Title:	Reporting New Safety Information		
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1 PURPOSE

1.1 Regulations require an organization to have written procedures for ensuring prompt reporting of changes in research activity; unanticipated problems involving risk to subjects or others; and any instances of serious or continuing non-compliance to the IRB, organizational officials, and applicable federal agencies. In order to comply with this requirement, the UNC-Chapel Hill has procedures to review issues that arise during the conduct of human subjects research conducted under the aegis of UNC-Chapel Hill. This policy describes the safety information that is promptly reportable to the Office of Human Research Ethics (OHRE).

2 RESPONSIBILITY

2.1 Researchers carry out these procedures.

2.2 The PI is responsible for reviewing and certifying new safety information prior to submission.

3 PROCEDURE

3.1 Reporting Requirements

Information previously unknown to the IRB that suggests new or increased risk to subjects or others (hereinafter referred to as New Safety Information) is promptly reportable to OHRE **within 7 calendar days** of the investigator becoming aware of the information. TABLE 1, New Safety Information, outlines the type of information that constitutes New Safety Information. Detailed examples of New Safety Information are provided in SUPPLEMENT 1.

3.1.1 Protocol deviations that did not harm subject(s) or others or place subject(s) or others at increased risk should be documented by the investigator in a deviation log. This log is subject to review by the IRB of other agency of the UNC-CH HRPP.

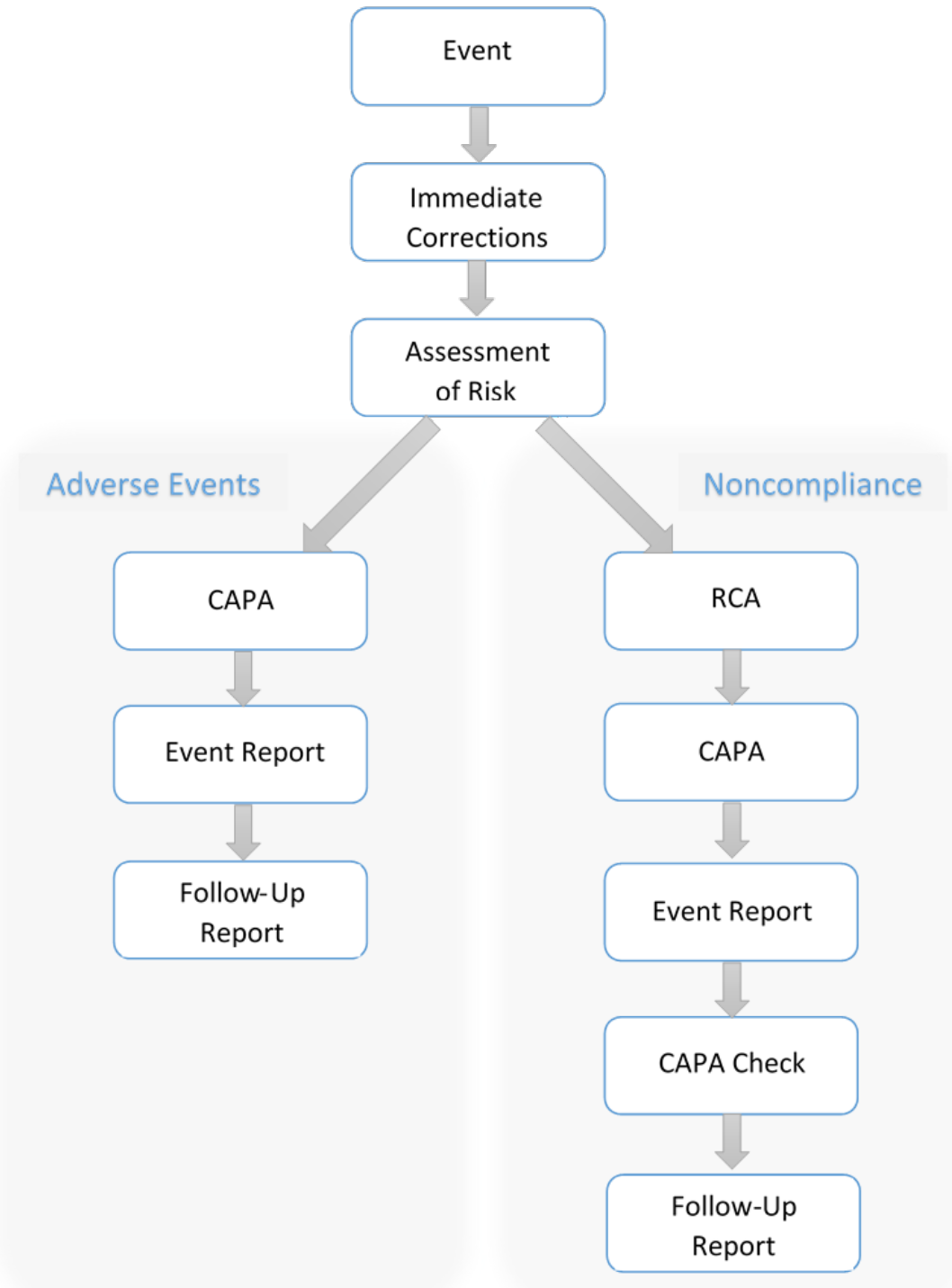
3.1.2 Researchers may consult with the OHRE Compliance Manager if they are uncertain about what information is reportable.

TABLE 1, New Safety Information

Reporting Requirements for studies for which the UNC IRB has oversight responsibilities
Internal adverse events that are (1) unexpected, (2) related or possibly related to participation in the research, and (3) serious or suggest that there are new or increased risk(s) to subjects
External adverse events that are (1) unexpected, (2) related or possibly related to participation in the research, (3) serious or suggest that there are new or increased risk(s) to subjects, and (4) warrant a change to the protocol or consent or subject notification (See 3.3 for additional information)
Interim analysis, data and safety monitoring report, findings from other studies, findings from animal or in-vitro testing, or other finding(s) that indicate (1) there are new or increased risks to subjects or others, or (2) subjects are less likely to receive any direct benefits from the research
Unanticipated adverse device effect
Protocol deviation that harmed subject(s) or others or placed subject(s) or others at increased risk of harm. **All other protocol deviations should be documented by the investigator in a deviation log. This log is subject to review by the IRB of other agency of the UNC-CH HRPP.**
Protocol deviation that is made to eliminate an immediate hazard to a subject without IRB approval
Intentional or unintentional failure to follow applicable federal human subject protection regulations, the requirements or determinations of the IRB, the IRB-approved study protocol, or University policies when that failure adversely affects the rights or welfare of participants, such as: • Conducting human subjects research without an IRB-approved protocol or exemption • Starting research prior to meeting the conditions required by the IRB and receiving an IRB notification of approval, or conducting research during a lapse in approval • Failure to obtain informed consent • Deviating from the informed consent or recruitment process approved by the IRB • Failure to provide a participant with new information about study risks or procedures that may affect the participant's willingness to continue/participate in the study (i.e., by not reconsenting participants or by using an old version of a consent document to consent a new participant) • Initiating changes to the protocol without IRB approval, including using unapproved materials (e.g., fact or information sheets, recruitment materials, questionnaires, focus group guides, scripts, or other materials provided to participants) • Failure to complete IRB- or institutionally-required human subjects protection training prior to engaging in human subjects research • Enrollment of participants beyond what has been approved by the IRB in a study that is greater than minimal risk
Breach or potential breach of subject confidentiality or privacy.
Complaint by or on behalf of a research subject that (1) indicates that the rights, welfare, or safety of the subject have been adversely affected, or (2) cannot be resolved by the investigator. Subject complaints about payment should be resolved by the study team. See SOP 1403 for additional information.
Allegation of noncompliance
Audit, inspection, or inquiry by a federal agency
Written report from a federal agency (e.g., FDA Form 483)
State board action that (1) will affect the ability to conduct or complete the research as approved by the IRB or (2) increases risks to subjects or others (e.g., suspension of professional license)
Incarceration of a subject enrolled in a research study that is not approved to involve prisoners
Institution-, investigator-, or sponsor-initiated hold or early closure as a result of safety concerns
Reporting requirements for studies ceding IRB review and oversight to an external IRB
Unanticipated Problem Involving Risk to Subjects or Others (UPIRSO) or Serious Noncompliance or Continuing Noncompliance determinations by an external IRB to which UNC cedes IRB review and oversight when the event involved UNC subjects or researchers
Suspension or termination by an external IRB to which UNC cedes IRB review and oversight

3.2 Reporting will flow as indicated in Figure 1; however, there may be instances where an alternative order of reporting is appropriate.

Figure 1, Steps to Reporting New Safety Information



3.2.1 Immediate Corrections

The first step is for investigators to eliminate immediate hazard to subject(s) or others. Immediate corrections does not require IRB approval prior to initiation, but should be described in the initial report of New Safety Information.

3.2.2 Assessment of Risk

Actual harm does not have to occur in order for there to be increased risk of physical, psychological, social, legal, or economic harm. The investigator's assessment of risk should be specific to the event, not the study overall, and it should be independent of benefit. An event that increases risk to subjects or others changes the risk/benefit ratio, but it may or may not change the IRB's assessment that the risks are reasonable in relation to the anticipated benefit(s), if any, to the subjects.

3.2.2.1 Assessment of risk of an adverse event. The first step in assessing whether an adverse event suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized is to determine whether the adverse event is serious.

3.2.2.1.1 For the purposes of this SOP, the adverse event is serious when the outcome for the subject is:

- death;
- life-threatening (places the subject at immediate risk of death from the event as it occurred);
- inpatient hospitalization or prolongation of existing hospitalization;
- persistent or significant disability/incapacity;
- congenital anomaly/birth defect; or

when the event does not fit the other outcomes but, 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 (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, persistent blood abnormality 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), and OHRP guidance: "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events," January 15, 2007)

3.2.2.1.2 OHRP and FDA consider adverse events that are unexpected, related or possibly related to participation in research, and serious to be the most important subset of adverse events representing unanticipated problems because such events always suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized and routinely 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 subject. (See examples 1 and 2 in SUPPLEMENT 1).

3.2.2.1.3 However, other adverse events that are unexpected and related or possibly related to participation in the research, but not serious, would also be unanticipated problems if they suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized. Again, such events routinely 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 or others (see examples 3 and 4 in SUPPPLEMENT 1).

3.2.3 Initial Report to the IRB

Investigators must report New Safety Information to OHRE in IRBIS. Generally, the report should contain the following:

3.2.3.1 Detailed information about the event or issue, including relevant dates. The report should identify the affected subjects by their study codes and not by their names or other personal identifiers.

3.2.3.2 An assessment of whether any subjects or others were placed at risk or suffered any harm (e.g., physical, social, financial, legal or psychological) as a result of the event.

3.2.3.3 If the event involves noncompliance, describe the result of the root cause analysis. For more details about root cause analysis see 3.2.4.

3.2.3.4 Any corrective and preventative actions, planned or already taken.

3.2.3.5 Any other information requested by OHRE, if applicable.

3.2.3.6 If the report cannot be completed in its entirety within the required time period, the report should describe what information is still needed and when the investigator anticipates that a follow-up report will be submitted.

3.2.4 Root Cause Analysis

Root cause analysis (RCA) is a class of problem solving methods used to identify the root causes of problems or events. For systemic problems, there may be multiple causes that require different actions. It may be relevant to perform an RCA so that appropriate corrective actions can be implemented to address the various contributing causes. Some corrective actions may require involvement of the institution (e.g., provisions of additional administrative support for the research team/activities).

3.2.4.1 Questions to ask to identify root causes:

What was the error?

How did it occur?

How widespread?

Why did it occur? Keep asking "why" until you identify root cause.

3.2.5 Corrective and Preventive Action (CAPA) Plans

Corrective actions are those taken to act on a problem that has already occurred. Preventive actions are those actions taken to eliminate the root cause of a potential problem. When reviewing a report of a UPIRSO, Serious Noncompliance, Continuing Noncompliance, Suspension or Termination of IRB approval, the HHS Office of Human Research Protections (OHRP) assesses most closely the adequacy of the actions taken by the institution to address the problem. In particular, OHRP assesses whether or not the corrective and preventative actions will help ensure that the incident will not happen again with the investigator or protocol in question, with any other investigator or protocol, or with the IRB. Therefore, OHRP recommends that, when appropriate, corrective actions be applied institution-wide. The FDA indicates that corrective and preventive actions are absolutely necessary to resolve problems and noncompliance in research. Although investigators have implemented CAPAs for decades, it is now an expectation that CAPAs are thoroughly documented, implemented, and evaluated over time for effectiveness, if appropriate.

3.2.5.1 CAPAs should include:

1. Description of the corrective and preventative actions taken or planned by the study team.
2. Date(s) on which the action(s) were taken or are planned.
3. The personnel who are responsible for the implementation the actions. The CAPA should describe whether different individuals are responsible for different actions.
4. If applicable, any plan/procedure to evaluate the implementation of the CAPA, personnel who are responsible for the evaluation, and the timeframe for the evaluation.

3.2.5.2 Documentation of CAPA. Suggested format:

1. Action type (corrective or preventive)
2. Action description

3. Responsible party
4. Due date
5. Plan for effectiveness check
6. Outcome of effectiveness check
7. If applicable, amendments to the CAPA

3.2.5.3 The IRB will make the final determination regarding the sufficiency of the CAPA.

3.2.6 Submission of Follow-up Report

Follow-up reports can be submitted any time during review or once a report has been resolved. An additional report to the IRB should be submitted if and when the CAPA has been evaluated for effectiveness. Reports will be screened by the OHRE Compliance Manager. Management of "New Safety Information" is described in SOP 1402.

3.3 External Adverse Event Reports

It is neither useful nor necessary under the regulations for reports of individual adverse events occurring in subjects enrolled in multicenter studies to be distributed routinely to investigators or IRBs at all institutions conducting the research. In general, the investigators and IRBs at all these institutions are not appropriately situated to assess the significance of individual external adverse events. Individual adverse events should only be reported to investigators and IRBs at all institutions when a determination has been made that the events meet the criteria for a UPIRSO. Ideally, adverse events occurring in subjects enrolled in a multicenter study should be submitted for review and analysis to a monitoring entity (e.g., the research sponsor, a coordinating or statistical center, or a DSMB/DMC) in accordance with a monitoring plan described in the IRB-approved protocol.

3.3.1 IND/IDE Safety Reports

The UNC IRB does not accept sponsor IND/IDE safety reports describing adverse events that have occurred at sites for which the UNC IRB does not have oversight responsibility ***unless*** the report is of an incident that is (1) unexpected, (2) related or possibly related to participation in the research, (3) serious or suggests that there are new or increased risk to subjects, and (4) warrants a change to the protocol or consent or subject notification. IND/IDE Safety Reports are submitted promptly as New Safety Information and must include an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents a UPIRSO. Changes to the research are submitted as a modification.

4 DEFINITIONS

4.1 IND Safety Report: A written report from a sponsor to the FDA of any adverse event associated with the use of the drug that was both serious and unexpected, or other adverse event or safety finding based on pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies that suggest a significant risk for human subjects and would cause the sponsor to modify the protocol-related documents or prompt other action to ensure the protection of human subjects.

4.2 Adverse event (AE): 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. Adverse events encompass both physical and psychological harms and occur most frequently in the context of biomedical research, although they can occur in the context of social and behavioral research.

4.3 Internal adverse event: Adverse events experienced by subjects at sites that are relying on the UNC IRB for review of the research. In the case of an internal adverse event the principal investigator typically becomes aware of the adverse event directly from the subject, co-investigator or other member of the study staff, or the subject's healthcare provider.

4.4 External adverse event: Adverse events experienced by subjects enrolled at sites that are not relying on the UNC for IRB review of the research. In the case of an external adverse event, the principal investigator typically becomes aware of the adverse event upon receipt of a report from the sponsor, coordinating center or other monitoring group, such as a Data and Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC), or collaborating investigator at another site.

4.5 Unanticipated Problem Involving Risk to Subjects or Others (UPIRSO): Any incident, experience, or outcome that

4.5.1 is 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 participant population being studied;

4.5.2 is related or possibly related to a participant's participation in the research; and

4.5.3 is serious or suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

4.6 Unexpected adverse event: Any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is not consistent with either:

4.6.1 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

4.6.2 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.

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

4.8 Possibly related to the research: The reasonable possibility that the adverse event, incident, experience or outcome may have been associated with 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)). Reasonable possibility means that the event is more likely than not related to participation in the research or, in other words, there is a >50% likelihood that the event is related to the research procedures.

4.9 Serious adverse event means any event temporally associated with the subject's participation in research that meets any of the following criteria:

4.9.1 results in death;

4.9.2 is life threatening (places the subject at immediate risk of death from the event as it occurred);

4.9.3 requires inpatient hospitalization or prolongation of existing hospitalization;

4.9.4 results in a persistent or significant disability/incapacity;

4.9.5 results in a congenital anomaly/birth defect; or

4.9.6 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 outcomes listed above (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).

4.10 Unanticipated Adverse Medical Device Effect: Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a medical device (if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the materials reviewed by the IRB); or, any other unanticipated serious problem associated with a medical device that relates to the rights, safety, or welfare of participants.

4.11 Protocol deviation: A variance from the approved study protocol. (Note: the term 'protocol deviation that harmed subject(s) or others or placed subject(s) or others at increased risk of harm' has replaced the term 'protocol violation').

4.12 Breach of Privacy: Privacy is the state of being free from the observation, intrusion, or attention of others. A breach of privacy in the context of human subjects research occurs when there is a failure to provide participants with the privacy protections described in the consent document. Breach of confidentiality: In the context of human subjects research, confidentiality is the condition that results when data are

maintained in a way that prevents inadvertent or inappropriate disclosure of participants' identifiable information. A breach of confidentiality occurs when a participant's private information is disclosed to a third party without his or her consent.

4.13 Noncompliance: Intentional or unintentional failure to follow applicable federal regulations, the requirements or determinations of the IRB, the IRB-approved study protocol, or University policies. Can occur as a result of performing an act(s) that violate(s) requirements. Can also occur as a result of failing to act when required.

4.14 Allegation of Noncompliance: An unproven assertion of "Noncompliance" by a subject or a third party.

4.15 Continuing Noncompliance: Any "Noncompliance" that occurs after implementation of an IRB-approved CAPA plan that is due to the failure of the investigator and/or research team to comply with that CAPA plan OR repeated instances of noncompliance within one study or across multiple studies that has a high likelihood of resulting in Serious Noncompliance.

4.16 Serious Noncompliance: "Noncompliance" that adversely and significantly affects the rights or welfare of participants.

4.17 Rights: The entitlement of human subjects for adequate protections based on the ethical principles and regulations underpinning human subjects research.

4.18 Welfare: A state of physical, psychological, social, economic and legal well-being.

4.19 Suspension: Temporary withdrawal of approval by the IRB of some or all research activities associated with a study. Research activities may include, but are not limited to the following: recruitment, screening/ enrollment, research intervention/interaction, follow-up. IRB approval may be suspended by either the Chair or the convened IRB. Suspended research remains under the jurisdiction of the IRB and is subject to continuing review.

4.20 Termination: Permanent withdrawal of IRB approval of all research activities associated with a study. IRB approval may only be terminated by the convened IRB. Terminated research is no longer subject to continuing review.

5 REFERENCES

5.1 DHHS Regulations: 45 CFR 46.103(b), 45 CFR 46.103(b)(4)(iii), 45 CFR 46.103(b)(5)

5.2 FDA Regulations: 21 CFR 56.103(a), 21 CFR 56.108(a)(3)

5.3 OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, January 15, 2007

5.4 FDA Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs — Improving Human Subject Protection, January 2009

5.5 FDA Guidance for Industry and Investigators — Safety Reporting Requirements for INDs and BA/BE Studies, December 2012

6 RELATED DOCUMENTS

6.1 SUPPLEMENT 1, Examples of New Safety Information

6.2 SOP 1402, Management of New Safety Information

SUPPLEMENT 1: Examples of New Safety Information

Examples of an Unanticipated Problem Involving Risk to Subjects or Others (UPIRSO; any incident, experience, or outcome that is (a) unexpected (in terms of nature, severity, or frequency); related or possibly related to a participant's participation in the research; and serious or otherwise one that suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized):

1. A participant with chronic gastroesophageal reflux disease enrolls in a phase 3 clinical trial at UNC evaluating a new investigational agent that blocks acid release in the stomach. Two weeks after starting study intervention the participant is hospitalized with acute kidney failure as a result of rhabdomyolysis. The known risk profile of the investigational agent does not include rhabdomyolysis, 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 participant reveals no other obvious cause for rhabdomyolysis. The UNC principal investigator reported the event to the Sponsor as possibly related. The sponsor agreed with the investigator's assessment of the event and notified the FDA and all participating investigators in an IND Safety Report. This is an example of a single, uncommon adverse event, known to be strongly associated with drug exposure. The adverse event meets the criteria for a UPIRSO because it is (a) unexpected in nature, (b) possibly related to the research, and (c) serious.

2. Participants 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 participants 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 participants are enrolled in the study, a DSMB conducts an interim analysis, as required by the IRB-approved protocol, and notes that 10 participants 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 participants have needed to undergo CABG greatly exceeds the expected rate and communicates this information to the sponsor and all investigators on the trial. The sponsor evaluates the information and concludes that the information represents an Unanticipated Adverse Device Effect (UADE). Consequently, the sponsor reports an analysis of the events to FDA and to all study investigators. The UADE meets the criteria for UPIRSO because (a) the frequency at which participants 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.

3. Participants with essential hypertension are enrolled in a phase 2, non-randomized multicenter 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. Two of the first ten participants are noted by the investigator XYZ Healthcare 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 believes that the GERD symptoms are most likely related to the investigational drug and reports the information to the Sponsor. Based on an aggregate analysis of all the data, the Sponsor determines that the occurrences of GERD at Alta Healthcare are not just isolated occurrences and warrant modification of the investigator brochure and informed consent document to include a description of GERD as a risk of the research. The Sponsor reports the information in an IND safety report to the FDA and all investigators on the trial, including UNC. The new risk of GERD represents an UPIRSO because it was (a) unexpected in nature; (b) 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

4. A behavioral researcher at UNC conducts a study in college students that involves completion of a detailed survey asking questions about early childhood experiences. During the completion of the survey, one student participant experiences 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 participant'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 a non-serious, internal adverse event that meets the criteria for a UPIRSO because it is (a) unexpected in nature, (b) related to the research, and (c) suggests that the research placed subjects at a greater risk of psychological harm than was previously known or recognized.

5. An investigator at UNC conducting behavioral research collects individually identifiable sensitive information about sexual behaviors by surveying college students. The data are stored on a laptop computer without encryption (encryption is required by the protocol), and the laptop computer is stolen from the investigator's car on the way home from work. The laptop was not recovered. This is an example of a breach of confidentiality as well as a protocol deviation that harmed a participant; it meets the criteria for a UPIRSO because the loss of the laptop was (a) unexpected (i.e., the investigators did not anticipate the theft); (b) related to participation in the research; and (c) placed the participants at a greater risk of psychological and social harm from the breach in confidentiality of the study data than was previously known or recognized.

6. During a routine monitoring visit by the sponsor, it is discovered that two consent documents are missing. The consent documents contain the participants' names and indicate that the participants were in a study concerning illicit drug use. Informed consent was obtained in the ABC hospital by a study coordinator and the signed consent form was possibly lost during transit to the study coordinator's office, which is located in a different building on the ABC campus. Despite an extensive

search of the file cabinets in the office and the clinic area, the forms were not found. This is an example of a potential breach of confidentiality that meets the criteria for a UPIRSO because it was (a) unexpected; (b) related to participation in the research; and (c) placed the participants at a greater risk of psychological, social, and economic harm than was previously known or recognized. Although the risk of a breach may be described in general terms in an informed consent document, a specific incidence of breach/ potential breach of confidentiality is considered 'unexpected'. Because the documents were transported from one building on campus to another, there is a possibility that the documents were lost in transit and that a participant's status as an illicit drug user was inadvertently disclosed to individuals outside the research team.

7. A participant receives a dose of an experimental agent that is 10-times higher than the dose dictated by the IRB-approved protocol. Although the participant experienced no detectable harm or adverse effect after an appropriate period of careful observation, the dosing error increased the risk of toxic manifestations of the experimental agent. This is an example of a protocol deviation that placed a participant at increased risk of physical harm. The incident meets the criteria for a UPIRSO because it was (a) unexpected; (b) related to participation in the research; and (c) placed the participants at a greater risk of physical harm than was previously known or recognized.

8. A blood test that is needed to monitor participant safety during the trial is missed for a participant participating in a phase 3, randomized, double-blind controlled clinical trial comparing the relative safety and efficacy of a new chemotherapy regimen. As a result, grade 3 neutropenia is not detected until the next study visit. The protocol stipulates a reduction in dosage if > grade 3 neutropenia occurs. This is an example of a protocol deviation that harmed a participant. The deviation meets the criteria for a UPIRSO because it was (a) unexpected; (b) related to participation in the research; and (c) placed the participants at a greater risk of physical harm than was previously known or recognized.

Examples of noncompliance (Failure to follow applicable federal regulations, the requirements or determinations of the IRB, provisions of the IRB approved research study, or University policies. The failure can occur as a result of performing an act(s) that violate(s) requirements or as a result of not acting when required to do so):

1. An investigator receives notification that the IRB has reviewed his/her research application but requires minor revisions before the study can be approved. The investigator submits the study revisions, as stipulated, but proceeds to enroll research participants prior to receiving final IRB approval.

2. An investigator neglects to submit the annual progress report and request for continuing review and the study's approval expires. After the expiration date, the investigator enrolls new participants and/or continues to interact with currently-enrolled participants to collect additional data.

3. Failure to obtain informed consent or deviating from the informed consent or recruitment process as described in the IRB approved protocol. For example, a student volunteer who has not completed

human participants research ethics training conducts the consent process; or, a researcher recruits and enrolls participants directly from among students enrolled in his/her class without having declared this approach as part of the recruitment plan that was approved by the IRB.

4. The consent form is revised to describe liver injury at a higher frequency than previously stated in the original consent form. The investigator enrolls several new participants using the outdated form, thereby failing to provide a participant with new information about procedures or risks that may affect the participant's willingness to continue/participate in the study.

5. After the first wave of focus group data collection, the investigator revises the focus group guide including new questions about illicit drug use that probe more deeply than the questions previously approved by the IRB. Similar problems may arise regarding the use of unapproved materials such as fact or information sheets, recruitment materials, questionnaires, scripts or other materials provided to participants.

6. A new researcher who has completed Good Clinical Practice (GCP) training but not human subjects protection training, performs a routine physical examination for a research participant. Failure to complete IRB- or institutionally-required human subjects protection training prior to engaging in human subjects research constitutes noncompliance.

7. A phase1 drug trial is approved to enroll 12 participants. At annual renewal, the investigator reports that more than 12 participants completed the study. Over enrollment of participants constitutes noncompliance.

When noncompliance has occurred, federal regulations require the IRB to determine whether the incident is serious, continuing or both.

Examples of Serious Noncompliance ("Noncompliance" that adversely and significantly affects the rights or welfare of participants):

1. A participant with diabetes is randomized to receive a medication designed to lower blood glucose. The investigational pharmacy misinterprets the physician's order and provides study medication at a dosage level 70% below what is described in the approved protocol. Two weeks into treatment the participant lapses into a diabetic coma and requires emergency treatment. This is an example of a protocol deviation that placed a participant at increased risk of physical harm. The incident meets the criteria for Serious Noncompliance because the participant's welfare was adversely and significantly affected. It is also a UPIRSO.

2. In order to locate a participant for follow-up, the researcher faxes the participant's name on the study letterhead to the HR department of the participant's current employer. The title of the study is on the letterhead and conveys sensitive information about HIV status. At intake, the participant identified several individuals that the researchers may contact for updated contact information at the time of follow-up if the participant cannot otherwise be reached. The employer was not listed as contact, but the investigator knew the participant's place of work. Upon receipt of the letter, an HR

representative from the participant's employer notified the UNC IRB. This is an example of a breach of confidentiality and a protocol deviation that places participants at increased risk of harm. The incident meets the criteria for Serious Noncompliance because the participant's rights (in this case, privacy and confidentiality) were adversely and significantly affected. It is also a UPIRSO.

3. The IRB learns of a project that involved retrospective review of patients' clinical data to examine the efficacy of a certain genetic testing process. The study team should have sought IRB approval prior to starting the project because the project involves a systematic investigation designed to contribute to generalizable knowledge and acquisition of private identifiable information (i.e., it constitutes human subjects research). This is an example of conducting research without approval. It meets the criteria for Serious Noncompliance because conducting research without approval adversely and significantly impacts the participants' right to privacy. It also represents a UPIRSO.

4. During an internal audit it is discovered that the fifth participant enrolled in a phase I, open-label, uncontrolled clinical study evaluating the safety and efficacy of an investigational study drug is taking an excluded concomitant medication that may interfere with the metabolism of the study drug and increase the levels of study drug in the body. The participant had disclosed that he was taking the concomitant drug at screening, but the study physician missed this important information during the eligibility review. The participant was enrolled despite taking the excluded drug. After taking study drug for two weeks, the participant is hospitalized with symptoms of liver dysfunction. Evaluation of the participant reveals no other obvious cause for liver dysfunction. This is an example of a deviation that harmed participants. The deviation meets criteria for Serious Noncompliance because treating the participant while he/she was taking the excluded medication adversely and significantly impacted the participant's the rights and welfare. It also represents a UPIRSO.

5. An investigator is evaluating the efficacy of cognitive training in adults with Alzheimer disease. Eager to meet the target enrollment number, the investigator sends a recruitment email not approved by the IRB to a public listserv that implies that the cognitive training will produce improvements in general cognition and in quality of life and well-being. The investigator also increased the monitory incentive from $100 to $1000. This a deviation that placed participants or others at increased risk of psychological harm. The deviation meets criteria for Serious Noncompliance because (1) offering an undue inducement to participate and (2) implying a certainty of favorable outcome or other benefits beyond what was outlined in the consent document and the protocol adversely and significantly impacts the rights and welfare of potential participants. It also represents a UPIRSO.

6. An industry Sponsor revises the investigator brochure, master protocol, and consent form to reflect a new risk associated with the study drug. Rather than submitting these new materials to the IRB promptly, per the New Safety Information reporting SOPs, the investigator submits them at annual renewal 7 months later. This noncompliance meets the criteria for Serious Noncompliance because not reporting new safety information adversely and significantly impacts the participants' right to receive new information that may influence their willingness to continue to participate in the study. It also represents a UPIRSO.

7. A participant 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. Two months into the study, the sponsor increases the time of birth control use after the last dose of anti-seizure agent from 8 weeks to 16 weeks. This change was implemented following the analysis of new data from a different trial indicating the investigational agent remains in the body longer than expected and can have adverse effects on a fetus. Three women of child bearing potential are not reconsented with this information, and one of the women becomes pregnant 10 weeks after the last dose of study medication. Upon learning about the error, the woman is very distressed and immediately withdraws from the study. The failure to reconsent participants with the new safety information adversely and significantly impacted the participants' rights (i.e., to receive new safety information) and welfare. It also meets the criteria for a UPIRSO.

8. A research protocol is IRB approved for enrollment of clinic patients for the collection of blood samples to be available for future research to isolate unknown genetic markers and develop novel gene therapies. The IRB approved consent and protocol specify that only adults may be enrolled. In the PI's clinic, many patients under 18 also present for treatments and blood is routinely drawn from them for clinical purposes. The PI decides to expand the cohort to include minors (ages 15-17), as there is minimal risk and the future studies could yield therapies for younger members of the cohort who could potentially benefit from decreased morbidity and mortality. The PI does not notify the IRB or request permission from the parents, however he does assent minor participants using the consent document approved for adults. Deviating from the IRB approved consent process and failing to obtain parental permission adversely and significantly impacted the participants' right for human subjects research protection under the law. It also represents a UPIRSO.

Examples of Continuing Noncompliance (Any "Noncompliance" that occurs after implementation of an IRB-approved CAPA plan that is due to the failure of the investigator and/or research team to comply with that CAPA plan OR repeated instances of noncompliance within one study or across multiple studies that has a high likelihood of resulting in Serious Noncompliance):

1. Multiple instances of not performing protocol-driven laboratory tests that are needed to monitor participant welfare and safety.

2. Repeated failure to respond to IRB inquiries or requests for documentation.

3. Multiple instances of an investigator using unapproved documents.

4. Failure to follow a directive or CAPA established by the IRB.