1.0 POLICY

1.1 Background.

1.1.1 Federal regulations require that organizations have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and appropriate federal officials of unanticipated problems involving risks to participants or others. These reports are necessary for investigator and institutional protection of human research participants. In some cases these reports may also be linked to allegation and investigation of investigator noncompliance, scientific misconduct, suspension, or termination.

1.1.1.1 Investigators are expected to conform to contractual and reporting requirements of various federal agencies (e.g., Department of Energy, Department of Education, Department of Justice, etc.) in their applications.

1.1.2 Key Term: Protocol Deviation. UA defines a protocol deviation as a one-time accidental or unintentional departure from the current IRB-approved protocol once a participant has been enrolled. The deviation may or may not affect participant risk and may or may not require changes to the study protocol or consent document. For example, collecting six small blood samples instead of five from a healthy participant or interviewing a participant outside of the specified time interval (say, two days late) are protocol deviations that usually do not affect participant risk or require changes to the study protocol. However, some deviations may qualify as Unanticipated Problems or Adverse Events. (See definitions below).

1.1.3 Key Terms: (Taken from OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, March 1, 2007).

1.1.3.1 In OHRP guidance the word “must” means that something is required under HHS regulations at 45 CFR 46. The word “should” means that something is recommended or suggested but not required.

1.1.3.2 Unanticipated Problems (UAPs): The phrase “unanticipated problems involving risks to subjects or others” is found but not defined in 45 CFR part 46. OHRP considers unanticipated problems, in general, to include any incident, experience, or outcome that meets ALL of the following criteria:
1.1.3.2.1 “Unexpected” in terms of nature, severity, or frequency, given (a) the research procedures described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

1.1.3.2.2 Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

1.1.3.3 **Adverse Events (AEs):** Any untoward or unfavorable occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding, 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. Although most often medical, Adverse Events include both physical and psychological harms and may occur in either biomedical or sociobehavioral research.

1.1.3.3.1 In the context of multicenter clinical trials, AEs can be divided into internal and external adverse events:

1.1.3.3.1.1 **Internal Adverse Events** are those experienced by participants enrolled by an investigator at that institution and under control of the UA IRB. The investigator typically becomes aware of the event from the subject, an on-site collaborator, or the subject’s healthcare provider. (NOTE: *In the case of a single-center clinical trial, all adverse events are considered internal.*)

1.1.3.3.1.2 **External Adverse Events** are those experienced by participants enrolled by investigators at other sites that do not fall under control of the UA IRB. The investigators at all participating sites learn of such events through reports distributed by the sponsor or the coordinating center of the multicenter clinical trial. External AEs often comprise the majority of AE reports submitted by investigators to the IRB.

1.1.3.3.2 Regardless of study type, AEs may also be expected or unexpected.

1.1.3.3.2.1 An **expected AE** is one that is consistent with the risks of procedures described in the protocol, other research-related documents (the IRB-approved protocol, investigator brochure, IRB-approved consent document) and other relevant sources of information such as product labeling or package inserts, or with the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the AE and the subject’s predisposing risk factor profile for the AE. For example, prolonged severe neutropenia and opportunistic infection occurring in subjects receiving an experimental chemotherapy regimen would be an expected
AE if the protocol documents identify these conditions as common risks for all subjects. Increased depression in a subject enrolled in a psychological study of bereavement or family caregiving for a demented elder would be an expected AE if identified as a possible risk in the protocol.

1.1.3.3.2.2 An unexpected AE is one that is NOT consistent with the above definition of an expected AE. For example, development of liver failure due to diffuse hepatic necrosis occurring in a subject without any underlying liver disease would be unusual and would be unlikely to be identified in the protocol as a potential risk.

1.1.3.3 A serious AE is one that is life-threatening (places a subject at immediate risk of death from the event) or results in death; results in hospitalization or prolongation of an existing hospitalization; results in a persistent or significant disability/incapacity or congenital anomaly or birth defect; or based on appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (e.g., allergic bronchospasm requiring intensive treatment in the emergency room or at home; development of drug dependency or drug abuse). Serious AEs are the most important subset of adverse events because they always suggest that research increases risks to subjects and routinely warrant consideration of substantive changes in the research protocol, informed consent document, or other corrective actions.

1.1.4 AEs and UAPs are related but not synonymous.

1.1.4.1 The great majority of Adverse Events are not unanticipated problems. For example, it would be anticipated that some patients with heart failure will die during a study of a new drug for heart failure or that patients in a trial of chemotherapy drugs will experience such reactions as nausea, weakness, weight loss, and anemia.

1.1.4.2 A small proportion of Adverse Events are unanticipated problems. (It would not generally be anticipated that a person without liver disease would develop liver failure.)

1.1.4.3 Unanticipated problems also include incidents, experiences, and outcomes that are not adverse events to participants. (For example, a flood that prevents an investigator from reaching the community where his research sample is located would not generally be anticipated in the research plan.)

1.1.4.4 The key question about a specific adverse event is whether it meets the three criteria described above in 1.1.3.2 for Unanticipated Problems: Is the Adverse Event unexpected? Is it related or possibly related to research participation? Does the Adverse Event suggest greater risk to participants than was previously
known of recognized? If all three questions are answered “Yes”, the Adverse Event is also an Unanticipated Problem.

1.1.4.4.1 OHRP considers “possibly related” to research participation to be an important threshold for determining whether an AE is also a UAP.

1.2 Policy Statement.

1.2.1 It is the policy of the University of Alabama that the following events be reported to the IRB:

1.2.1.1 Internal or External Adverse Events, injuries, side effects, breaches of confidentiality (such as when a laptop with identifiable data is stolen or the identity of local persons with HIV/AIDS is disclosed by a community interviewer), or other problems that occur any time during or after the research study, which in the opinion of the Principal Investigator:

1.2.1.1.1 Involve harm to one or more participants or others, or placed one or more participants or others at increased risk of harm;

1.2.1.1.2 Are related to the research procedures.

1.2.1.2 Information that indicates a change to the risks or potential benefits of the research in terms of frequency or severity. For example,

1.2.1.2.1 An interim analysis indicates that participants have a lower rate of response to treatment than initially expected;

1.2.1.2.2 Safety monitoring indicates that a particular side effect is more severe or more frequent than initially expected;

1.2.1.2.3 A paper is published from another study showing that an arm of a research study is of no therapeutic value.

1.2.1.3 A change in FDA labeling (package inserts/instructions for use) or withdrawal from marketing of a drug, device, or biological used in a research protocol.

1.2.1.4 A change in the protocol made without prior IRB review to eliminate an apparent immediate hazard to a research participant.

1.2.1.5 Incarceration of a research participant in a study not approved to enroll prisoners.

1.2.1.6 Event that requires prompt reporting to the sponsor.

1.2.1.7 Sponsor-or investigator-imposed suspension of study for risk.

1.2.1.8 Sponsor-imposed suspension of the UA investigator.

1.2.1.9 A complaint from a participant that indicates unexpected risks or a complaint that cannot be resolved by the research team.
1.2.1.10 A protocol deviation (a one-time accidental or unintentional change to the IRB-approved protocol).

1.2.1.10.1 A common protocol deviation, especially in survey research but sometimes in intervention studies, is the participation or enrollment of more subjects than was approved by the IRB. Technically, this is noncompliance and a reportable event.

1.2.1.10.2 To guard against this possibility, investigators should specify the desired number of subjects but also give a range whose upper limit is likely to cover a surprisingly high response rate.

1.2.1.11 Unanticipated adverse device effect: Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, that that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

1.2.1.12 A report from a sponsor (e.g., DSMB report).

1.2.1.13 Any fatal or life-threatening experience of research participants, whether expected or unexpected, must be reported with the following exception: After study intervention is completed, report only expected deaths that occur in the first 30 days following the last intervention.

1.2.1.14 Reports of a fatal or life-threatening experience of a research participant at any site that was “unexpected”, was a risk of participation that was not identified in the consent document, and was more likely than not caused by the research procedures.

1.2.1.15 Investigators are free to report any other event that in their judgment is desirable to report.

1.2.2 Reporting of UAPs and AEs is the responsibility not only of investigators but of others who recognize their occurrence, such as project staff. Other persons besides the PI may file and sign a report of a problem.

1.2.3 The IRB shall establish timeframes for reporting of events. Investigators who fail to report events within the established times may be subject to stricter oversight by IRB or even to charges of misconduct.

1.2.4 At this time the UA IRB shall adopt a conservative stance about reportable events and not identify events that need not be reported.

1.2.5 The Director of Research Compliance and/or the IRB shall consider the relevance of reported events for investigator and IRB education and quality improvement of the HRPP.
1.2.6 The IRB shall ensure that unanticipated problems and serious adverse events are reported to the Institutional Official, federal and non-federal sponsors, and to OHRP as appropriate.

1.2.7 Objective

1.2.8 Implementation of this policy will enable the IRBs to address unanticipated problems involving risks to research participants or others, thus protecting their welfare, and ensure that the IRBs are in compliance with sponsor requirements and federal regulations.

1.3 Responsibility.

1.3.1 The Vice President for Research is ultimately responsible for this policy. Enabling parties include the Director of Research Compliance, Research Compliance Specialists, the IRB chairs and members, and principal investigators and research staff.

2.0 PROCEDURE

2.1 Investigator Responsibilities And Actions

2.1.1 Principal Investigators and their research staffs will be aware of this policy and of the GUIDANCE: Events and Information that Require Prompt Reporting to the IRB.

2.1.2 Principal Investigators monitor the progress of their research studies, the welfare of their participants, and communications from their sponsors so that they are aware of adverse events and unanticipated events as soon as possible. (GUIDANCE: General Responsibilities of Investigators).

2.1.3 The PI or other research staff member makes a preliminary determination of whether the event meets the criteria for a reportable event. When in doubt, call the Research Compliance Specialist.

2.1.4 The PI (or other research staff member) reports all problems/adverse events that are unanticipated OR which are related to the study procedures using FORM: Report of Study Problem and decides upon the tentative classification of the event (e.g., Protocol Deviation, Adverse Event, Serious Adverse Event, Unanticipated Event). “Not Sure” is an option, as are selections of more than one category, as when adverse events are also unanticipated.

2.1.5 The PI or other reporter reports all events within these time frames:

2.1.5.1 All deaths that are related to the study procedures and involve death must be reported immediately or within no more than 48 hours after the death. Initial reports of participant deaths may be made by telephone, e-mail, or in person, followed by the completed appropriate form;
2.1.5.2 Events involving unanticipated life-threatening experiences must be reported within 7 calendar days of the investigator’s receipt of the information.

2.1.5.3 All other serious and unanticipated problems—short of death or life-threatening experiences—must be reported within 14 calendar days of the investigator’s receipt of the information.

2.1.5.4 All deaths that are not related to the study procedures (such as those due to progression of an underlying disease) must be reported at the time of continuing renewal on FORM: IRB Renewal Application.

2.1.6 If the PI recognizes that the problem/event involves risk to subjects or others and the information is not already in the consent/assent document, s/he submits a revised consent/assent document with changes underlined.

2.1.7 If the PI recognizes that the problem affects the protocol or research description, s/he submits a revised research description containing the underlined changes.

2.1.8 The PI responds to any requirements or recommendations made by the IRB on its requested schedule.

2.1.9 Any proposed changes to a research study in response to a reported problem must be approved by the IRB before they are implemented, unless the change was made to eliminate an immediate apparent hazard to participants.

2.1.10 If the PI has concerns regarding the IRB decision or recommendations for changes, s/he may submit those concerns to the IRB in writing, including a justification for changing the IRB decision. The IRB will review that request, make a final determination, and notify the PI of their decision.

2.2 IRB Management of Reports of Internal Problems

2.2.1 For reports of participant death or other serious events submitted by phone, e-mail, or in person by the investigator, the recipient of the report directs the reporter to complete the appropriate form. Research Compliance Specialists who receive such reports alert the Director of Research Compliance who decides whether or not to inform the IRB promptly.

2.2.2 For reports of problems submitted via a form, the Research Compliance Specialist (RCS) screens the report to determine whether it is complete, requests any missing information, notes whether the report was submitted within the allowable timeframe for the event (information is available on the report form), enters the report on the IRB database and study file, notifies the IRB chair, and places the report on the IRB agenda.

2.2.3 The RCS, the Director of Research Compliance, and the IRB chair identify a primary reviewer for the report and forward the report, the protocol, the consent form, and any related material to that person.
2.2.4 The IRB members receive all available information about reported problems prior to the convened meeting at which the problem will be reviewed, including information from the RCS about whether the report was submitted within the specified timeframe and whether the investigator has failed to report events promptly before.

2.2.5 The IRB reviews reported internal events and problems at a convened meeting using standard procedures for initial full board review.

2.2.6 If the investigator has a history of failure to meet reporting deadlines, the IRB may initiate discussion of persistent noncompliance and impose other disciplinary measures of its choice.

2.3 IRB Management of Reports of External Problems

2.3.1 For reports of participant death or other serious events submitted by phone, e-mail, or in person by the investigator, the recipient of the report directs the reporter to complete the appropriate form. Research Compliance Specialists who receive such reports alert the Director of Research Compliance who decides whether or not to inform the IRB promptly.

2.3.2 The Research Compliance Specialist (RCS) screens the report for completeness, requests any missing information, and notifies the Director of Research Compliance and the IRB chair.

2.3.3 The RCS sends the report and all related material (revised consent documents, revised protocols, etc.) to the IRB chair or designee. The chair or designee serve as an expedited reviewer and reviews the report using expedited review procedures (POLICY: Expedited Review, FORM: IRB Checklist for Reviewers and Investigators).

2.3.4 If the expedited reviewer determines that the unanticipated event is a UAP involving risks to subjects or others, he completes the IRB portion of FORM: Report of Study Problem and returns the report and the PI's submitted materials to the RCS. The RCS places the report on the agenda for the next convened meeting and sends copies of the completed report, any related materials, and the expedited reviewer's comments in the agenda packet to each IRB member.

2.3.5 If the expedited reviewer determines that the report is not a UAP involving risk to subjects or others, s/he documents the review by signing the original FORM: Report of Study Problem and lists any concerns or recommendations for the investigator.

2.3.6 The RCS places the original report in the protocol file and lists the external problem/event on the IRB agenda for the next convened meeting as a specific item. (That is, it is not simply listed on the form that reports approved exempt and expedited applications.)

2.3.7 The expedited reviewer gives an oral report on the problem/event. Any IRB member may request to review the entire IRB file and the expedited reviewer's
recommendations. In the absence of such a request, the IRB discusses the event and votes on an action.

2.4 Reporting of Problems/Adverse Events for Continuing Renewal

2.4.1 The PI provides a written report of all problems/AE/UAPs occurring within the 12 months prior to continuing review as part of FORM: IRB Renewal Application. Investigators may use FORM: Log of Study Problems or a form supplied by the sponsor or the DSMB. This report includes all events, whether anticipated or unanticipated, serious or not serious, life-threatening or not life-threatening, or related or not related, and the PI’s assessment of whether the events warrant changes in the protocol, consent process, or risk-benefit ratio. Both qualitative and quantitative assessments are desirable.

2.5 IRB Review Outcomes (For Either Internal or External Events)

2.5.1 IRB actions may include:

2.5.1.1 Acknowledgement/acceptance without further recommendations;

2.5.1.2 A request for further clarification from the investigator;

2.5.1.3 Changes in the protocol (e.g., additional tests or visits to detect similar events in a timely fashion);

2.5.1.4 Changes in the consent/assent documents;

2.5.1.5 A requirement to inform enrolled and prospective participants about additional risks;

2.5.1.6 A change in frequency of continuation review (approval for less than one year);

2.5.1.7 Further inquiry into other protocols using the particular drug, device, or procedure in question;

2.5.1.8 Suspension or termination of the study;

2.5.1.9 Request for post-approval monitoring;

2.5.1.10 Recommendations for quality improvement review or investigator education or any other action deemed appropriate by the IRB.

2.5.1.11 Decisions of whether, to whom, and by whom reports beyond the IRB will be submitted.

2.6 Reporting of Problems Beyond IRB

2.6.1 The principal investigator reports problems to the study sponsor as required by the sponsor, both in regard to report content and report timing. This may occur before or with the reporting of the problem to the IRB.
2.6.1.1 If the study is under FDA jurisdiction, the PI must notify the FDA within 24 hours of the event.

2.6.2 The Director of Research Compliance or the Institutional Official report serious adverse events that are unanticipated problems to department chairs and/or Associate Deans/Directors of Research.

2.6.3 The Director of Research Compliance reports internal adverse events that are unanticipated problems to the Vice President for Research/Institutional Official within 5 days.

2.6.4 The Institutional Official reports unanticipated problems to any federal department that has oversight due to funding, conduct, or assurance, including but not limited to OHRP, FDA, NIH, DOD, and DOE within 30 days.

2.6.5 For multi-site studies, only the institution at which the problem occurred must report the event to the supporting agency head or designee, or the central monitoring entity may be designated to submit reports of unanticipated problems to the supporting agency or designee and OHRP.

2.7 Letters reporting internal serious adverse events/unanticipated problems will include the following:

2.7.1.1 Investigator name;

2.7.1.2 IRB number and study title;

2.7.1.3 Applicable grant and OSP numbers;

2.7.1.4 Description of the event;

2.7.1.5 IRB actions and rationale;

2.7.1.6 Findings of studying monitoring, if any;

2.7.1.7 Investigator actions and preventive/corrective measures;

2.7.1.8 Plan for continued evaluation by investigator and IRB.

3.0 REFERENCES

3.1 DHHS OHRP. Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, March 1, 2007. http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm. Investigators are urged to read this guidance as it includes more examples of relevant decision-making processes and distinctions among types of events.

3.2 OHRP Guidance on Reporting Incidents to OHRP
3.3 OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events

3.4 45 CFR §46.103(b)(5)(i)

3.5 45 CFR §46.116(b)(5)

3.6 21 CFR §50.25(b)(5)

3.7 21 CFR §56.108(b)(l)

3.8 21 CFR §812.150(a)(l)

3.9 FDA Information Sheets: Continuing Review after Study Approval; Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs—Improving Human Subject Protection

3.10 DoD: SECNAVINST 3900.39D, para. 8d(2), para. 8d(6), and para. 8g(6)

3.11 DOE: DOE 0 443.1.A Contractor Requirements Document

3.12 DOJ: 28 CFR 512. 19,20

4.0 RELATED SECTIONS

4.1 GUIDANCE: Events and Information That Require Prompt Reporting to the IRB

4.2 FORM: Report of Study Problem

4.3 FORM: IRB Renewal Application

4.4 FORM: Request for Study Closure (Investigator)

4.5 FORM: Log of Study Problems

4.6 POLICY: Monitoring of Previously Approved Research for Cause: Suspension and Termination