Institutional Review Board (IRB) - Unanticipated Problems and Adverse Event Reporting

I. Policy Statement:

Investigators conducting research must assess events that happen to or are experienced by the research participants and possibly others as it relates to the conduct of research. Monitoring and evaluation of adverse events and unanticipated problems which may need to be reported to the IRB, sponsor and/or others is the responsibility of the Principal Investigator and involved study team members. This policy provides relevant definitions, defines reporting timelines, and outlines the process for assessment and reporting of unanticipated problems and adverse events. This Policy applies to all individuals who are involved in the conduct of research within the Trinity Health West Region and/or utilize the Trinity Health West Region Institutional Review Board for regulatory oversight in the conduct of human subject research.

Internal adverse events are those events experienced by participants enrolled in a clinical trial or clinical investigation conducted by an investigator within the Trinity Health West Region. External adverse events are those adverse events experienced by participants enrolled by investigators at other institutions engaged in a clinical trial. It is neither useful nor necessary, under the Department of Health and Human Services (DHHS) regulation at 45 CFR 46 and 21 CFR parts 56, 312, and 812, for reports of individual adverse events-- occurring in subjects at unaffiliated sites enrolled in multi-center studies be reported to local IRBs at all institutions conducting the research. Regulatory guidance states that IRBs and the local investigators are not appropriately positioned to assess the significance of individual externally occurring adverse events.

II. Definitions:

Unanticipated Problem (as defined by FDA):
In general, adverse events observed during the conduct of a study should be considered an unanticipated problem involving risk to human subjects, and reported to the IRB, only if it is:

- unexpected,
- serious, and
- would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/ exclusion criteria or including a new monitoring requirement, informed consent, or investigator's brochure).

The FDA states that only the following adverse events should be considered as unanticipated problems that must be reported to the IRB:

1. A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure.

2. A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy).
3. Multiple occurrences of an adverse event (AE) that, based on an aggregate analysis, are determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to participants (e.g., a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control). A summary and analyses of data supporting the determination is recommended and should accompany the event report.
4. An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator's brochure and hepatic necrosis is observed in study participants, hepatic necrosis would be considered an unanticipated problem involving risk participants. The FDA recommends that a notation explaining the divergence from the expected specificity or severity accompany the report.
5. A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison). The FDA recommends that a notation explaining the divergence from the expected rate accompany the report.
6. Any other AE or safety finding (e.g., based on animal or epidemiologic data) that would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human participants. The FDA recommends that an explanation of the conclusion accompany the report.

Unanticipated Problem (as defined by OHRP):
The phrase 'unanticipated problems involving risks to subjects or others' is found but not defined in the HHS regulations at 45 CFR part 46. OHRP considers unanticipated problems, in general, to include any incident, experience, or outcome that meets **all** the following 3 criteria:

1. Unexpected (in terms of nature, severity, or frequency) given:
    a. The research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; **and**
    b. The characteristics of the participant population being studied; **and**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); **and**
3. Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

An incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes to the research protocol or informed consent process/document or other corrective actions to protect the safety, welfare, or rights of participants or others.

Examples of corrective actions or substantive changes that might need to be considered in response to an unanticipated problem include:

- Changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to participants.
- Modification of inclusion or exclusion criteria to mitigate the newly identified risks.
- Implementation of additional procedures for monitoring participants.
- Suspension of enrollment of new participants.
- Suspension of research procedures in currently enrolled participants.
- Modification of informed consent documents to include a description of newly recognized risks; and,
- Provision of additional information about newly recognized risks to previously enrolled participants.

Other types of Unanticipated Problems (per OHRP):
There are other types of incidents, experiences, and outcomes that may occur during the conduct of research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems may place participants or others at increased risk of harm, but no harm occurs. These types of unanticipated problems to be reported to the IRB.

Adverse Event or Experience (as defined by FDA):
The FDA use various terms when referring to an adverse event, such as adverse effect (21 CFR 312.64), adverse experience (21 CFR 312.32), and unanticipated adverse device effect (21 CFR 812.3).

FDA regulation 21 CFR 312.32(a) defines adverse experience as: "Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related." Examples of an adverse event include an abnormal physical exam or laboratory finding.

Adverse Event (as per OHRP):
The HHS regulations at 45 CFR part 46 do not define or use the term adverse event, nor is there a common definition of this term across government and non-government entities. However, OHRP guidance contains the following definition:

"Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, 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."

Unexpected Adverse Event or Experience (as defined by FDA):
21 CFR 312.32(a) defines an unexpected adverse experience as follows: An adverse event or suspected adverse reaction is considered 'unexpected' if it is:

1. not listed in the investigator brochure or,
2. is not listed [in the investigator brochure] at the specificity or severity that has been observed; or,
3. if an investigator brochure is not required or available,

4. [if the event/experience] is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

Unexpected:
As used in the FDA definition, refers to "adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation" [FDA 21 CFR 312.32(a)].

Unexpected adverse event (as defined by OHRP):
Any adverse event occurring in one or more participants, where the nature, severity, or frequency of which is **not** consistent with either:

1. The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in:
    a. the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, **and**
    b. other relevant sources of information, such as product labeling and package inserts; **or**
2. The expected natural progression of any underlying disease, disorder, or condition of the participant experiencing the adverse event and the participant's predisposing risk factor profile for the adverse event. [Adapted from OHRP guidance which was modified from the definition of unexpected adverse drug experience in FDA regulations at 21 CFR 312.32(a)]

Examples of unexpected adverse events include the following:

- By virtue of its unexpected nature, liver failure due to diffuse hepatic necrosis occurring in a participant without any underlying liver disease would be an unexpected adverse event if the protocol-related documents and other relevant sources of information did not identify liver disease as a potential adverse event.
- By virtue of its unexpected nature, Hodgkin's disease (HD) occurring in a participant without predisposing risk factors for HD would be an unexpected adverse event if the protocol-related documents and other relevant sources of information only referred to acute myelogenous leukemia as a potential adverse event.
- By virtue of its unexpected greater severity, liver failure due to diffuse hepatic necrosis occurring in a participant without any underlying liver disease would be an unexpected adverse event if the protocol-related documents and other relevant sources of information only referred to elevated hepatic enzymes or hepatitis as potential adverse events related to the procedures involved in the research.
- By virtue of greater specificity, cerebral thromboembolism and cerebral vasculitis would be unexpected if the investigator brochure listed only cerebral vascular accidents.

Expected adverse events that do not meet the first criterion for an unanticipated problem under the OHRP definition do not need to be reported. In general, most adverse events occurring in the context of research are expected in light of HHS regulations 45 CFR part 46.103(a) and 46.103(b)(5):

1. the known toxicities and side effects of the research procedures;

2. the expected natural progression of participants' underlying diseases, disorders, and conditions; **and**
3. participants' predisposing risk factor profiles for the adverse events.

Serious Adverse Event or Experience (as defined by FDA):
A serious adverse event or serious suspected adverse reaction is defined in consideration of the identification of an adverse event. The adverse event is considered *serious* if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death,
- a life-threatening adverse event,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- or a congenital anomaly/birth defect.

In addition, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the [participant] and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious Adverse Event (as defined by OHRP):
Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- Results in death.
- Is life-threatening (places the participant at immediate risk of death from the event as it occurred).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in a persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect; or

Any other adverse event that, based upon appropriate medical judgment, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition Examples of such events include:

- allergic bronchospasm requiring intensive treatment in the emergency room or at home,
- blood dyscrasias or convulsions that do not result in inpatient hospitalization, or
- the development of drug dependency or drug abuse [modified from the definition of serious adverse drug experience in FDA regulations at 21 CFR 312.32(a)].

Unanticipated Adverse Device Effect (UADE) (as defined by FDA):
A medical device is any item that is used for the diagnosis, treatment, or prevention of a disease, injury, or other condition and is **not** a drug or biologic. The investigational device exemption (IDE) regulations define an Unanticipated Adverse Device Effects (UADE) as:

1. any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or
2. any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" [21 CFR 812.3(s)].

Device User Facilities:
A "device user facility" is a hospital, ambulatory surgical facility, nursing home, outpatient diagnostic facility, or outpatient treatment facility, which is not a physician's office. User facilities must report a suspected medical device related death or medical device related injury to both the FDA and the manufacturer.

Adverse Event Causality Assessment Definitions:

OHRP:

Possibly Related to the Research:
There is a reasonable possibility that the adverse event, incident, experience, or outcome may have been caused by the procedures involved in the research.

FDA:

Relationship Term	Relationship Explanation	Relationship Definition
Definitely	The adverse event is ***clearly related*** to the study drug/device/intervention.	The event has a sequential relationship to the administration of the drug, device, and/or intervention, follows known pattern of response, and no alternative cause is present.
Probably	The adverse event is **likely related** to the study drug/device/intervention.	The event has a sequential relationship to the administration of the drug, device, and/or intervention, follows a known or suspected pattern of response, but an alternative cause may be present.
Possibly	The adverse event ***may be related*** to the study drug/device/intervention.	The event has a sequential relationship to the administration of the drug, device, and/or intervention, follows a suspected pattern of response, but an alternative cause is present**.**
Unlikely	The adverse ***event is probably not related*** to the study drug/device/ intervention.	The event has a sequential relationship to the administration of the drug, device, and/or intervention, but follows no known or suspected pattern of response, and an alternative cause is present.

Relationship Term	Relationship Explanation	Relationship Definition
Not Related	The adverse **event is clearly not related** to the study drug/device/intervention.	The event has a sequential relationship to the administration of the drug, device, and/or intervention, but follows no known or suspected pattern of response, and an alternative cause is present.

III. Equipment: None

IV. Procedure PI Expectations:

A. Responsibility

Investigators are required to report promptly "to the IRB… all unanticipated problems involving risks to human subjects or others," including adverse events that would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or investigator's brochure) [§56.108(b)(1), §312.53(c)(1)(vii), and 312.66].

B. Reporting Requirements: <u>INTERNAL</u> Unanticipated Problems and Adverse Events for FDA regulated research involving drugs and/or biologics.

1. The following internal adverse events and/or experiences must be reported to the IRB when the event is found to be:
   a. Unexpected, and
   b. Serious, and
   c. Possibly, Probably, or Definitely due to the study intervention, drug, or device.
2. Investigators are required to report promptly "to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect **<u>immediately</u>** [§ 312.64(b)]".
3. Participant deaths that are anticipated or expected due to disease progression should be reported at continuing review or study closure, whichever comes first.

C. Reporting Requirements: <u>EXTERNAL</u> Unanticipated Problems and Adverse Events for FDA regulated research involving drugs and/or biologics.

1. As per the Department of Health and Human Services (DHHS) regulation at 45 CFR 46 and 21 CFR parts 56, 312, and 812, **it is neither useful nor necessary for reports of individual adverse events-- occurring in subjects at unaffiliated sites enrolled in multi-center studies be reported to local IRBs** at all institutions conducting the research.
2. Regulatory guidance states that IRBs and the local investigators are not appropriately positioned to assess the significance of individual externally occurring adverse events.

D. Reporting Requirements: <u>INTERNAL</u> Unanticipated Problems and Adverse Events for FDA regulated research involving devices:

1. All unanticipated serious problems or effects associated with a device (UADEs) must be reported by the PI to the sponsor and the IRB.
2. Internal events that are serious and either anticipated or not/probably not related to the study must be reported at continuation or study closure, whichever occurs first.

3. Do not report any event that occurred during data collection or analyses (that is after treatment and follow up has concluded).

E. Reporting Requirements: <u>EXTERNAL</u> Unanticipated Problems and Adverse Events for FDA regulated research involving devices.

1. External events reported to the PI in an Action Letter or other communication from the sponsor that requires a change to the informed consent, protocol, or investigator brochure due to a new risk or a change in the risk/benefit ratio must be reported to the IRB within a timely manner of knowledge using the Amendment form found within IRB Manager. (include any supporting documentation available, i.e., updated protocol, consent, IB).
2. See above C.1.

F. Reporting Requirements: Unanticipated Problems and Adverse Events for OHRP regulated research.

1. All internal adverse events or experiences that are unanticipated problems (including incidents, experiences, or outcomes) that meet the following criteria must be promptly reported to the IRB:
   a. Unexpected
   b. Relared or possibly related to participation in the research, and
   c. suggests that the research places the participants or others at a greater risk of harm than was previously known or recognized,
2. Events that involve social or economic harm instead of physical or psychological harm are also reported.
3. In other cases, unanticipated problems may place participants or others at increased risk of harm, but no harm occurs. These types of unanticipated problems are not adverse events but must be reported under the HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).
4. Participant deaths that are anticipated or expected due to disease progression at continuation or study closure, whichever occurs first.
5. Internal events that are serious or cause greater risk of harm than was previously known and either anticipated and are **not/probably not related to the study** must be reported at continuation or study closure, whichever occurs first.

G. Summary of Reporting Requirements and Timelines

Investigators are expected to notify the IRB of any internal unanticipated problems or adverse events involving risks to participants or others that occur in research according to the following table:

Event	Reporting Expectation	Reporting Procedure
Adverse event or unanticipated problem that is: ➢ internal and ➢ unexpected in nature, severity, or frequency and ➢ possibly/probably/definitely related to the study, **and either:** ➢ serious (for FDA regulated study) or ➢ suggests greater risk of harm than known or serious (for OHRP regulated study)	1) Must be reported within **3 business days** of the knowledge of the event or as dictated by the protocol. 2) Summary information must be provided at continuing review or study closure, whichever occurs next or be available for IRB review.	**Adverse Event and Unanticipated Problem Form** within IRB Manager. **Continuing Review** or **Study Closure Form** within IRB Manager.
Adverse event or unanticipated problem that is: ➢ **external and results in a change** to the informed consent, protocol, or investigator brochure, **and** ➢ unexpected in nature, severity, or frequency, **and** ➢ possibly/probably/definitely related to the study, **and either:** ➢ serious (for FDA regulated study) or ➢ suggests greater risk of harm than known or serious (for OHRP regulated study).	Report these external events to the IRB **within 5 business** days of knowledge.	**Amendment Form** within IRB Manager (including action letter or summary/rationale of changes).

Participant death that is: ➢ internal **and** ➢ unanticipated **and,** ➢ possibly, probably, or definitely related to the study	1) Must be reported to the IRB within 24 hours of the knowledge of the death either by email, phone, or fax. 2) A signed Adverse Event form must be received by the IRB **within 5 business days** of knowledge of the event. 3) Summary information must be provided at continuing review or study closure, whichever occurs next or be available for IRB review.	**Internal Adverse Event and Unanticipated Problem Form** within IRB Manager. Consider need to log the event in to the Hospital **VOICE system** when applicable. **Continuing Review or Study Closure form** within IRB Manager.
Participant death that is: ➢ internal **and,** ➢ anticipated **or,** ➢ due to disease progression **or** ➢ not related or unlikely related or not a greater risk of harm than was previously known (if OHRP regulated).	Report to the IRB at continuing review or study closure, whichever occurs first.	**Continuing Review or Study Closure Form** within IRB Manager. Do **not** report via an Internal Adverse Event and Unanticipated Problem for
Event that is: ➢ anticipated **or** ➢ unlikely to be related or not serious **or** ➢ not a greater risk of harm than was previously known (if OHRP-regulated).	Report to the IRB at continuing review or study closure, whichever occurs first.	**Continuing Review or Study Closure Form** within IRB Manager. Do **not** report via an Internal Adverse Event and Unanticipated Problem for

For device studies, **PI report of an Unanticipated Adverse Device Effect (UADE**) that is: ➢ unanticipated ➢ serious problem or effect associated with a device	1) **Deaths** - notify IRB **within 24 hours** of knowledge of death and using the Adverse Event and Unanticipated Problem Form within IRB Manager. 2) Report to IRB within **5 business days.** Updates may need to be submitted, such as cause of death, attribution, etc. 3) **UADEs that were not fatal: report as soon as possible,** but in no event later than **10 business days** after the investigator first learns of the event [21 CFR 812.150(a) (1)] 4) Per the FDA, **Sponsors** must immediately conduct an evaluation of a UADE and **must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators** within **10 business days** after the sponsor first receives notice of the effect [21 CFR 812.46(b), 21 CFR 812.150(b)(1)]. 5) Sponsors who determine that an unanticipated adverse device effect presents an unreasonable risk to participants will terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination must occur no later than **5 working days** after the sponsor makes the determination and no later than **15 working days** after the sponsor first received notice of the effect [21 CFR 812.46(b(2)]. 6) Terminated studies require FDA and IRB approval to resume [see 21 CFR 812 for more details]. 7) Summary information must be provided at continuing review or study closure, whichever occurs next or be available for IRB Review.	Report to the: ➢ sponsor and ➢ THWR IRB **Internal Adverse Event and Unanticipated Problem Form** within IRB Manager. Consider need to log the event in to the Hospital **VOICE system** when applicable. Letter from the sponsor to the PI and forward it to the IRB. **Continuing Review or Closure Form** within IRB Manager.
For device studies where the hospital (which is not a physician's office) is a **Device User Facility**, the PI or hospital must report: ➢ participant deaths that are suspected to be medical device-related* ➢ participant serious injuries that are suspected to be medical device-related* *You are not required to evaluate or investigate the event by obtaining or evaluating information that you do not reasonably know.	Per 21 CFR 803.30: 1) Report participant death within **10 business days** of becoming aware of information, from any source, that reasonably suggests* that a device has or may have caused or contributed to a participant death at this facility to: ➢ FDA ➢ manufacturer of the device 2) Report participant serious injury within **10 business days** of becoming aware to the: ➢ manufacturer (or to FDA if manufacturer is unknown). 3) Annual summary of death & serious injury reports sent to the FDA by **January 1** for the preceding year	Form FDA 3500A See FDA Guidance document: Medical Device Reporting for User Facilities at: Medical Device Reporting for User Facilities | FDA Form FDA 3419
Action Letters-from sponsors	As soon as feasible so that participants can be informed of new information should it include changes to the informed consent, investigator brochure, and/or protocol.	**Amendment Form** within IRB Manager

H. How to Report Unanticipated Problems and Adverse Events to the IRB

The investigator must complete an Internal Adverse Event and Unexpected Problem Form within IRB Manager for all reportable, internal adverse events and unexpected problems that affect participants or others; **and** all Unanticipated Adverse Device Effects (device studies); as directed in this policy and described in the prior table.

The report must contain enough information to allow the IRB to judge the impact on the overall risk/benefit ratio. Any corrective action or anticipated substantive change should be included on the form.

All adverse events and unanticipated problems that have occurred since the last continuing review, regardless of whether they have been previously reported, must be reported in summary at continuing review or at study closure, whichever occurs next.

V. Procedure: IRB Review of Unanticipated Problems and Adverse Events

All reportable internal adverse events and unanticipated problems and Unanticipated Adverse Device Effects (device studies) are reviewed by the IRB at a full board convened meeting.

A. During the meeting, the IRB considers and determines whether:

1. The conditions under which the research was initially approved have not been altered.
2. The risks to participants are still minimized and reasonable in relation to the anticipated benefits, if any, and also in relation to the importance of the knowledge that may result from the research.
3. Whether the research may continue or needs to be revised because of the impact of the adverse event, unexpected problem, or Unanticipated Adverse Device Effects (device studies.
4. A revision of the consent and/or protocol is required and to what extent rereconsenting and/or participant notification regarding the new information is warranted.
5. The IRB may also require notification to current research participants of the risk of the event and/or revision of the informed consent document.

B. IRB Action

The investigator is notified in writing of the IRB's determinations, even if no further action is necessary, and as applicable, the correspondence will indicate if there was a change in continuing review cadence from the initial approval.

VI. Reporting Adverse Events, Unanticipated Problems and Unanticipated Adverse Device Effects to Institutional Officials and Governmental Authorities

A. When to Report

The IRB Chairperson or his/her designee is responsible for providing prompt written notification to the Trinity Health West Region Institutional Official and to relevant federal agencies including OHRP (regardless of the source of funding) and/or FDA as applicable, of any serious adverse event or serious unanticipated problem involving risks to participants or others that:

1. occur in local participants and
2. changes the risk/benefit determination, and
3. causes the IRB to halt the research as per 21 CFR 56.108(b)(1) and 45 CFR 46.103(a) & (b)(5).

B. Timing of reporting

1. More serious events should be reported promptly. Per OHRP guidance, the requirements for prompt reporting may be met by submitting a preliminary report to the IRB, appropriate institutional officials, the supporting HHS agency head (or designee), and OHRP, with a follow-up report submitted at a later date, when more information is available.

2. Other events should be reported within one month of the IRB's receipt of the report of the problem from the investigator (OHRP guidance).

C. Unanticipated Adverse Device Effects

Per the FDA, Sponsors must immediately conduct an evaluation of Unanticipated Adverse Device Effects and must report the results of the evaluation to the FDA, all reviewing IRBs, and participating investigators within 10 business days after the sponsor first receives notice of the effect (21 CFR 812.46(b), 812.150(b)(1))

VII. Ministry Specific Related Addendums, Procedures, and/or Policies:

A. Saint Agnes Medical Center: None

B. Saint Alphonsus Health System: None

VIII. Additional Approval: Not applicable.

VII: References:

Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs — Improving Human Subject Protection, FDA, January 2009: Adverse Event Reporting to IRBs — Improving Human Subject Protection | FDA

Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events: OHRP Guidance (2007): Unanticipated Problems Involving Risks & Adverse Events Guidance (2007) | HHS.gov

Reporting Incidents to OHRP (2022): Reporting Incidents | HHS.gov