1. PURPOSE

The purpose of this procedure is to establish the reporting requirement of reportable new information, which includes Unanticipated Problems (UPs), serious adverse events (SAE), and adverse events (AE) involving risks to participants or others. This procedure also establishes the process to determine which events involve risks to participants and others, and which events are reportable to the IRB.

2. PROCEDURE

Federal regulations (21 CFR 56.108(b)(1) and 45 CFR 46.108) require the IRB to ensure that PI promptly report "any unanticipated problems involving risks to human subjects or others." It is important to delineate the definitions that form reporting requirements to prevent confusion and improper reporting. In particular, it is important to understand the difference between "adverse events" (AE) and "unanticipated problems" (UP) because many AEs are not reportable. OHRP and FDA have issued guidance that clarifies what should be reported to the IRB, and this policy is based on that guidance. The federal guidance clarifies that PI need only report UPs. AEs that are not UPs are not required to be reported to the IRB.

Refer to SOP 412 for Review of Non-Reportable Events

3. DEFINITIONS:

Adverse Event: An undesirable and unintended event as a result of therapy or other intervention (ex: headache following spinal tap or intestinal bleeding associated with aspirin therapy)

Or

Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (ex: abnormal physical exam or laboratory finding) symptom or disease, temporally associated with the human subjects participation in the research, whether or not considered related to the human subjects participation in the research (Office of Human Research Protections – OHRP).

Or

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

- **External adverse event**: From the perspective of one particular institution engaged in a multicenter clinical trial, *external adverse events* are those adverse events experienced by human subjects enrolled by PI *at other institutions* engaged in the clinical trial.

- **Internal adverse event**: From the perspective of one particular institution engaged in a multicenter clinical trial, *internal adverse events* are those adverse events experienced by human subjects enrolled by the PI(s) at that institution. In the context of a single-center clinical trial, all adverse events would be considered *internal adverse events.*

Serious Adverse Event: Any untoward medical occurrence temporally associated with a human subject's participation in research that meets any of the following criteria:

- results in death, if related or possibly related to the research;
- is life threatening (places the subject at immediate risk of death from the event as it occurred);
- requires or prolongs hospitalization;
- causes persistent or significant disability or incapacity;

- results in congenital anomalies or birth defects; or
- based upon an PI's medical judgment may require medical or surgical intervention to present one of the other outcomes listed in this definition (ex: allergic bronchospasm requiring intensive treatment in the emergency room or at home).

Unanticipated Problem: Any incident, experience or outcome that meets all of the following criteria:

1. Unexpected

   An event is unexpected if it occurs in one or more human subjects or others participating in a research protocol, and the event's nature, severity or frequency is not consistent with either:
   - 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 PI brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
   - the expected natural progression of any underlying disease, disorder, or condition of the human subject(s) experiencing the adverse event and the human subject's predisposing risk factor profile for the adverse event.

2. Related or possibly related

   Events that are related, or possibly related, to participation in the research may be caused by one or more of the following:
   - The procedures involved in the research;
   - An underlying disease, disorder or condition of the subject; and/or
   - Other circumstances unrelated to the research or any underlying disease, disorder or condition of the subject.

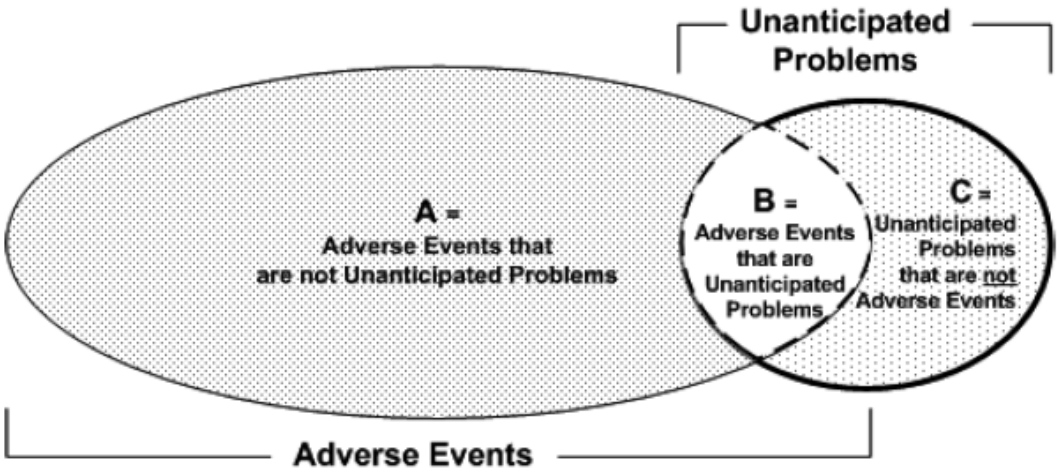
   In general, events that are determined to be at least partially caused by the procedures in a study would be considered related to participation in the research, whereas events determined to be solely caused by the subject's condition or state of illness or other circumstances clearly outside of the study would be considered unrelated 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.
   Not related: The experience is clearly related to other factors such as the patient's clinical state, therapeutic intervention or concomitant therapy.

3. Increased Risk (either serious or not serious)

   AEs that are unexpected, related or possibly related to participation in research, and serious are the most important subset of adverse events representing UPs, because such events always suggest that the research places human subjects or others at a greater risk of physical or psychological harm than was previously known or recognized. These events 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 subjects.

Other AEs that are unexpected and related, or possibly related, to participation in the research, but not serious, would also be UPs if they suggest that the research places human subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

The following Venn diagram summarizes the general relationship between adverse events and unanticipated problems:



Under 45 CFR part 46: Do not report A, Do report (B+C)

https://www.hhs.gov/ohrp/sites/default/files/ohrp/policy/advevntguid.pdf

4. Deciding if an event meets the criteria for an UP

Only Adverse Events that meet the criteria of an Unanticipated Problem are reportable to the IRB. The IRB relies on the Avera researcher or PI to provide an assessment of whether local UP criteria are met for a given event. (See above for explanation of the required elements to meet this definition.) As the person most familiar with, and ultimately responsible for the conduct of the study, the PI should provide his or her informed opinion of whether an event meets UP criteria. The IRB will then review the PIs assessment of the event to determine if any changes to the approved study should be made as a result of the report.

4.1 Problems and Adverse Events (AEs) (Non-reportable events):

1. For internal adverse events (AEs) that are expected and related and are consistent with the frequency and severity listed in the informed consent document, these reports do not need to be submitted to the IRB.
2. For external adverse event (AE) reports that do not require prompt reporting to the IRB, the PI should follow the internal clinical research processes. These reports do not need to be submitted to the IRB.

4.2 Reporting Unanticipated Problems

1. Local UPs: All local UPs should be reported to the IRB by using the designated IRB submission software, and provide all available information within 5 business days of the date that the study staff became aware of event.

2. SAEs do not need to be reported to the IRB, unless they meet the definition of a UP.

3. External SAEs: Individual Investigator New Drug (IND) safety reports from external sites are generally not reportable to the IRB, because their implications for the study cannot be understood. External events should not be reported to the IRB unless accompanied by an aggregate analysis that establishes their significance and a corrective action plan that addresses the problem.

4. Reports from a Data Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC) or other independent safety monitoring group should be submitted to the IRB with the annual continuation/renewal if there are no new identified risks and the study can continue as planned. Only when there are new identified risks should the report be submitted to the IRB upon receipt.

4.3 Review of the Event or Problem

The Chair or designee(s) of the IRB will review all reports of UPs. If a reported event poses serious risk to subject safety, the Chair, IRB Staff or IRB may immediately suspend the study. Any unanticipated problem involving more than minimal risk(s) to human subjects or others will be reviewed by the convened IRB. All members at the meeting will receive the report and materials describing the unanticipated problem as well as any correspondence with the PI to date.

a. UPs are evaluated by comparing information provided in the informed consent with information in the submitted UP report.

b. After primary review by the IRB designee or full board, they will recommend one of the following:

i. Concur with PI and accept report as presented; or
ii. Request additional information from the PI

c. The IRB will determine if any actions to mitigate harm to participants need to be taken. These may include any of the following:

i. Require project specific corrective action;
ii. Require a plan for corrective action, based on the type and nature of the issues;
iii. Require education of the PI and research team;
iv. Require that subjects be re-contacted and provided with updated information or consent;
v. Suspension of the research;
vi. Notification of current participants when such information might relate to participants' willingness to continue to take part in the research;
vii. Terminate the study;
viii. More frequent intervals of continuing review; and/or
ix. Other actions as determined by the IRB.

d. The determination and vote will be reported and the PI will be notified.

4.4 Notification

No further action required: If the event is determined not to be an unanticipated problem involving risks to participants or others, and/or the IRB accepts the corrective action plan, the PI will be sent notification indicating that the IRB has received the report and that no further action will be required.

Follow-up requested: If the IRB does not concur with the PI's report of the event, or requests further information, the PI will be sent a notification requesting additional information.

4.5 Prompt Reporting

IRB Staff will notify the Institutional Official of Unanticipated Problems (UPs) involving risks to human subjects or others.

The Sponsor, or study PI, will have the responsibility of notifying one or more of the following agencies of UP(s) involving risk to human subjects or others, as applicable:

- FDA, when the research is FDA-regulated;
- OHRP; and/or
- Other federal agencies when the research is overseen by those agencies, and they require reporting separate from that to OHRP.

5. RESPONSIBILITY

IRB staff or designee are responsible for initial review of reports of unanticipated problems involving risks to participants and others. All UPs will be brought to the full IRB at a convened meeting.

IRB staff or designee is responsible for notifying the Institutional Official of UPs.

IRB staff or designee is responsible for sending out notifications to the PI.

6. APPLICABLE REGULATIONS AND GUIDELINES

45 CFR 46.108
21 CFR 56.108(b)(1)
21 CFR 312.32
21 CFR 812.3(s)

REVISION HISTORY

Revision Number	Version Date	Approved By, Date Approved
02.1	07/03/2019	Avera Institutional Official 7/23/19
• Including the specific process and responsibilities the IRB has for reporting UPs, instead of having that in a separate SOP.		
02	1/28/2019	Avera Institutional Official 3/19/2019
• Further defined and explained what does need to be reported to the IRB in regards to AEs, SAEs, and UPs. • Only events that are defined as Unanticipated Problems will need to be reported to the IRB.		

• Corrected the name of the form that should be used to submit UP, since it is all electronic now. • DSMB Reports should only be submitted to the IRB at annual continuation time, instead of upon receipt, unless there are newly identified risks. • Updated applicable regulations • Removed section titled Procedures Employed to Implement This Policy with individual tasks and who is responsible for each item.			
01	August 2016	Director HSRP	August 2016