Department: **UAMS Institutional Review Board**
Policy Number: **10.2**
Section: **Principal Investigator Responsibilities**
Effective Date: **July 31, 2002**
Revision Dates: **February 8, 2005; July 7, 2004; October 10, 2002**

Subject: Unanticipated Problems Involving Risks to Participants or others and Imminent Threat of Adverse Event – Investigator Reporting Requirements and IRB Actions

Definitions:

1. Unanticipated Problem Involving Risks to Participants or Others: Any event that was serious, unanticipated and related to the research
2. Unanticipated: An event is "unanticipated" when it was unforeseeable at the time it occurred. Unanticipated is not a synonym for unexpected. A researcher can monitor for an unexpected event, but cannot monitor for an unforeseen event. All unanticipated events are unexpected, but not *vice versa*.
3. Imminent Threat of an Adverse Event (AE) in Research: Any situation in which an adverse event in research has not yet occurred but is likely to occur, as determined by an IRB, research, or clinical team member, without preventative measures. Examples include potential harm to subjects due to stolen records and possible release of confidential data, or an error in research billing that puts the subject at potential financial harm. For reporting purposes, this will be treated as an Unanticipated Problem Involving Risks to Participants or Others.
4. Serious: An event is "serious" if it involves considerable detriment to one or more persons (who may or may not be subjects), or required intervention to prevent one or more persons from experiencing considerable detriment or harm.
5. Related: An event is "related: if it is likely to have been caused by the research activity
6. Unexpected: An event is "unexpected" when its specificity, nature, severity or incidence are not accurately reflected in the information previously reviewed and approved by the IRB.
7. 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. For reporting purposes, this will be treated as an Unanticipated Problem Involving Risks to Participants or Others..
8. Serious Adverse Event: Any adverse event that results in any of the following outcomes; death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event. When, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition
9. Unexpected Adverse Event: Any adverse event not specified in or not consistent with the risk information in the protocol, investigator's brochure or device manual Unexpected, as used in this definition, refers to an adverse event that has not been previously observed.

10. Sponsor: One who initiates a clinical investigation but who does not actually conduct the investigation.
11. Funding Source: The industry or government sponsor and/or grant holder for a study. Examples are National Institutes of Health, pharmaceutical companies, private foundations.

A. Unanticipated Problems Involving Risks to Participants or Others

Investigator Responsibilities

1. The UAMS IRB requires that Investigators report any unanticipated problems that may have brought risk to subjects or others involved in the study. Such reporting is due in ARIA no later than 10 days of the investigator's first knowledge of the event. The following must be reported to the IRB by the Investigator:
    a. Any event that in the Investigator's opinion was unanticipated, involved risk to participants or others and was possibly related to the research
    b. Any event that required prompt reporting, according to the protocol, to the Sponsor or to the FDA
    c. An accidental or unintentional change to the IRB-approved protocol that increases risk or decreases benefit, affects the participant's rights, safety, welfare, or affects the integrity of the data
    d. Any accidental or unintentional change to the IRB-approved protocol that has the potential to recur
    e. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant
    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
    g. Any adverse event that is both a serious adverse event and an unexpected adverse event, which in the investigator's opinion is more likely than not to be attributable to the research activity
    h. A breech in confidentiality that may involve risk to a subject or others
    i. Any independent safety monitoring reports or Data and Safety Monitoring Board Reports
    j. Any Complaint of a subject that indicates an unanticipated risk

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

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

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
2. The narrative should be attached to the completed Local or Non-Local AE or Death form in ARIA

IRB Chair/Designee Responsibilities- Initial Review

1. The IRB chair or designee will review the report within 10 days
2. Items for review will include
    a. The report and all attachments
    b. The ARIA study file
3. The Chair/Designee will determine and record in ARIA whether the event represents unanticipated problems involving risk to participants or others according to the following criteria
    a. The event is serious and represents an adverse alteration in the risk/benefit relationship of the research
    b. The event was unanticipated (not foreseeable)
    c. Relationship to the research (likely to have been caused by the research
4. If a full determination of the event cannot be made, it will be referred for placement on a committee agenda for these decisions.
5. If determined that the event met all three criteria, then it will be considered an unanticipated problem involving risks to participants or others and the following actions will occur:
    a. The event will be referred to the convened IRB for actions
    b. The event will be reported according to IRB policy 2.6
    c. 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
6. If determined that the event does not meet one or more of the three criteria, then the event will be considered not to represent an unanticipated problem involving risks to participants or others and the report will be filed to the ARIA study file and placed in the notification to committee section of an upcoming agenda with no further action needed.

IRB Committee Responsibilities when full determination cannot be made

1. The Chair/Designee will attend the meeting and serve as a primary reviewer. The Chair may assign a secondary reviewer(s).
2. The IRB will determine whether the reported event represented an unanticipated problem involving risks to subjects or others (was serious, unanticipated and related)
3. If the IRB requires additional information, it will determine the need for a clinical hold on the research until a final decision can be made.
4. If the IRB determines that the event met the criteria for unanticipated problem involving risks to subjects or others, the following actions may be taken:
    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 subjects or require notification to subjects (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 target reviews by the Office of Research Compliance or additional monitoring from an independent monitor.
g. Place a clinical hold on the study
h. Report to federal oversight bodies *per* IRB policy 2.6
i. 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
j. Terminate the study for cause and report the event per IRB Policy 2.6

5. The IRB will determine and record whether the event represents serious or continuing noncompliance
6. 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.
7. If the IRB determines that the event does not meet one or more of the three criteria, then the event will be considered not to represent an unanticipated problem involving risks to participants or others, and the report will be filed to the study file with no further actions.

B. Imminent Threat of an Adverse Event in Research

An AE in research, such as any untoward occurrence (physical, psychological, social, or economic), in a human subject participating in research can be any unfavorable or unintended event including abnormal laboratory findings, symptom, disease, or death associated with the research. An AE in research may occur even in the absence of any error or protocol deviation, and does not necessarily have to be caused by any identifiable aspect of the research.

An Imminent threat of an adverse event is any situation in which an AE in research has not yet occurred but is likely to occur, as determined by an IRB, research, or clinical team member, without preventative measures. VA requirements include the reporting of imminent threat of adverse events to the Office for Research Oversight.

Examples include the loss of a laptop computer on which subject identifies are stored, inadvertent loss or destruction of study records, problems with drug supplies or labeling, *etc*.

<u>Investigator Reporting Process for Imminent Threat of an Adverse Event</u>

The UAMS IRB requires that Investigators report any event that is a real or potential imminent threat of adverse event. Such reporting is due in ARIA within 10 days of the investigator's first knowledge of the event.

The investigator should describe the event in narrative format. Included in this narrative should be

a. Description of the imminent adverse event
b. Nature of the potential risk
c. Relationship of the imminent adverse event to the research

The narrative should be attached to the completed appropriate ARIA AE or Death form.

If the study is reviewed by the VA R&D committee, the investigator should send this group a copy of the report.

IRB Chair/Designee Responsibilities- Initial Review

1. The IRB Chair or Designee will review the report within 10 days
2. Items for review will include
    a. The report and all attachments
    b. The ARIA study file
3. The Chair/Designee will determine and record in ARIA whether the event represents an Imminent Threat of an Adverse Event according to the following criteria
    a. The likelihood an event may occur
    b. The potential seriousness of the event to the subject
    c. The need for substantive action for the convened IRB
4. If a full determination of the event cannot be made, it will be referred for placement on a committee agenda for these decisions.
5. If determined that the event if very likely to occur and is serious, the event will be referred to the convened IRB.

IRB Committee Responsibilities

1. The Chair/Designee will attend the meeting and serve as a primary reviewer. The Chair may assign a secondary reviewer(s).
2. The IRB will determine whether the reported imminent adverse event requires substantive action
3. If the IRB requires additional information, it will determine the need for a clinical hold on the research until a final decision can be made.
4. The IRB will request substantive actions to decrease the potential for the adverse event to occur and notify the Investigator.
5. The IRB may require further follow up information or investigation to assure that the risk/benefit ratio remains the same as approved for the study.
6. UAMS IRB will consider all Imminent Threats of an AE in Research or related Substantive Actions by the IRB as Unanticipated Problems and report as *per* IRB policy 2.6.