meet the criteria for incarceration if the commitment has been made as an alternative to a criminal prosecution or incarceration. However, an individual in mental health or substance abuse facility is not considered incarcerated if he/she has voluntarily commit his/herself or has been civilly committed. Probation and parole are usually not considered as incarceration unless the parolee is detained in a treatment center as a condition of parole.

[Private Information](#) includes information about behavior that occurs in a setting in which an individual can reasonably expect that no observation or recording is taking place. It includes information, which has been provided for specific purposes by an individual, and the individual can reasonably expect will not be made public (e.g., a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the Investigator or associated with the information) in order to be considered information to constitute research involving human participants.

[Privacy](#) refers to a person's desire to control the access of others to themselves. *For example, a person may not wish to be seen entering a place that might stigmatize them, such as a pregnancy counseling center.*

[Protected Health Information \(PHI\)](#) individually identifiable health information transmitted by electronic media, maintained in electronic media, or transmitted or maintained in any other form or medium.

[Public Health Service \(PHS\)](#) means the unit within the Department of Health and Human Services that includes the Office of Public Health and Science and the following Operating Divisions: Agency for Healthcare Research and Quality, Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Food and Drug Administration, Health Resources and Services Administration, Indian Health Service, National Institutes of Health, and the Substance Abuse and Mental Health Services Administration, and the offices of the Regional Health Administrators.

Radiation-Emitting Device is an electrically-powered product that can emit any form of radiation on the electromagnetic spectrum. These include a variety of medical and non-medical products such as mammography devices, magnetic resonance imaging (MRI) devices, laser toys, laser pointers, liquid crystal displays (LCDs), and light emitting diodes (LEDs).

Recruitment is a component of the consent process, is the process of distributing or presenting information which describes the research project and eligibility criteria so that a prospective subject may consider enrollment.

Reliant Review is an IRB review model that allows Investigators to identify a single IRB as the “IRB of Record” for protocols conducted by any organization (or multiple organizations) while at the same time allowing each site to retain local context review and oversight. Through written contracts called “IRB Authorization Agreements (IAA)” participating institutions may allow Institution A to act as the “IRB of Record” for Institution B “Relying IRB.”

Relying IRB is an institution that cedes IRB review to an external IRB, [IRB of Record] for an instance of research, or multiple research protocols.

Research means a systematic experiment, study, evaluation, demonstration or survey designed to develop or contribute to general knowledge (basic research) or specific knowledge (applied research) relating broadly to public health by establishing, discovering, developing, elucidating or confirming information about, or the underlying mechanism relating to, biological causes, functions or effects, diseases, treatments, or related matters to be studied.

Research Records means the record of data or results that embody the facts resulting from scientific inquiry, including, but not limited to, research proposals, laboratory records, both physical and electronic, progress reports, abstracts, theses, oral presentations, internal reports, journal articles, and any documents and materials provided to HHS or an Institutional Official (IO) by a respondent in the course of the research misconduct proceeding.

Serious Injury means an injury or illness that is life threatening, results in permanent impairment of body functions or permanent damage to a body structure or necessitates medical or surgical intervention to preclude permanent impairment.

Serious Noncompliance occurs when an action or omission in the conduct or oversight of research involving human subjects that affects the rights and welfare of research participants, increases risks to research participants, decreases potential benefits or compromises the integrity or validity of the research. **Examples** of serious noncompliance include but are not limited to:

- *exposing research subject’s to a significant risk of substantive harm;*
- *conducting research involving human subjects without IRB approval;*
- *compromising the privacy and confidentiality of research subject’s;*
- *causing damage to scientific integrity of the research data that has been collected;*
- *engaging in willful or knowing noncompliance; (6) impacting ethical principles adversely.*

Severely Debilitating is a disease or condition 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.*

Suspension is when research on an approved protocol is partially or completely stopped pending future action by the IRB. **Examples** include:

- *an unanticipated problem in research involving greater than minimal risks to subjects or others;*
- *unexpected serious harm to subjects;*

- *or when the IRB is investigating a research protocol for possible issues of human subject noncompliance or continuing noncompliance with federal regulations, or with the determinations of the IRB.*

Systematic Investigation is an activity that is planned in advance, and that uses data collection and analysis to answer a question.

Termination is when the IRB stops permanently some or all research procedures.

Test Article is any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to FDA regulation.

Treatment IDE use of an investigational device facilitates the availability of promising new devices to desperately ill patients as early as possible before general marketing begins. Such use may occur when: (i) the patient has a serious or immediately life-threatening condition; (ii) there is no comparable or satisfactory alternative available; (iii) the device is under investigation in a controlled trial for the same use (or such trials have been complete); (iv) the Sponsor is pursuing marketing approval/clearance; (v) the Sponsor has submitted, and the FDA has approved an IDE under 21 CFR 812.36. Such use permits wide access to the device dependent upon patient need. IRB review and approval and informed consent are required.

Treatment IND during the clinical investigation of a drug, it may be appropriate to use the drug in treatment of patients not in clinical trials. Such use required FDA approval under a treatment protocol (21 CFR 312.35) or a treatment IND (21 CR 312.34), as well as IRB review and approval and informed consent.

Unanticipated Problem Involving Risk (UPIR) referring to the phrase “unanticipated problems involving risks to subjects or others” is not defined in the HHS regulations, however OHRP considers *unanticipated problems*, in general, to include any incident, experience, or outcome that meets all of the following criteria:

- Unexpected
- Related or Possibly Related to participation in the research
- Suggests that the research places subjects or others at a greater risk of harm

Ward refers to a child who is placed in the legal custody of the State or other agency, institution, or entity, consistent with applicable Federal, State, or Local Law. A court may take responsibility of the legal protection of the child and will generally stand in place of the parents to the child. Generally, this entails assuming all lawful authority to make medical and legal decisions on the child’s behalf.