1. **PURPOSE**

1.1. This document describes the information and events that must be reported to the Institutional Review Board (IRB), as well as the time frame and procedures for the reporting.

1.2. OHRP and FDA have issued guidance which clarifies that investigators need only report “unanticipated problems involving risks to subjects or others” (or UPIRSOs). The UGA policy is based on this guidance.

1.3. Events requiring prompt reporting may involve physical, psychological, social, legal, or economic harms. Unanticipated problems, therefore, can occur in any type of research (bio-medical or socio-behavioral) and may include adverse events, subject complaints, protocol deviations, and other unforeseen problems or findings that suggest participants, research staff, or others are placed at greater risk by the research than previously expected. These events must be reported promptly to the IRB, appropriate institutional officials, and federal agencies.

2. **DEFINITIONS**

2.1. **Unanticipated problem involving risks to subjects or others (UPIRSO):** Any incident, experience, or outcome that meets all of the following three criteria:

   2.1.1. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are 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;

   2.1.2. related or possibly related to a subject’s participation in the research; and

   2.1.3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

2.2. **Related to the research:** An incident, experience or outcome that is likely to have resulted from participation in the research study.

2.3. **Possibly related to the research:** There is a reasonable possibility that the event may have been caused by the procedures involved in the research (modified from the definition of associated with use of the drug in FDA regulations at 21 CFR 312.32(a)).

2.4. **Adverse event (AE):** Any undesirable and unintended (although not necessarily unexpected) effect occurring as a result of interventions, interactions, or collection of identifiable private information in research. In biomedical research, any untoward or unfavorable medical 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 (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

2.5. **Serious adverse event:** Any adverse event temporally associated with the subject’s participation in research that meets any of the following criteria:
2.5.1. results in death;
2.5.2. is life-threatening (places the subject at immediate risk of death from the event as it occurred);
2.5.3. requires inpatient hospitalization or prolongation of existing hospitalization;
2.5.4. results in a persistent or significant disability/incapacity;
2.5.5. results in a congenital anomaly/birth defect; or
2.5.6. any other adverse event that, based upon 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 (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).)

2.6. Unexpected adverse event: Any adverse event occurring in one or more subjects in a research protocol, the nature, severity, or frequency of which is not consistent with either:
2.6.1. 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 investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
2.6.2. the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject’s predisposing risk factor profile for the adverse event.
(Modified from the definition of unexpected adverse drug experience in FDA regulations at 21 CFR 312.32(a).)

2.7. External event: An event occurring in research at a site(s) other than UGA, over which an external (non-UGA) IRB has jurisdiction.

2.8. Internal event: An event occurring in a UGA research at a site(s) under its IRB’s jurisdiction.

2.9. Protocol violations and deviations: These terms are typically used to refer to non-compliance with IRB-approved procedures. They may be unintentional or deliberate. They should be reported to the IRB only when they meet the criteria and definitions of information and events that require reporting as described in this policy.

3. POLICIES and PROCEDURES: RESEARCHERS
3.1 Events Requiring Prompt Reporting
3.1.1 Investigators and research staff are responsible for reporting to the IRB unanticipated problems involving risks to subjects or others. Such reports may include adverse events, subject complaints, protocol deviations, and other untoward events involving risk.
3.1.2 Adverse events and serious adverse events that meet all three criteria set forth in 2.1 (above) and are therefore an UPIRSO are reportable to the IRB. If investigators are unsure whether an AE is an UPIRSO, the event should be reported. The IRB will review the report and make a final determination as to whether the event constitutes an UPIRSO.
3.1.3 Reportable events are submitted using the IRB using Click IRB’s Event and Information Reporting Form.

3.1.4 The convened IRB is responsible for making the final determination that a reported event is an UPIRSO.

3.1.5 The following events may represent unanticipated problems involving risks to subjects or others and thus should be promptly reported:

3.1.5.1 Adverse device effects that are unanticipated

3.1.5.2 Adverse events or injuries that are serious, unexpected, and related to research

3.1.5.3 Breaches in confidentiality resulting from a disclosure of confidential information or from lost or stolen confidential information

3.1.5.4 Data and Safety Monitoring Board (DSMB) reports, interim analyses, or other oversight committee/monitoring reports altering the risk/benefit profile

3.1.5.5 Events requiring prompt reporting according to the protocol, sponsor, or funding agency

3.1.5.6 Investigator’s brochure updates/revisions to safety information (excluding routine updates)

3.1.5.7 New information indicating an unexpected change in risks or potential benefits (e.g., literature/scientific reports or other published findings)

3.1.5.8 Major protocol deviations, violations, or other accidental or unintentional changes to the protocol or procedures involving risks or with the potential to recur

3.1.5.9 Subject complaints indicating an unanticipated risk, or complaints that cannot be resolved by the research staff

3.1.5.10 Unapproved changes made to the research to eliminate an apparent immediate hazard to a subject

3.1.5.11 Other problem or finding (e.g., loss of study data or forms, a subject becomes a prisoner while participating in research, etc.) that an investigator or research staff member believes could influence the safe conduct of the research

3.1.6 All internal and external events that may represent an UPIRSO should be reported, regardless of whether they occur during or after the study, or involve a subject who has withdrawn from or completed study participation.

3.2 Timeframe for Reporting

3.2.1 The events described above should be reported using the IRB using Click IRB’s Event and Information Reporting Form within 10 business days of the investigator’s or research staff member’s learning of the event.

3.2.2 Events resulting in temporary or permanent interruption of study activities by the investigator or sponsor to avoid potential harm to subjects should be reported within 48 hours whenever possible.

3.2.3 If the report cannot be completed in its entirety within the required time period, a preliminary report should be submitted. The report should be amended once the event is resolved and/or more information becomes available.

3.3 Events Not Requiring Prompt Reporting

Potential risks and adverse events that may be reasonably anticipated (i.e., “expected”) should be described in the informed consent process/form and do not require prompt reporting to the IRB by
investigators and/or research staff. The following are examples of events that do not require prompt reporting:

3.3.1.1 Adverse device effects that are non-serious, anticipated, or unrelated to research
3.3.1.2 Adverse events or injuries that are non-serious, expected, or unrelated
3.3.1.3 Deaths not attributed to the research, e.g., from “natural causes,” accidents, or underlying disease and the investigator has ruled out any connection between the study procedures and the participant’s death
3.3.1.4 DSMB reports; interim analyses; or other reports, findings, or new information not altering the risk/benefit profile
3.3.1.5 Investigator’s brochure updates not involving safety information
3.3.1.6 Minor protocol deviations or violations unlikely to recur or not involving risks to subjects
3.3.1.7 Subject complaints that were resolved or complaints not involving risks
3.3.1.8 Problems or findings not involving risk (unless the investigator or research staff member believes the information could affect participants’ willingness to continue in the research).

3.4 Related internal and external events involving risk but not meeting the prompt reporting requirements should be reported to the IRB in summary form at the time of continuing review. In lieu of a summary of external events, a current DSMB report can be submitted for research subject to oversight by a DSMB (or other monitoring entity).

3.5 External events that do not meet the reporting requirements (e.g., not related or not involving risk) and that are not relevant to the protection of participants in UGA research should not be reported. Investigators should retain copies of all individual event reports on file.

3.6 The IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB’s requirements or that has been associated with unexpected serious harm to subjects.

3.7 Related adverse events and other problems involving risk that do not meet the reporting requirements and do not represent potential unanticipated problems involving risks to subjects or others should be reported in summary form at the time of continuing IRB review. However, any problem or adverse event that an investigator believes could influence the safe conduct of the research should be reported promptly.

4. PROCEDURES: Institutional Review Board

4.1.1 HSO Staff screens event reports and accompanying information for completeness, and makes an initial determination if the event represents a possible unanticipated problem involving risks to subjects or others. Reports of events determined during screening to represent possible UPIRSO will be forwarded to the IRB for convened review. Reports of events that do not meet the requirements for prompt reporting may be returned to the submitter. All other event reports will be reviewed by Non-Committee Review.

4.1.2. Non-Committee Review

Event reports and accompanying information will be reviewed by the IRB Chair and/or designee. Reviewers will have access to the complete protocol file, including previously reported events, for review. The Chair or designee will determine if the report raises new concerns about risks and will recommend further review by the convened IRB, as necessary. The IRB Chair or designee may suspend or terminate approval of an investigator’s research if necessary to assure the protection
of research participants. The Chair or designee will consider the rights and welfare of participants when suspending, terminating, or modifying research.

4.1.2.1 If the event is determined not to be an UPIRSO, the reviewer will make any necessary recommendations for action (see below), which will be communicated to the principal investigator by reviewer or HSO staff. IRB members will be informed of these designated reviews.

4.1.3. Convened Review

4.1.3.1. Reports of events determined during screening or Non-Committee IRB review that represent a possible UPIRSO will require Convened Review. Modifications (proposed by the investigator or IRB reviewer) that represent more than minor changes will also be reviewed by the convened IRB. The Chair or other member with relevant expertise will serve as the primary reviewer.

4.1.3.2. The IRB will determine by convened review whether the event is an UPIRSO and if further action is necessary. Action(s) will be based on the nature of the event, degree to which research participants are placed at risk, occurrence of previous problems, etc. The IRB will consider the rights and welfare of participants when suspending, terminating, or modifying research.

4.1.3.3. The IRB’s determination and action(s), including votes taken, will be recorded in the meeting minutes. The requirements for quorum and majority apply.

5. IRB Actions

5.1. The types of actions that the IRB may consider for any event include, but are not limited to:

5.1.1 Modification(s) of the research protocol or procedures
5.1.2 Modification(s) of the consent process or consent form
5.1.3 Providing additional information to current research participants (required when such information may relate to their willingness to continue in the research)
5.1.4 Providing additional information to past research participants
5.1.5 Reconfirming consent of current research participants
5.1.6 Requiring additional follow-up/monitoring for current and/or past research participants
5.1.7 Monitoring of the research (including audits) or consent process
5.1.8 Education or mentoring for the principal investigator and/or research staff
5.1.9 Additional reporting, including modification of the continuing review schedule
5.1.10 Requiring additional resources to support the investigator’s research activities
5.1.11 Placing limitations (e.g., restriction to co-investigator status) on the investigator’s research activities or use of research data
5.1.12 Suspending or terminating the research
5.1.13 Referral to other appropriate university process (e.g., misconduct review).

5.2 Investigators will be notified in writing by HSO staff of IRB decisions regarding events determined not to represent UPIRSO. Suspended IRB approval may be reinstated, as appropriate, based on the outcome of the convened review. Investigators (and others) will be notified of IRB actions regarding events determined to be UPIRSO as described below.

6. Institutional Reporting

If the IRB determines that an event is an UPIRSO, or if the Board suspends or terminates approval of research that is associated with unexpected serious harm to subjects, the investigator(s), IRB, Institutional Official, and the respective Dean and Department Chair (or equivalent) will be notified of the reasons for the IRB’s action in writing by HSO staff within 14 days of the determination. OHRP, FDA (as applicable for FDA-regulated research), the sponsor or any other sponsoring federal Department or Agency, and others (e.g.,
Office of Sponsored Programs) as necessary, in accordance with UGA’s Federalwide Assurance, will be notified in writing within 30 days.

7. Record Retention
Records of reports and reviews of events representing possible unanticipated problems involving risks to subjects or others, including submission materials and communications, are retained by HSO according to federal regulations, applicable state and local laws, and university policies for record retention.

8. MATERIALS
8.1 Event and Information Reporting Form in Click IRB

9. REFERENCES
9.2. OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (January 15, 2007)
9.3. FDA Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs — Improving Human Subject Protection

Appendix A
Examples of Unanticipated Problems that Do Not Involve Adverse Events and Need to be Reported under the HHS Regulations at 45 CFR Part 46

1. An investigator conducting behavioral research collects individually identifiable sensitive information about illicit drug use and other illegal behaviors by surveying college students. The data are stored on a laptop computer without encryption, and the laptop computer is stolen from the investigator’s car on the way home from work. This is an unanticipated problem that must be reported because the incident was (a) unexpected (i.e., the investigators did not anticipate the theft); (b) related to participation in the research; and (c) placed the subjects at a greater risk of psychological and social harm from the breach in confidentiality of the study data than was previously known or recognized.

2. As a result of a processing error by a pharmacy technician, a subject enrolled in a multicenter clinical trial receives a dose of an experimental agent that is 10-times higher than the dose dictated by the IRB-approved protocol. While the dosing error increased the risk of toxic manifestations of the experimental agent, the subject experienced no detectable harm or adverse effect after an appropriate period of careful observation. Nevertheless, this constitutes an unanticipated problem for the institution where the dosing error occurred that must be reported to the IRB, appropriate institutional officials, and OHRP because the incident was (a) unexpected; (b) related to participation in the research; and (c) placed subject at a greater risk of physical harm than was previously known or recognized.

3. Subjects with cancer are enrolled in a phase 2 clinical trial evaluating an investigational biologic product derived from human sera. After several subjects are enrolled and receive the investigational product, a study audit reveals that the investigational product administered to subjects was obtained from donors who were not appropriately screened and tested for several potential viral contaminants, including the human immunodeficiency virus and the hepatitis B virus. This constitutes an unanticipated problem that must be reported because the incident was (a) unexpected; (b) related to participation in the research; and (c) placed subjects and others at a greater risk of physical harm than was previously known or recognized.

The events described in the above examples were unexpected in nature, related to participation in the research, and resulted in new circumstances that increased the risk of harm to subjects. In all of these
examples, the unanticipated problems warranted 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. In addition, the third example may have presented unanticipated risks to others (e.g., the sexual partners of the subjects) in addition to the subjects. In each of these examples, while these events may not have caused any detectable harm or adverse effect to subjects or others, they nevertheless represent unanticipated problems and should be promptly reported to the IRB, appropriate institutional officials, the supporting agency head and OHRP in accordance with HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

Appendix B
Examples of Adverse Events that Do Not Represent Unanticipated Problems and Do Not Need to be Reported under the HHS Regulations at 45 CFR Part 46

1. A subject participating in a phase 3, randomized, double-blind, controlled clinical trial comparing the relative safety and efficacy of a new chemotherapy agent combined with the current standard chemotherapy regimen, versus placebo combined with the current standard chemotherapy regimen, for the management of multiple myeloma develops neutropenia and sepsis. The subject subsequently develops multi-organ failure and dies. Prolonged bone marrow suppression resulting in neutropenia and risk of life-threatening infections is a known complication of the chemotherapy regimens being tested in this clinical trial and these risks are described in the IRB-approved protocol and informed consent document. The investigators conclude that the subject’s infection and death are directly related to the research interventions. A review of data on all subjects enrolled so far reveals that the incidence of severe neutropenia, infection, and death are within the expected frequency. This example is not an unanticipated problem because the occurrence of severe infections and death – in terms of nature, severity, and frequency – was expected.

2. A subject enrolled in a phase 3, randomized, double-blind, placebo-controlled clinical trial evaluating the safety and efficacy of a new investigational anti-inflammatory agent for management of osteoarthritis develops severe abdominal pain and nausea one month after randomization. Subsequent medical evaluation reveals gastric ulcers. The IRB-approved protocol and informed consent document for the study indicated that there was a 10% chance of developing mild to moderate gastritis and a 2% chance of developing gastric ulcers for subjects assigned to the active investigational agent. The investigator concludes that the subject’s gastric ulcers resulted from the research intervention and withdraws the subject from the study. A review of data on all subjects enrolled so far reveals that the incidence of gastritis and gastric ulcer are within the expected frequency. This example is not an unanticipated problem because the occurrence of gastric ulcers – in terms of nature, severity, and frequency – was expected.

3. A subject is enrolled in a phase 3, randomized clinical trial evaluating the relative safety and efficacy of vascular stent placement versus carotid endarterectomy for the treatment of patients with severe carotid artery stenosis and recent transient ischemic attacks. The patient is assigned to the stent placement study group and undergoes stent placement in the right carotid artery. Immediately following the procedure, the patient suffers a severe ischemic stroke resulting in complete left-sided paralysis. The IRB-approved protocol and informed consent document for the study indicated that there was a 5-10% chance of stroke for both study groups. To date, 25 subjects have been enrolled in the clinical trial, and 2 have suffered a stroke shortly after undergoing the study intervention, including the current subject. The DSMB responsible for monitoring the study concludes that the subject’s stroke resulted from the research intervention. This example is not an unanticipated problem because the occurrence of stroke was expected and the frequency at which strokes were occurring in subjects enrolled so far was at the expected level.

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4. An investigator is conducting a psychology study evaluating the factors that affect reaction times in response to auditory stimuli. In order to perform the reaction time measurements, subjects are placed in a small, windowless soundproof booth and asked to wear headphones. The IRB-approved protocol and informed consent document describe claustrophobic reactions as one of the risks of the research. The twentieth subject enrolled in the research experiences significant claustrophobia, resulting in the subject withdrawing from the research. This example is not an unanticipated problem because the occurrence of the claustrophobic reactions – in terms of nature, severity, and frequency – was expected.

5. A subject with advanced renal cell carcinoma is enrolled in a study evaluating the effects of hypnosis for the management of chronic pain in cancer patients. During the subject’s initial hypnosis session in the pain clinic, the subject suddenly develops acute chest pain and shortness of breath, followed by loss of consciousness. The subject suffers a cardiac arrest and dies. An autopsy reveals that the patient died from a massive pulmonary embolus, presumed related to the underlying renal cell carcinoma. The investigator concludes that the subject’s death is unrelated to participation in the research. This example is not an unanticipated problem because the subject’s pulmonary embolus and death were attributed to causes other than the research interventions.

6. An investigator performs prospective medical chart reviews to collect medical data on premature infants in a neonatal intensive care unit (NICU) for a research registry. An infant, about whom the investigator is collecting medical data for the registry, dies as the result of an infection that commonly occurs in the NICU setting. This example is not an unanticipated problem because the death of the subject is not related to participation in the research, but is most likely related to the infant’s underlying medical condition.

NOTE: For purposes of illustration, the case examples provided above represent generally unambiguous examples of adverse events that are not unanticipated problems. OHRP recognizes that it may be difficult to determine whether a particular adverse event is unexpected and whether it is related or possibly related to participation in the research. In addition, the assessment of the relationship between the expected and actual frequency of a particular adverse event must take into account a number of factors including the uncertainty of the expected frequency estimates, the number and type of individuals enrolled in the study, and the number of subjects who have experienced the adverse event.

Appendix C
Examples of Adverse Events that Represent Unanticipated Problems and Need to be Reported Under the HHS Regulations at 45 CFR Part 46

1. A subject with chronic gastroesophageal reflux disease enrolls in a randomized, placebo-controlled, double-blind, phase 3 clinical trial evaluating a new investigational agent that blocks acid release in the stomach. Two weeks after being randomized and started on the study intervention the subject develops acute kidney failure as evidenced by an increase in serum creatinine from 1.0 mg/dl pre-randomization to 5.0 mg/dl. The known risk profile of the investigational agent does not include renal toxicity, and the IRB-approved protocol and informed consent document for the study does not identify kidney damage as a risk of the research. Evaluation of the subject reveals no other obvious cause for acute renal failure. The investigator concludes that the episode of acute renal failure probably was due to the investigational agent. This is an example of an unanticipated problem that must be reported because the subject’s acute renal failure was (a) unexpected in nature, (b) related to participation in the research, and (c) serious.

2. A subject with seizures enrolls in a randomized, phase 3 clinical trial comparing a new investigational anti-seizure agent to a standard, FDA-approved anti-seizure medication. The subject is randomized to the group receiving the investigational agent. One month after enrollment, the subject is hospitalized
with severe fatigue and on further evaluation is noted to have severe anemia (hematocrit decreased from 45% pre-randomization to 20%). Further hematologic evaluation suggests an immune-mediated hemolytic anemia. The known risk profile of the investigational agent does not include anemia, and the IRB-approved protocol and informed consent document for the study do not identify anemia as a risk of the research. The investigators determine that the hemolytic anemia is possibly due to the investigational agent. This is an example of an unanticipated problem that must be reported because the hematologic toxicity was (a) unexpected in nature; (b) possibly related to participation in the research; and (c) serious.

3. The fifth subject enrolled in a phase 2, open-label, uncontrolled clinical study evaluating the safety and efficacy of a new oral agent administered daily for treatment of severe psoriasis unresponsive to FDA-approved treatments, develops severe hepatic failure complicated by encephalopathy one month after starting the oral agent. The known risk profile of the new oral agent prior to this event included mild elevation of serum liver enzymes in 10% of subjects receiving the agent during previous clinical studies, but there was no other history of subjects developing clinically significant liver disease. The IRB-approved protocol and informed consent document for the study identifies mild liver injury as a risk of the research. The investigators identify no other etiology for the liver failure in this subject and attribute it to the study agent. This is an example of an unanticipated problem that must be reported because although the risk of mild liver injury was foreseen, severe liver injury resulting in hepatic failure was (a) unexpected in severity; (b) possibly related to participation in the research; and (c) serious.

4. Subjects with coronary artery disease presenting with unstable angina are enrolled in a multicenter clinical trial evaluating the safety and efficacy of an investigational vascular stent. Based on prior studies in animals and humans, the investigators anticipate that up to 5% of subjects receiving the investigational stent will require emergency coronary artery bypass graft (CABG) surgery because of acute blockage of the stent that is unresponsive to non-surgical interventions. The risk of needing emergency CABG surgery is described in the IRB-approved protocol and informed consent document. After the first 20 subjects are enrolled in the study, a DSMB conducts an interim analysis, as required by the IRB-approved protocol, and notes that 10 subjects have needed to undergo emergency CABG surgery soon after placement of the investigational stent. The DSMB monitoring the clinical trial concludes that the rate at which subjects have needed to undergo CABG greatly exceeds the expected rate and communicates this information to the investigators. This is an example of an unanticipated problem that must be reported because (a) the frequency at which subjects have needed to undergo emergency CABG surgery was significantly higher than the expected frequency; (b) these events were related to participation in the research; and (c) these events were serious.

5. Subjects with essential hypertension are enrolled in a phase 2, non-randomized clinical trial testing a new investigational antihypertensive drug. At the time the clinical trial is initiated, there is no documented evidence of gastroesophageal reflux disease (GERD) associated with the investigational drug, and the IRB-approved protocol and informed consent document do not describe GERD as a risk of the research. Three of the first ten subjects are noted by the investigator to have severe GERD symptoms that began within one week of starting the investigational drug and resolved a few days after the drug was discontinued. The investigator determines that the GERD symptoms were most likely caused by the investigational drug and warrant modification of the informed consent document to include a description of GERD as a risk of the research. This is an example of an adverse event that, although not serious, represents an unanticipated problem that must be reported because it was (a) unexpected in nature; (b) possibly related to participation in the research; and (c) suggested that the research placed subjects at a greater risk of physical harm than was previously known or recognized.

6. A behavioral researcher conducts a study in college students that involves completion of a detailed survey asking questions about early childhood experiences. The research was judged to involve no more than minimal risk and was approved by the IRB chairperson under an expedited review
procedure. During the completion of the survey, one student subject has a transient psychological reaction manifested by intense sadness and depressed mood that resolved without intervention after a few hours. The protocol and informed consent document for the research did not describe any risk of such negative psychological reactions. Upon further evaluation, the investigator determines that the subject’s negative psychological reaction resulted from certain survey questions that triggered repressed memories of physical abuse as a child. The investigator had not expected that such reactions would be triggered by the survey questions. This is an example of an unanticipated problem that must be reported in the context of social and behavioral research because, although not serious, the adverse event was (a) unexpected; (b) related to participation in the research; and (c) suggested that the research places subjects at a greater risk of psychological harm than was previously known or recognized.

In all of these examples, the adverse events warranted 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. NOTE: For purposes of illustration, the case examples provided above represent generally unambiguous examples of adverse events that are unanticipated problems. OHRP recognizes that it may be difficult to determine whether a particular adverse event is unexpected and whether it is related or possibly related to participation in the research.

Appendix D
The list of examples below is intended for purposes of general guidance only. The characterization of a violation or deviation as major in any particular case will depend on the specific facts and circumstances of that case. Examples of major violations or deviations may include, but are not limited to:

1. Failure to obtain informed consent, i.e., there is no documentation of informed consent, or informed consent is obtained after initiation of study procedures;
2. Enrollment of a subject who did not meet all inclusion/exclusion criteria;
3. Performing study procedure not approved by the IRB;
4. Failure to report serious unanticipated problems/adverse events involving risks to subjects to the IRB and (if applicable), to the sponsor;
5. Failure to perform a required lab test that, in the opinion of the PI, may affect subject safety or data integrity;
6. Drug/study medication dispensing or dosing error;
7. Study visit conducted outside of required time frame that, in the opinion of the PI or IRB, may affect subject safety;
8. Failure to follow safety monitoring plan.

Appendix E
A minor violation or deviation is one that does not impact subject safety or does not substantially alter risks to subjects. The list of examples below is intended for purposes of general guidance only. The characterization of a violation or deviation as minor in any particular case will depend on the specific facts and circumstances of that case. Examples may include, but are not limited to:

1. Implementation of unapproved recruitment procedures;
2. Missing original signed and dated consent form (only a photocopy available);
3. Missing pages of executed consent form;
   Inappropriate documentation of informed consent, including: Missing subject signature; Missing investigator signature; Copy not given to the person signing the form; Someone other than the subject dated the consent form; Individual obtaining informed consent not listed on the IRB approved study personnel list.
4. Use of invalid consent form, i.e., consent form without IRB approval stamp or outdated or expired consent form;
5. Failure to follow the approved study procedure that, in the opinion of the PI, does not affect subject safety or data integrity including: Study procedure conducted out of sequence; Omitting an approved portion of the protocol;
6. Failure to perform a required lab test;
7. Missing lab results;
8. Enrollment of ineligible subject (e.g., subject's age was 6 months above age limit);
9. Study visit conducted outside of required timeframe.
10. Over-enrollment beyond what was approved by the IRB;
11. Enrollment of subjects after IRB-approval of study expired or lapsed;
12. Failure to submit continuing review application to the IRB before study expiration.

If either a protocol deviation or protocol exception occurs without prior IRB review and approval, the principal investigator is responsible for reporting within ten (10) business days of the occurrence. If applicable, the principal investigator is responsible for reporting protocol violations or deviations to the sponsor, and/or FDA.