Institutional Review Board Procedure No. 23

EFFECTIVE DATE: ***August 25, 2022***

PROCEDURE TITLE:

Unanticipated Problem and Adverse Event Reporting

To be reviewed every three years by:
Institutional Review Board

REVIEW BY: ***August 24, 2025***

PROCEDURE

This Procedure implements the requirements of Institutional Review Board Policy No. 1 *Authority of the Institutional Review Board,* which requires the Trinity Health Mid-Atlantic (THMA) Institutional Review Board (IRB) establish policies and procedures to ensure that the THMA's IRB operations fully comply with applicable laws, regulations, professional standards, and the *Ethical and Religious Directives for Catholic Health Care Services*, including promoting the conduct of ethical and compliant research.

SCOPE

Only a small subset of adverse events (AE) occurring in human participant research are unanticipated problems (UP) that must be reported under 45 CFR 46; 21 CFR 310, 312, or 803. The reporting and review of unanticipated problems and adverse events should occur in a timely, meaningful way so that human participants will be better informed of and protected from risk.

Definitions and Examples

Food and Drug Administration (FDA) regulated studies are any experiments that involve a test article (i.e., investigational drug, device, biologic, vaccine) and one or more human participants, and either meets requirements for prior submission to FDA under 505(i) or 520(g), or does not meet these requirements, but results are intended to be submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit.

Studies not under the purview of the FDA should follow the Office of Human Research Protections (OHRP) regulations. Some studies may be regulated by both the FDA and OHRP.

See the Addendum that follows this policy for the definition of the terms that appear in this policy.

I. Reporting of Internal Unanticipated Problems and Adverse Events to the IRB

A. What to Report

Investigators must assess events that occur with participants and others to determine which adverse events are unanticipated problems that need to be reported to the IRB, sponsor and/or others.

Internal adverse events or unanticipated problems are those events experienced by participants enrolled by an investigator at THMA. FDA and OHRP regulations differ in their application to research studies.

FDA Regulated Studies:

Do report promptly all ***internal*** adverse events or experiences (drugs and biologics; see devices below) to the IRB that are:

- ***unexpected***
- ***serious and***
- ***possibly, probably or definitely due to the study intervention, drug or device***.

See the definition section for full definitions. 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 immediately [§ 312.64(b)]".

Do report all *internal* unanticipated problems (drugs and biologics; see devices below) to the IRB involving risks to participants or others: Investigators are required to report promptly "to the IRB… all unanticipated problems involving risks to human subjects or others," including adverse events that should be considered unanticipated problems [§56.108(b)(1), §312.53(c)(1)(vii), and 312.66]. In general, an adverse event observed during the conduct of a study should be considered an unanticipated problem involving risk to human participants, and reported to the IRB, only if it were 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).

However, at THMA participant deaths that are anticipated or expected due to disease progression should be reported at continuing review or closure, whichever comes first.

Do report all *internal* Unanticipated Adverse **Device** Effects (UADE): All unanticipated serious problem or affect associated with a device (UADEs) must be reported by the PI to the sponsor and the IRB. See definition section for a full definition.

Do NOT report adverse events or experiences that are *anticipated or expected*, *unless*:
Most individual adverse events do not meet the criterion of being unexpected and do not need to be reported under FDA regulations (see definition of FDA regulated

research above). Do not report any event that did not occur during the study (data collection timeframe).

However, at THMA *do report*:

- Participant deaths that are anticipated or expected due to disease progression must be reported at continuation or closure, whichever occurs first.
- 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 *THMA Modification Form* (include any supporting documentation available, i.e. updated protocol, consent, IB).
- All external events are not required to be submitted, however if the sponsor requires that they be submitted, do so in summary form at continuing review (or as soon as received after this point if not available at continuing review) or closure, whichever occurs first.

OHRP regulated studies:

Do report promptly all internal adverse events or experiences that are unanticipated problems:
All unexpected problems should be reported. For studies that are *OHRP* regulated this means an incident, experience, or outcome that is:

- ***unexpected,***
- ***related or possibly related*** to participation in the research, ***and***
- suggests that the research places the participants or others at a **greater *risk* of harm** than was previously known or recognized

See definition section for full definitions.

Do report all internal unanticipated problems that are *not* adverse events or experiences:
Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems 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 46.108(a)(4)(i).

Do NOT report adverse events or experiences that are anticipated or expected (anticipated problems) ***unless:***
Most individual adverse events do not meet the first criterion for an unanticipated problem (unexpected) and do not need to be reported under OHRP regulations 45 CFR part 46.108(a)(4)(i). See definitions in the addendum to this policy.
However, at THMA *do report*:

- Participant deaths that are anticipated or expected due to disease progression must be reported at continuation or closure, whichever occurs first.
- External events that result in changes to key documents (such as the informed consent, investigator brochure, protocol, etc.) must be reported to the IRB within a timely manner of knowledge by submitting the Action Letter from the sponsor and/or any communication that requests these changes via a *THMA Modification Form*.
- All other external events are not required to be submitted, however if the sponsor requires that they be submitted, do so in summary form at continuing review (or as soon as received after this point if not available at continuing review) or closure, whichever occurs first.

A. When to Report

Investigators are to notify the IRB of any internal unanticipated problems or adverse events involving risks to participants or others that occur in research conducted under the purview of the THMA IRB according to the following schedule:

What	When	How
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*)	Must be reported within **3 business days** of the knowledge of the event or as dictated by the protocol.	IRBManager – *THMA AE/UP Form*
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***	Report these external events to the IRB within **5 business days** of knowledge.	IRBManager – *THMA Modification Form* plus the Action Letter or other communication that required the changes.

suggests greater *risk* of harm than known *or* serious (*for OHRP regulated study*).		
Participant death that is: ✓ internal *and* ✓ ***un*anticipated** *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 or phone. 2. A *THMA AE/UP Form* must be received by the IRB within **5 business days** of knowledge of the event.	1. Email or phone 2. IRBManager – *THMA AE/UP Form*
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 closure, whichever occurs first.	IRBManager – *THMA Continuing Review* or *Study Close-Out Report form* *Do **not*** report via a *THMA AE/UP Form*
For <u>device studies</u>, PI report of a **Unanticipated Adverse Device Effect** (UADE) that is: ✓ unanticipated ✓ serious problem or affect ✓ associated with a device to the: • sponsor ***and*** • THMA IRB	1. **Deaths-** notify IRB within **24 hours** of knowledge of death and submit a *THMA AE/UP Form* to IRB within **5 business days**. Updates may need to be submitted, such as cause of death, attribution, etc. 2. **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)] 3. Per the FDA, <u>Sponsors</u> must immediately conduct an evaluation of a UADE and <u>must report the results of the evaluation to FDA</u>, <u>all reviewing IRBs, and participating investigators</u> within **10 business days** after the sponsor first receives notice of the effect [21 CFR 812.46(b), 21 CFR 812.150(b)(1)]. 4. Sponsors that 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 <u>5 working days</u> after the sponsor makes the	IRBManager – *THMA AE/UP Form* IRBManager – *Study Close-Out Report form*

	determination and no later than 15 working days after the sponsor first received notice of the effect [21 CFR 812.46(b(2)]. Terminated studies require FDA and IRB approval to resume [see 21 CFR 812 for more details].	
What	**When**	**How**

B. How to Report

1. **Reporting internal adverse events and unexpected problems**
   The investigator must complete a *THMA AE/UP Form* for all reportable, internal adverse events and unexpected problems; and all Unanticipated Adverse Device Effects (device studies); as directed in the grid above. The form is located in IRBManager. The report must contain a sufficient amount of 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.

2. **Changes to the research:** Any proposed changes to a research study in response to an adverse event or unexpected problem must be reviewed and approved by the IRB before being implemented, except when necessary to eliminate apparent immediate hazards to participants.

II. Reporting of External Adverse Events and Unanticipated Problems to the IRB

The THMA IRBs follow the OHRP and FDA guidelines advising that:

> "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 [external adverse events] – to be distributed routinely to local investigators or local IRBs at all institutions conducting the research".

Both guidelines state that IRBs and the local investigators are not appropriately positioned to assess the significance of individual external adverse events. The THMA IRB follows these guidelines and does not accept submissions of external adverse events that relate to events occurring with participants at research sites other than THMA or a THMA-affiliate site.

Action letters: Action letters or investigator alerts require prompt submission to the IRB. Action letters or investigator alerts are typically reviewed via the expedited method.

III. IRB Review Process

All *reportable* internal adverse events and unexpected problems and Unanticipated Adverse Device Effects (device studies) are reviewed by the IRB at full board IRB convened meeting. The IRB considers and determines:

- The conditions under which the research was approved have not been altered.
- Whether 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.
- Whether, as a result of the impact of the adverse event or unexpected problem or Unanticipated Adverse Device Effects (device studies), the research will be permitted to continue as proposed or whether changes are required,
- Whether a revision of the consent and/or protocol is required and to what extent re-consenting and/or participant notification regarding the new information is warranted.
- The IRB may also require notification of current research participants of the risk of the event and/or revision of the informed consent document.

The investigator is notified in writing of the IRB's determinations, even if no further action is necessary, and if the continuing review should be conducted more frequently than stipulated at initial approval.

IV. Reporting of Adverse Events and Unexpected Problems and Unanticipated Adverse Device Effects to Officials

The IRB Chairperson or his/her designee is responsible for providing prompt written notification to Trinity Health Mid-Atlantic's Institutional Official and to relevant federal agencies including OHRP and/or FDA **as applicable,** of any *serious adverse event* or *serious unanticipated problem* involving risks to participants or others that occur in local participants and change the risk/benefit determination which causes **the IRB to halt the research as** per 21 CFR 56.108(b)(1) and 45 CFR 46.103(a) & (b)(5).

More serious events should promptly be reported; other events within one month of the IRB's receipt of the report of the problem from the investigator (OHRP guidance). 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.

Unanticipated Adverse Device Effects (device studies) must also be reported, as indicated in the reporting grid, above. Per the FDA, Sponsors must immediately conduct an evaluation of an 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)).

RESPONSIBLE DEPARTMENT

Further guidance concerning this Procedure may be obtained from the Trinity Health Mid-Atlantic Institutional Review Board.

APPROVALS

Initial Approval: August 25, 2022

Subsequent Review/Revision(s):

Definitions and Examples Addendum

The following section provides detailed definitions and examples of each of the terms that appear in the federal regulations under FDA and OHRP. Terms that are defined include:

1) **Unanticipated Problem** (UP; including those that are not adverse events; OHRP & FDA)
2) **Adverse Event or Experience** (AE; including internal and external; OHRP & FDA)
3) **Unexpected Adverse Event or Experience** (OHRP & FDA)
4) **Serious Adverse Event or Experience** (SAE; OHRP & FDA)
5) **Unanticipated Adverse Device Effect** (UADE; FDA)
6) **Adverse Event Causality Assessment Definitions** (OHRP & FDA)

FDA regulated studies are any experiment that involves a test article (i.e., investigational drug, device, biologic, vaccine) and one or more human participants, and either meets requirements for prior submission to FDA under 505(i) or 520(g), or does not meet these requirements, but results are intended to be submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit.

Studies not under the purview of the FDA should follow the **OHRP regulations**. Some studies may be regulated by both the FDA and OHRP.

1) Unanticipated Problem

The FDA's definition of an unanticipated problem:
(as per *Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs — Improving Human Subject Protection*, FDA, January 2009):
"In general, an 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 were 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). An individual adverse event occurrence ***ordinarily*** does not meet these criteria because, as an isolated event, its implications for the study cannot be understood. The FDA believes that only the following adverse events should be considered as ***unanticipated problems*** **that must be reported to the IRB**:

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).

- 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).
- Multiple occurrences of an adverse event (AE) that, based on an aggregate analysis, is 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). We recommend that a summary and analyses supporting the determination accompany the report.
- 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 discussion of the divergence from the expected specificity or severity accompany the report.
- 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 discussion of the divergence from the expected rate accompany the report.
- 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."

OHRP guidance definition of an unanticipated problem:

As stated in **OHRP's Guidance** (Office of Human Research Protections): "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** of the following 3 criteria:

a) Unexpected (in terms of nature, severity, or frequency) given:
   (1) The research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; **and**
   (2) The characteristics of the participant population being studied; **and**
b) 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**
c) 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."

Only a small subset of adverse events occurring in human participants research will meet the three criteria for an unanticipated problem. An incident, experience, or outcome that meets

the three criteria above generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order 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.

Unanticipated problems that are not adverse events (OHRP):
There are other types of incidents, experiences, and outcomes that occur during the conduct of human participant 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 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).

2) Adverse Event or Experience

FDA regulation definition:
The FDA regulations use different 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.

OHRP guidance definition:
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, in OHRP guidance the term *adverse event* is used very broadly and includes any event meeting 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.

Modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice".

Adverse events under the OHRP definition 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.

In the context of multicenter clinical trials, adverse events are characterized as either *internal adverse events* or *external adverse events*:

Internal adverse events are those adverse events experienced by participants enrolled by an investigator at THMA or affiliate.

External adverse events are those adverse events experienced by participants enrolled by investigators at other institutions engaged in the clinical trial. In the context of a single-center clinical trial, all adverse events would be considered *internal adverse events.*

3) Unexpected Adverse Event or Experience

The FDA regulations 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:

a) not listed in the investigator brochure or
b) is not listed [*in the investigator brochure*] at the specificity or severity that has been observed; or
c) if an investigator brochure is not required or available,
d) [*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 also 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)].

OHRP guidance defines an *unexpected adverse event* as follows:
Any adverse event occurring in one or more participants; the nature, severity, or frequency of which is **not** consistent with either:

a) The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in:
   (i.) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, ***and***
   (ii.) other relevant sources of information, such as product labeling and package inserts;
   or
b) 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)]

In general, the majority of adverse events occurring in the context of research are ***expected*** in light of:

a) the known toxicities and side effects of the research procedures;
b) the expected natural progression of participants' underlying diseases, disorders, and conditions; and
c) participants' predisposing risk factor profiles for the adverse events.

Thus, most individual adverse events do not meet the first criterion for an unanticipated problem under the OHRP definition and do not need to be reported under the HHS regulations 45 CFR part 46.103(a) and 46.103(b)(5).

Examples of *unexpected* adverse events under both definitions 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.

Examples of *expected* adverse events under both definitions include:

- Prolonged severe neutropenia and opportunistic infections occurring in participants administered an experimental chemotherapy regimen as part of an oncology clinical

trial, where the protocol-related documents described prolonged severe neutropenia and opportunistic infections as common risks for all participants.

4) <u>Serious Adverse Event or Experience</u>:

<u>FDA regulation</u> 21 CFR 312.32(a) defines a *serious adverse event* or *serious suspected adverse reaction* as follows:

> "An adverse event or suspected adverse reaction 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."

Per the FDA regulation, "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".

<u>OHRP guidance</u> similarly defines ***"serious adverse event"*** as:
"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)]."

5) <u>Unanticipated Adverse Device Effect (UADE):</u>
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.

FDA: The investigational device exemption (IDE) regulations define an Unanticipated Adverse Device Effects (UADE) as:

> "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 any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" [21 CFR 812.3(s)].

6) 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		**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.
Not Related	The adverse event ***is clearly not related*** to the study drug/device/intervention.	The event has no sequential relationship to the administration of the drug, device and/or intervention, follows no known response or suspected pattern of response, and an alternative cause is present.