Title:	IRB Review of New Safety Information		
SOP Number:	1402	**Effective Date:**	9.9.2019
Previous Version Dates:	6.2.2017		

1 PURPOSE

1.1 This SOP establishes written procedures for ensuring prompt review and reporting of any Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO), Serious Noncompliance, Continuing Noncompliance, Suspension or Termination of IRB approval in accordance with 45 CFR 46.103(a) and (b)(5), and 21 CFR 56.108(b).

1.2 This SOP begins when the UNC Office of Human Research Ethics (OHRE) receives a New Safety Information (NSI) submission.

1.3 This SOP ends when the Principal Investigator (PI), and if applicable, the Institutional Official (IO) and designee, and Federal Regulatory Agencies have been notified of the outcome of the NSI review.

2 RESPONSIBILITY

2.1 The convened IRB; the Safety Welfare Analysis Group (SWAG); the IO and designee; the IRB Chair, Co-Chairs, and Vice-Chairs; OHRE leadership; and the Safety/Compliance team are responsible for carrying out the procedures described in this SOP.

3 PROCEDURES

3.1 NSI Triage

Upon receipt of NSI, the OHRE Safety/Compliance team in consultation with OHRE leadership will promptly triage the NSI.

3.1.1 NSI that suggests that participants or others may be at risk of imminent serious harm is triaged to an IRB Chair, Co-Chair or Vice-Chair. The OHRE Director is also notified.

3.1.2 All other NSI is referred to SWAG.

3.1.3 Information that does not represent NSI is resolved or re-triaged within the IRB.

3.2 Interim Suspension

The IRB Chair(s) will review the referred NSI. If it is determined that participants may be at risk of imminent serious harm, the IRB Chair, Co-Chair or Vice-Chair will

3.2.1 Initiate an interim suspension of IRB approval of all activities or a subset of activities.

3.2.2 Refer the interim suspension and associated NSI for review by the convened IRB. An interim suspension must be reviewed by the convened IRB to either uphold or lift the suspension.

3.2.3 Notify the PI and designated personnel, the IRB Chair or Co-Chair of the IRB that will review the interim suspension, and OHRE leadership.

3.3 SWAG NSI Review

SWAG, a group of two or more individuals with expertise in clinical research and an IRB Chair, Co-Chair or Vice-Chair, reviews NSI and proposed Corrective and Preventative (CAPA) plans and conducts fact-finding.

3.3.1 If the NSI suggests that participants or others may be at risk of imminent serious harm, SWAG will:

3.3.1.1 Initiate an interim suspension of IRB approval of all activities or a subset of activities.

3.3.1.2 Refer the interim suspension and associated NSI for review by the convened IRB. An interim suspension must be reviewed by the convened IRB to either uphold or lift the suspension.

3.3.1.3 Notify the PI and designated personnel, the IRB Chair or Co-Chair of the IRB that will review the interim suspension, and OHRE leadership.

3.3.2 If the NSI may represent an Unanticipated Problem Involving Risks to Subjects or Others (UPIRSO), Serious Noncompliance, or Continuing Noncompliance, SWAG will:

3.3.2.1 Refer the NSI to the convened IRB for review.

3.3.2.2 Notify the PI and designated personnel, and the IRB Chair(s) of the IRB that will be assigned the NSI.

3.3.3 If the NSI represents Noncompliance or other information that is not an UPIRSO, Serious Noncompliance, or Continuing Noncompliance, SWAG will:

3.3.3.1 Work with the PI to ensure that the proposed CAPA plan is appropriate.

3.3.3.2 Notify the PI and designated personnel of the determination and the approved CAPA.

3.3.3.2.1 If Minor Noncompliance, notify the PI and designated personnel to document the Minor Noncompliance in the research record (i.e. deviation log) and implement a CAPA plan that addresses the root cause of the Minor Noncompliance.

3.3.3.2.2 Provide education on reporting requirements.

3.3.4 If the reported information is not NSI, SWAG will:

3.3.4.1 Notify the PI and designated personnel

3.3.4.2 Provide education on reporting requirements

3.3.5 If SWAG is uncertain about what the reported information represents, it will refer the information to the convened IRB for review.

3.3.6 If the NSI is applicable to other UNC parties (e.g. University Counsel, UNC Hospitals Risk Management, Research Integrity Officer, Privacy Office), SWAG will notify the appropriate parties.

3.4 **NSI Review by the Convened IRB**

The convened IRB serves in accordance with 45 CFR 46, and 21 CFR 50 and 56 (See SOP 401 for more information about the function of the convened IRB). NSI Review follows the same processes as outlined in SOP 701, in addition to the following:

3.4.1 NSI referred to the IRB and any supporting documentation will be distributed to IRB Chair(s) and members for review approximately 7 calendar days prior to the date of the convened meeting.

3.4.2 The PI and study team may be invited to participate to answer questions or to clarify information.

3.4.3 The IRB will use a review worksheet to guide the NSI discussion.

3.4.4 The IRB support personnel will document the NSI review, including discussion, controverted issues, determinations, the approved CAPA plan, stipulations, motions and votes.

3.4.5 Following NSI Review, the Safety/Compliance team will notify the PI of the outcome of the review.

3.4.5.1 The PI notification will include the IRB's determination, including the rationale for the determination, the approved CAPA plan, stipulations and any other information as directed by the Board.

- Copy to: IO and designee, the IRB Chair/Co-Chair, OHRE leadership, and other relevant parties at the discretion of the IO and designee, and Director of OHRE if the NSI is determined to constitute an UPIRSO, Serious Noncompliance, Continuing Noncompliance, a Suspension or Termination of IRB Approval.

- Copy to: The PI's Department Chair, Division Chair, Director, and/or Dean if the NSI is determined to constitute Serious Noncompliance, Continuing Noncompliance, or a Suspension or Termination of IRB Approval.

3.5 **Notification of Federal Agencies**

3.5.1 Federal regulations require that the IRB follow written procedures for ensuring prompt reporting of any UPIRSO, Serious Noncompliance, Continuing Noncompliance, Suspension or Termination of IRB Approval to the appropriate federal agencies. The appropriate federal agency is:

- The Department of Health and Human Services (HHS), Office of Human Research Protections (OHRP), when research is federally funded.
- The Food and Drug Administration (FDA), when the research is FDA-regulated.
- Other federal agencies, when the research is overseen by those agencies and they require reporting separate from OHRP.

3.5.2 The Safety/Compliance team in collaboration with the Chair/Co-Chair and OHRE leadership will:

3.5.2.1 Prepare a report that includes:

- Title of the study;
- Name of the PI;
- IRB Study number;
- The number of any applicable federal award(s) (grant, contract, or cooperative agreement);
- IND or IDE number;
- A detailed description of the NSI;
- The reason for the suspension or termination of IRB approval, as applicable.
- A CAPA plan that addresses the root cause of the NSI. Of note, when reviewing a report of a UPIRSO, Serious Noncompliance, Continuing Noncompliance, Suspension or Termination of IRB approval, OHRP assesses most closely the adequacy of the actions taken by the institution to address the problem. Specifically, OHRP assesses whether the CAPA plan will 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, the CAPA plan be applied institution wide.
- Copy to: IO and designee, Director of OHRE, IRB Chairs, PI, Office of University Counsel, Office of Clinical Trials, Office of Sponsored Research
- Copy to: PI's Department Chair, Division Chair, Director, and/or Dean, if the NSI represents Serious Noncompliance, Continuing Noncompliance, a Suspension of IRB Approval, or a Termination of IRB Approval.
- Copy to: Other relevant parties at the discretion of the IO and designee and Director of OHRE.

3.5.2.2 Send the draft report to the PI for review of the study description and event details.

3.5.2.3 If UNC is the reviewing IRB for another institution, and the NSI involves researchers or participants at that institution, provide the relying institution a reasonable opportunity to review and comment on the report.

3.5.2.4 Send draft report to the IO and designee for review and approval.

3.5.2.5 Typically, send the report within 30 days of suspension or termination of approval, or within 30 days of identifying an event as meeting the criteria for an Unanticipated Problem Involving Risks to Subjects or Others, Serious Noncompliance, or Continuing Noncompliance.

3.5.2.6 The report is described as a preliminary report when it concerns an UPIRSO, Serious Noncompliance, or Continuing Noncompliance for which information is still being gathered, or for which proposed corrective and preventative actions have not yet been approved by the convened IRB.

3.5.2.6.1 The final (i.e., follow-up) report is sent within 30 days of final resolution.

3.5.3 The Safety/Compliance team, IRB Chair/Co-Chair, OHRE leadership and the IO will review all responses received from Federal Agencies. All correspondence will be maintained on file in the OHRE.

3.5.4 Reports to funding agencies (e.g., NIH) will be sent under separate cover by the IO or designee.

3.6 Notification of the Association for the Accreditation of Human Research Protection Programs (AAHRPP)

3.6.1 AAHRP requires notification of the following information, generally within 48 hours after the institution or researchers become aware of the information:

3.6.1.1 Any negative actions by a government oversight office, including, but not limited to, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated, FDA Restrictions on Investigators, and any corresponding compliance actions taken under non-US authorities related to human research protections.

3.6.1.2 Any litigation, arbitration, or settlements initiated related to human research protections.

3.6.1.3 Any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding human subjects research conducted at or by UNC-CH or about UNC-CH's Human Research Protection Program (HRPP).

3.6.2 Information received by OHRE outside of IRBIS is triaged to the Safety/Compliance team and OHRE leadership.

3.6.3 The Safety/Compliance team and OHRE leadership will notify AAHRPP without delay.

3.7 **Reconsideration**

As required by regulations, any decision of the IRB with respect to research involving human subjects is final. However, the PI may request that the convened IRB reconsider its determination and/or CAPA plan based on new information that was not available or considered at the time the determination was made. No other circumstances warrant a reconsideration. The petition must be made within 10 calendar days of notification of the IRB's findings. At the IRB's discretion, the PI may be invited to the IRB meeting at which his or her petition will be considered.

3.8 **Participant or Third-Party Complaint or Allegation of Noncompliance**

3.8.1 Participants are encouraged to ask questions or voice any concerns or complaints they may have about the research. The PI is responsible for answering all questions, addressing all concerns, and responding to all complaints raised by participants to the best of his/her ability. The name and contact information of the PI responsible for the conduct of the research is required in all UNC consent documents.

3.8.2 Participants are also encouraged to discuss their rights or to voice their concerns or complaints about the research with OHRE. The telephone number and email of the OHRE is required in all UNC consent documents. OHRE contact information is also available to participants and third parties on the OHRE website.

3.8.3 When the UNC IRB waives the requirement for the PI to obtain a signed consent document, contact information for the PI is included in a study information sheet or other written information about the research.

3.8.3.1 Complaints received by the PI or study personnel:

3.8.3.1.1 The PI is responsible for ensuring that complaints are reviewed thoroughly and respectfully. Participants should not be penalized or lose any benefits they are receiving or have a right to receive as a result of the complaint.

3.8.3.1.2 The PI will address the complaint promptly and communicate its resolution to the complainant, generally within 30 days.

3.8.3.1.3 The PI must document all complaints received from participants or third parties and their resolution.

3.8.3.1.4 If the complaint meets NSI reporting requirement per SOP 1401, an NSI submission is required.

3.8.3.1.5 The PI and the study team will work with OHRE to resolve complaints.

3.8.3.2 Complaints received by OHRE:

3.8.3.2.1 The Safety/Compliance team reviews all complaints with consultation by the OHRE leadership and the IRB Chair(s) as applicable. OHRE will maintain privacy of the complainant where privacy is a concern or when requested by the complainant.

3.8.3.2.2 Complaints received outside of IRBIS, regardless of point of origin, are recorded in writing and provided to the Safety/Compliance Manager.

3.8.3.2.3 The Safety/Compliance team will notify the PI of the complaint.

3.8.3.2.3.1 If the complaint meets the criteria for NSI, an NSI submission with a response to the complaint is required. The NSI submission will be reviewed as described in this SOP.

3.8.3.2.3.2 Complaints regarding minor administrative issues such as a brief delay in compensation does not require an NSI submission. Upon resolution of a minor administrative complaint, the PI is required to summarize the response to the complaint in an email to the Safety/Compliance Manager.

3.8.3.2.4 The OHRE Safety/Compliance team will work with the PI, the IRB Chair(s) and OHRE leadership to resolve the complaint, and will communicate its resolution to the complainant, generally within 30 days of receipt of the complaint.

3.8.3.2.5 OHRE will maintain records of complaints and their resolution, and a copy will be retained in the applicable protocol file.

3.9 **NSI Review when UNC is Ceding IRB Review**

If UNC is ceding review and oversight to another IRB and that IRB has made a regulatory determination of Serious Noncompliance, Continuing Noncompliance, an Unanticipated Problem Involving Risks to Subjects or Others that involve UNC participants or researchers, the determination and the approved CAPA is reportable as NSI (see SOP 1401).

3.9.1 SWAG will:

3.9.1.1 Review the CAPA plan to ensure that it appropriately addresses the event.

3.9.1.1.1 If the CAPA is determined to be inadequate, SWAG will refer the NSI and SWAG's findings to the convened IRB.

3.9.1.1.2 If the CAPA is deemed adequate, confirm that the CAPA plan has been implemented at UNC.

3.9.1.2 Request update on participants and others that may have been harmed.

3.9.1.3 Notify the IO and other relevant parties of the NSI.

3.9.1.4 If not previously received, request a copy of the notification letter to Federal Agencies, as applicable.

3.9.2 The convened IRB will:

3.9.2.1 Review the NSI, the approved CAPA plan and SWAG's findings, and propose updates to the CAPA plan as applicable .

3.9.2.2 Notify the IRB of record and the UNC IO and designee of the UNC IRB's findings and proposed CAPA plan.

4 DEFINITIONS

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

4.1.1 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;

4.1.2 Is related or possibly related to a participant's participation in the research; and

4.1.3 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.

4.2 Allegation of Noncompliance: An unproven assertion of "Noncompliance" by a participant or a third party.

4.3 Noncompliance: Intentional or unintentional failure to follow applicable federal regulations, the requirements or determinations of the IRB, provisions of 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.

4.4 Minor Noncompliance: Any "Noncompliance" that does not (1) suggest that the research placed participants or others at increased risk of harm, (2) and adversely affects the safety, rights, or welfare of participants; and/or (3) and adversely affects the integrity of the research. (2) does not adversely affect subjects' rights or welfare.

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

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

4.7 Suspension: Temporary withdrawal of approval by the IRB of some or all research activities associated with a study. The convened IRB can suspend approval of research that is (1) not being conducted in accordance with the IRB's requirements or (2) has been associated with unexpected serious harm to subjects. Suspended research remains under the jurisdiction of the IRB and is subject to continuing review.

4.8 Termination: Permanent withdrawal of approval by the IRB of all research activities associated with a study. The convened IRB can terminate approval of research that is (1) not being conducted in accordance with the IRB's requirements or (2) has been associated with unexpected serious harm to subjects. IRB approval may only be terminated by the convened IRB.

5 REFERENCES

5.1 DHHS Regulations: 45 CFR 46.103(a) and (b)(5)

5.2 FDA Regulations: 21 CFR 56.108(b)