Department: **UAMS Institutional Review Board**
Policy Number: **10.2**
Section: **Principal Investigator Responsibilities**
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Subject: Unanticipated Problems Involving Risks to Participants or Others – Investigator Reporting Requirements and IRB Actions

Definitions:

1. Unanticipated Problem Involving Risks to Participants or Others: Any event that is a) Unanticipated, b) caused harm or placed a person at increased risk of harm and c) is Related to the research procedures.
2. Unanticipated: An event is "unanticipated" when it was unforeseeable at the time it occurred.
3. Serious: An event is "serious" if it involves considerable detriment or harm to one or more persons (who may or may not be participants), or required intervention to prevent one or more persons from experiencing considerable detriment or harm. Serious adverse events include
   - ●Death
   - ●Life-threatening experience – Disease or condition where the likelihood of death is high unless the course of the disease/condition is interrupted or diseases/conditions with potentially fatal outcomes where the end point of the clinical trial analysis is survival
   - ●Inpatient hospitalization or prolongation of hospitalization
   - ●Persistent or significant disability/incapacity
   - ●Congenital anomaly/birth defect in participant's offspring
   - ●Any other important medical event that, based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, the development of drug dependency or drug abuse, suicidal ideation or attempts, or the unintentional revealing of some genetic information to insurers.
4. Related: An event is "related" if more likely than not it was caused by the research activity.
5. Unexpected: An event is "unexpected" when its specificity, nature, severity or incidence are not accurately reflected in the consent form previously reviewed and approved by the IRB. Examples include a lower rate of response to treatment or a side effect that is more severe that initially expected.

6. Substantive Action by the IRB: An action taken by the IRB that materially alters the substance and meaning of a protocol, informed consent form or process, or investigator status, including, but not limited to, restriction, suspension or termination of a study or investigator participation, and actions taken to prevent future occurrence(s) of the AE in research.
7. Sponsor: One who initiates a clinical investigation but who does not actually conduct the investigation.
8. Funding Source: The industry or government sponsor and/or grant holder for a study. Examples are National Institutes of Health, pharmaceutical companies, private foundations.
9. Risk – The probability of harm or injury (physical, psychological, social or economic) occurring as a result of participation in a research study.

A. Investigator Reporting Responsibilities due either Immediately or no later than 10 days after Notification

1. The following must be reported to the IRB by the Investigator, and, except where noted, such reporting is due in ARIA no later than 10 days after the investigator's first knowledge of the event:
    a. Deaths that are Related to the research must be reported immediately upon Investigator notification (NOTE: A death due to a terminal condition of the research participant would be considered anticipated and not related to the research and therefore not reportable under this policy, UNLESS the research hastened the death. However, it would need to be accounted for at the time of the next continuing review.)
    b. Any event that in the Investigator's opinion was Serious, Unexpected and Related to the research regardless of whether participant is on or off study (Note: This would include any Unanticipated adverse device effects and both on-site and off-site adverse events that are serious, unexpected and related.)
    c. Any event that required prompt reporting, according to the protocol, to the Sponsor or to the FDA
    d. An accidental or unintentional change (protocol violation) to the IRB-approved protocol that increases risk or decreases benefit, affects the participant's rights, safety, welfare, affects the integrity of the data, or has the potential to occur again. (NOTE: Any protocol violation that does not meet this definition should be reported with the next continuing review.)
    e. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant (NOTE: For all other deviations, the Investigator must submit an modification to the IRB and receive written approval prior to implementation of any change to the protocol.)
    f. Any publication in the literature, safety monitoring report including a Data and Safety Monitoring Report, interim result or other finding

that indicates an unexpected change to the risk/benefit ratio of the research (Examples include MedWatch reports indicating a lower rate of response to a treatment than expected, or that a side effect is more frequent or severe than expected, or a publication showing that an arm of study is of no therapeutic value.)

g. A breach in confidentiality that may involve risk to a participant or others (Examples include the loss of a laptop computer on which subject identifies are stored or inadvertent loss study records)
h. Any Complaint of a participant that indicates an unanticipated risk
i. Incarceration of a participant if study was not previously reviewed with the anticipation of enrolling prisoners (NOTE: No further interactions may occur with the participant until reviewed by IRB Prisoner Representative.)
j. Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol
k. Restrictions, suspension or termination of study by the Sponsor, Principal Investigator, Funding Source, regulatory body, or institutional administration.
l. Notifications of pending audits or inquiries by external bodies (e.g. Sponsor, FDA, NCI or NIH). This includes any communication that questions the conduct of the research or suggests an impending inquiry, audit or investigation. It does not include notice of any routine monitoring visits. NOTE: The PI must inform the IRB through ARIA and provide a copy of the notification to the Office of Research Compliance.
m. Any other event which in the opinion of the investigators was unexpected, caused harm or placed a person at increased risk of harm (regardless of the seriousness of the harm) and is related to the research procedures

2. The Investigator is required to report any of the unanticipated problems listed above to the IRB even after the participant has completed the study or has withdrawn from the study until the study is closed in the IRB files.

<u>Investigator's Reporting Process for Unanticipated Problems involving Risks to Participants or Others to the UAMS IRB</u>

1. The investigator should describe the event in narrative format. Included in this narrative should be
    a. Description of the event
    b. Nature of the risk incurred
    c. Relationship of the event to the research
    d. Reasons for any deviations from the protocol or the use of any modifications not yet approved by the IRB
    e. Any required modifications to the consent or protocol

2. The narrative should be attached to the completed Local or Non-Local AE or Death form in ARIA.
3. If the study is subject to review by the CAVHS R&D Committee, the investigator should send make sure the R&D Committee receives a copy of the report and a copy of any Substantive Actions by the IRB. The R&D Committee shall be responsible for any required reporting to the Office of Research Oversight Regional Office.

IRB Chair/Designee Responsibilities- Initial Review

1. The IRB Chair or designee will review the report, all attachments, and as necessary the ARIA study file.
2. The Chair/Designee will determine and record in ARIA whether the event represents an Unanticipated Problems Involving Risk to Participants or Others as defined above.
3. If a full determination of the event cannot be made, the Chair/Designee will request additional information from the Investigator.
4. If the IRB Chair or designee determined that the event meets the definition of an unanticipated problem involving risks to participants or others, then the following actions will occur:
    a. The event will be referred to the convened IRB for action
    b. If participants are at immediate risk of harm and there is insufficient time to wait for review by the convened IRB, the Chair/Designee may immediately institute a suspension for cause or clinical hold according to IRB policy 7.9
    c. The event will then be reported according to IRB policy 2.6
5. If the IRB Chair or designee determined that the event does not meet the definition of an Unanticipated Problem Involving Risk to Participants or Others, then the Chair/Designee will acknowledge the event and approve any minor changes and the report will be placed in the notification to committee section of an upcoming agenda with no further action needed. If changes are determined to be major, the event will be acknowledged and the modifications will be placed in the updates to be reviewed by two reviewers section of an upcoming agenda.

IRB Committee Responsibilities relating to Unanticipated Problems Involving Risk to Participants or Others:

1. The Chair/Designee will attend the meeting and serve as a primary reviewer and present the Problem to the Committee in sufficient detail to allow Committee to take appropriate actions. The Chair may assign a secondary reviewer(s). All reviewers will have access to the reported event in order to follow along with report from the Chair/Designee, and as applicable secondary reviewer.
2. The IRB will take one of the following actions:

a. Accept the report
b. Accept the report, but require changes to the protocol and or the informed consent documents to address the changes in risk/benefit potential
c. Request re-consent of participants or require notification to participants (including past participants) of the changes. These changes must be reviewed by the IRB prior to notification
d. Request further information from the Investigator or Data and Safety Monitoring Board
e. Increase the frequency of continuing review
f. Request targeted reviews by the Office of Research Compliance or additional monitoring from an independent monitor.
g. Place a clinical hold on the study
h. Suspend the study for cause *per* IRB policy 7.9 with
    i. Suspension of recruitment
    ii. Suspension of screening and enrollment
    iii. Suspension of intervention and interaction
    iv. Suspension of follow-up
i. Terminate the study for cause
j. Reporting to the Privacy Officer if the event involved any unauthorized use, loss, or disclosure of individually-identifiable patient information.
k. Reporting to the appropriate VHA Information Security Officer if the event involved violations of VA information security requirements.

3. The IRB will also determine and record whether the event represents serious or continuing noncompliance.
4. If deviations from the protocol occurred without prior IRB review to eliminate apparent immediate hazard to a research participant, the IRB will consider whether the changes were consistent with the rights and welfare of participants.
5. If the IRB determines that the event does not meet the definition of Unanticipated Problems Involving Risks to Participants or Others then the report will be acknowledged and filed to the study file with no further actions.