1. **Purpose**
   Regulations require an organization to establish and follow written procedures for ensuring prompt reporting and review of unanticipated problems involving risk to subjects or others (UPIRSO), serious or continuing non-compliance, suspensions and terminations of IRB approval, changes made to research without IRB approval, and other significant information to the IRB, organizational officials, and federal agencies, as applicable. This SOP provides examples and procedures for the reporting of promptly reportable information (PRI) to the UNC-Chapel Hill IRB.

   In conducting a review of noncompliance, UPIRSO, and other reportable events, the IRB will also consider whether the event or issue was caused by, contributed to, or otherwise related to other determinations (e.g., a report submitted as UPIRSO, may also be considered for serious, and continuing noncompliance).

   In previous versions of the UNC-Chapel Hill SOP’s and electronic submission system this was known as New Safety Information (NSI); however, as not all information that requires prompt reporting is due to safety issues or changes in risk, the nomenclature has been revised to Promptly Reportable Information (PRI).

2. **Responsibility**
   Investigators and study personnel are responsible to evaluate and report PRI. Also, any individual (e.g., subject, family member, colleague, or other personnel) may report to the UNC-OHRE leadership, IRB Chairs, Vice Chancellor for Research’s Office, or the Institutional Official any allegations of noncompliance or other problems they have observed.

3. **Definitions**
   Definitions are located in SOP 6001.

4. **Reporting**
   Investigators must report events or issues as defined below to the IRB as soon as possible but within 7 calendar days after the investigator identifies that an event has occurred. Reporting is done primarily through the “Promptly Reportable Information” submission type in IRBIS (subsequently referred to as a PRI submission). If IRBIS is not available to the submitter, notify OHRE Leadership, including the Compliance Manager, for alternate methods of reporting.

   Adverse events (AEs) in FDA-regulated clinical trials must be reported to the sponsor in compliance with FDA regulations and sponsor requirements. Unless specifically required by the IRB for a given protocol, the UNC-CH IRB does not accept reports of AEs that are not also an unanticipated problem involving risks to subjects or others (UPIRSO).
Study 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 UNC-CH OHRE, IRBs or other components of the UNC-CH HRPP.

Noncompliance may be minor or sporadic or it may be serious or continuing. Any noncompliance that is not potential Serious Noncompliance or Continuing Noncompliance (refer to SOP 6001 for definitions) is not promptly reportable information and must be documented in the research record (e.g., study deviation log) with a Corrective and Preventive Action (CAPA) Plan, as applicable. Although in many scenarios a CAPA is appropriate, other deviations, such as out of study window visit due to subject needing to travel would not necessitate a CAPA, provided appropriate documentation is included. The documentation is subject to review by the IRB and agents of the UNC-CH HRPP.

Anyone may report concerns of possible noncompliance, complaints, or concerns to the OHRE or IRB verbally, by email, or other means. In such cases, the reporting party is responsible for making these reports in good faith, maintaining confidentiality and, unless reporting anonymously, cooperating with any subsequent fact-finding in relation to the report. Noncompliance on the part of the IRB is handled as outlined in SOP 201.

The PI and all other research team members are responsible for the safety and welfare of all subjects enrolled in their studies. When investigators or team members are made aware of complaints or concerns from subjects, the investigator or team members should try to resolve the complaint. A PRI submission is required to be submitted if the investigators or team members are unable to resolve the issue or it otherwise meets the criteria as outlined in Sections 3.1- 3.3. Investigators are encouraged to contact the OHRE Leadership or Compliance Manager when they are having difficulty resolving a complaint or concern, and whenever circumstances warrant.

If an individual, whether investigator, study staff or other, is uncertain whether there is cause to report any event or information that may be considered Promptly Reportable Information, a report should be submitted, or they can directly consult with the UNC-Chapel Hill’s OHRE leadership or compliance staff to discuss the situation informally.

4.1 UPIRSOs

A UPIRSO is any incident, experience, outcome, or new information that is unexpected; related or at least possibly related to participation in the research; and indicates that subjects or others are at a greater risk of physical, psychological, economic, legal or social harm, as defined in SOP 6001.

UPIRSOs are reported to the reviewing IRB. In the case of studies with a reliance agreement designating an IRB other than UNC-CH IRB as the reviewing IRB, note that the UNC-CH IRB must also be notified of certain events. Events requiring notification to the UNC-CH IRB even when it is not serving in the role as reviewing IRB are specially noted below.

Examples:
- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome)
• A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (such as tendon rupture, progressive multifocal leukoencephalopathy)

• Multiple occurrences of an adverse event (AE) that, based on an aggregate analysis, are determined to constitute an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (such as a comparison of event rates across treatment groups reveals a higher event rate in the drug treatment arm versus control arm). The determination should be accompanied by a summary and analysis.

• An AE that is described or addressed in the Investigator Brochure (IB), protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the IB yet hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an UPIRSO. A discussion of the divergence from the expected specificity or severity should accompany the report.

• A serious AE (SAE) that is described or addressed in the IB, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison). A discussion of the divergence from the expected rate should accompany the report.

• AEs involving direct harm to subjects enrolled by the local investigator, in the opinion of the investigator or sponsor.

• Unanticipated adverse device effects (UADEs).

• Any other AE or safety finding (e.g., based on animal or epidemiologic data) that indicates subjects or others might be at risk of serious, unanticipated harms that are reasonably related to the research. These would cause the sponsor to modify the IB, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects. An explanation of the conclusion should accompany the report.

• Reports (including reports from DSMBs/DMCs) that indicate risks are greater than previously known or that indicate the research should be modified, suspended, or halted.

• Sponsor or lead investigator/coordinating center-imposed suspension or termination of some or all research activities.

• An unanticipated event related to the research that exposes subjects or others (who may include investigators, research assistants, students, or the public) to risk of harm even if not directly.

• An event that involves a potential inappropriate sharing or disclosure of a participant’s personal identifiers and/or protected health information; privacy incident; security incident; or breach of privacy or confidentiality (must also be reported to UNC-CH IRB if UNC-CH IRB is not the reviewing IRB).

• New information (e.g., interim analysis, safety monitoring report, or publication) that indicates increased or new risk(s), a decrease to potential benefit from what was previously understood, or that indicates the merit of the research, or the frequency or magnitude of harms or benefits may be different than initially presented to the IRB.

• Any determination of UPIRSO by the reviewing IRB, when the reviewing IRB is not UNC-CH IRB (e.g., there is a reliance agreement with an institution, NCI or commercial IRB to rely on...
its IRB services). The UNC-CH OHRE Compliance Manager must be contacted prior to sending any determinations to regulatory agencies.

4.2 Serious or Continuing Noncompliance

Serious or continuing noncompliance is any serious or continuing failure to follow applicable federal regulations, state or local laws, institutional policies, or other institutional oversight governing human subject protections; or the requirements or determinations of the IRB, including the requirements of the approved investigational plan (i.e., protocol), as defined in SOP 6001.

Reports of serious or continuing noncompliance are submitted to the reviewing IRB. In the case of studies with a reliance agreement designating an IRB other than UNC-CH IRB as the reviewing IRB, note that the UNC-CH IRB must also be notified of certain events. Events requiring notification to the UNC-CH IRB even when it is not serving in the role as reviewing IRB are specially noted below.

Examples:

- A protocol deviation that harmed subject(s) or others or placed subject(s) or others at increased risk of harm.
- 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 or reconsent as required by the IRB
- Written report from a federal agency (e.g., FDA Form 483) indicative of noncompliance (must also be reported to UNC-CH IRB if UNC-CH IRB is not the reviewing IRB)
- 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 (such as not reconsenting subjects, or consenting a new subject using an outdated version of a consent document)
- For non-exempt research, Initiating changes to the study without IRB approval, including using unapproved materials (such as fact or information sheets, recruitment materials, questionnaires, focus group guides, scripts, or other materials provided to participants)
- For exempt studies, failure to comply with the exemption as granted which may affect the rights and welfare of participants, including incomplete disclosure of study procedures to the IRB, may require submission of a PRI.
- Failure to complete institutionally required human subjects protection training prior to engaging in human subjects research
- Failure to complete the IRB application or other forms related to human subjects research in a true and accurate manner
- Enrollment of participants beyond what has been approved by the IRB in a study that is greater than minimal risk
- Any determination of serious or continuing noncompliance by the reviewing IRB, when the reviewing IRB is not UNC-CH IRB (e.g., there is a reliance agreement with an institution, NCI or commercial IRB to rely on its IRB services). The UNC-CH OHRE Compliance Manager must be contacted prior to sending any determinations to regulatory agencies.
4.3 Other Promptly Reportable Information

Other promptly reportable information includes any other incident, experience, outcome, or new information that is required to be reported in a timely matter to the OHRE but does not meet the criteria of UPIRSO or serious or continuing noncompliance.

Other promptly reportable information is submitted to the reviewing IRB. In the case of studies with a reliance agreement designating an IRB other than UNC-CH IRB as the reviewing IRB, note that the UNC-CH IRB must also be notified of certain events. Events requiring notification to the UNC-CH IRB even when it is not serving in the role as reviewing IRB are specially noted below.

Examples:

- IND Safety Reports from sponsors that meet the criteria for reporting to the FDA under 21 CFR 312.32. Such reports must be accompanied by confirmation that the sponsor has submitted the report to the FDA.
- A complaint or concern expressed by subjects or others about the conduct of the study or a subject’s participation (must also be reported to UNC-CH IRB if UNC-CH IRB is not the reviewing IRB).
- Protocol deviation that is made to eliminate an immediate hazard to a subject without IRB approval.
- Allegation of noncompliance.
- Audit, inspection, or inquiry by a federal agency (must also be reported to UNC-CH IRB if UNC-CH IRB is not the reviewing IRB).
- State board action that will affect the ability to conduct or complete the research as approved by the IRB; or increases risk to subjects or others (such as with a suspension of a professional license) (must also be reported to UNC-CH IRB if UNC-CH IRB is not the reviewing IRB).
- Incarceration of a subject who is actively participating 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 (must also be reported to the UNC-CH IRB if UNC-CH IRB is not the reviewing IRB).
- Any event, incident, or situation that has generated adverse media attention or congressional interest (must also be reported to UNC-CH IRB if UNC-CH IRB is not the reviewing IRB).

5. Management and Evaluation of Promptly Reportable Information

A. Eliminate Immediate Hazard to Subjects

The first step is for investigators to eliminate any apparent immediate hazard to subject(s) or others. Immediate corrections do not require IRB approval prior to initiation so long as the actions are necessary to eliminate apparent immediate hazards but must be reported to the IRB by including a description in the initial report of Promptly Reportable Information. Immediate corrections may include, but are not limited to: notification of subjects, stopping enrollment or administration of investigational product.

B. Evaluate and Report Event.
Once apparent immediate hazards to the subject have been eliminated, the next step is to evaluate the event to determine if the event represents an UPIRSO, serious or continuing noncompliance, or other information constituting promptly reportable information. If the event does not meet the criteria for promptly reportable information, maintain a record of the event in the study record or deviation log, as appropriate. If the event meets the criteria of a PRI, prepare a PRI submission to include the following information:

- 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.
- A detailed evaluation of unexpectedness, relatedness, and increased risk.
- Summaries, reports, discussions, explanations, etc., of circumstances or conclusions
- In the case of a report from an external IRB, the external IRB's determination letter

C. **Identify Root Cause.**

After the event has been identified the root cause of an event or a problem must be identified to establish an appropriate Corrective and Preventive Action Plan. Root Cause Analysis (RCA) is a formal process for identifying and documenting the root cause and the downstream effects. Some methods of RCA include brainstorming, the 5 Whys, flowcharting, fishbone diagrams and affinity diagrams. For more information about completing a formal Root Cause Analysis, please contact the Office of Clinical Trials.

The root cause can be identified by asking basic questions, such as:

- What was the error?
- How did it occur?
- How widespread?
- Why did it occur?

The results of the root cause should be included in the PRI Submission.

D. **Establish a Corrective and Preventive Action (CAPA) Plan**

Once the root cause has been identified, the next step is to develop a corrective and preventive action plan (CAPA) to eliminate the root cause. Consistent with quality improvement methodology, it is expected that CAPA plans are thoroughly documented, implemented, and that the effectiveness of the CAPA plan is evaluated over time, as appropriate. When reviewing a report of UPIRSO, Serious Noncompliance, Continuing Noncompliance, Suspension or Termination of IRB approval, HHS Office of Human Research Protection and the FDA assesses most closely the adequacy of the actions taken by the institution to address the problem. The following information should be included in the PRI Submission to meet the expectation from regulatory and accreditation bodies.

CAPA plan elements:

1. Description of the corrective and preventive actions taken or planned by the study team.
   
   i. If subjects will be reconsented, or have information shared with them, ensure that the submission describes the subjects’ current participation
and outlines who will be re-consented vs notified and draft notification, addendum section and guidance on what is appropriate when), how they will be reconsented or notified, and when will subjects be reconsented or notified. Outline to the IRB as to why the reconsent or notification plan is appropriate considering the population, the subjects’ status in the study lifecycle in relation to the new risk or event.

2. Date(s) on which the action(s) were taken or are planned.
3. The personnel who are responsible for the implementation of each action.
4. Plan/procedures to evaluate the effectiveness of the CAPA plan, personnel who are responsible for the evaluation, and the timeframe for the evaluation.
5. Process by which the CAPA plan will be amended if it is found to be ineffective.

Documentation of CAPA plan. 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. Plan for amending the CAPA

6. Submission
The UNC-Chapel Hill requires that the PI sign-off on PRI submissions to ensure they have evaluated the risk and ensure no additional changes or immediate actions to reduce risks to subjects need to occur, unless there are extenuating circumstances as permitted by OHRE Leadership or IO (e.g., PI left the institution or was hospitalized unexpectedly). The IRB or OHRE Staff may request additional information to assess the event and CAPA. 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. The IRB will review the report and make the final determination regarding the sufficiency of the CAPA as outlined in SOP 1402.

During large study or department audits where multiple findings or events have occurred, please contact OHRE Leadership or the Compliance Manager prior to submitting to identify the most appropriate way to submit in the electronic system.

7. Promptly Reportable Information Follow-up Reports
Follow-up reports can be submitted once a Promptly Reportable Information Report has been resolved. Follow-up reports can be submitted if there is a request to follow-up from the IRB, additional information about the event is identified, an appeal of determinations is requested or a revised CAPA needs to be submitted.

8. 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.