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| **Title:** | Management of New Safety Information | | |
| **SOP Number:** | 1402 | **Effective Date:** | 6.2.2017 |
| **Previous Version Dates:** | | | |

## 1 PURPOSE

1.1 This procedure establishes the process to manage New Safety Information.

1.2 This procedure begins when OHRE receives New Safety Information (regardless of whether the information is reportable).

1.3 This procedure ends when the New Safety Information has been resolved administratively or the Principal Investigator (PI), Institutional Official, and if applicable, Federal Regulatory Agencies have been notified of final determinations made by the convened IRB.

## 2 RESPONSIBILITY

2.1 The OHRE Director appoints members of the Safety Welfare Analysis Group (SWAG).

2.2 The OHRE Compliance Manager triages all New Safety Information.

2.3 The Safety Welfare Analysis Group (SWAG) reviews New Safety Information and determines which information needs review by the IRB Safety Committee. SWAG consists of a minimum of 3 members who have experience with research. These members may include a physician, physician assistant, nurse practitioner, a clinical researcher, and the OHRE Compliance Manager.

2.4 The IRB Safety Committee reviews New Safety Information that has been referred to the Committee by SWAG and determines if the New Safety Information represents Serious Noncompliance, Continuing Noncompliance, an Unanticipated Problem Involving Risks to Subjects or Others, a Suspension of IRB Approval or a Termination of IRB Approval. The Safety Committee serves as an IRB in accordance with 45 CFR 46, and 21 CFR 50 and 56 (SOP 401).

2.5 Members of SWAG and the IRB Safety Committee, the Compliance Manager, and the IRB Analyst are responsible for carrying out the procedures described in this SOP.

## 3 PROCEDURE

3.1 Upon receipt of New Safety Information, the OHRE Compliance Manager will:

- 3.1.1 Promptly complete a preliminary review of the New Safety Information.
  - 3.1.1.1 If the Compliance Manger determines that subjects may be in imminent serious harm, the information is reported immediately to the Chair. If the Chair concurs, suspension of IRB approval may be initiated by the Chair, after which the study must be reviewed by the Safety Committee to either uphold or lift the suspension.
- 3.1.2 Notify SWAG of the New Safety Information.

3.2 Upon receipt of New Safety Information, SWAG will:

- 3.2.1 Ask the following questions 6 questions
  - 3.2.1.1 Does the information represent an Allegation of Noncompliance? If yes:
    - 3.2.1.1.1 Evaluate the Allegation of Noncompliance to determine whether there is a basis in fact.
    - 3.2.1.1.2 If the Allegation of Noncompliance has basis in fact, then this represents Noncompliance.

3.2.1.1.3 If the Allegation of Noncompliance has basis and was received by means other than directly from the investigator via IRBIS, the Compliance Manager will notify the PI of the allegation and ask the PI to submit a UP report.

3.2.1.2 Does the information represent Noncompliance? If yes:

3.2.1.2.1 Evaluate the Noncompliance to determine potential Serious or Continuing Noncompliance.

3.2.1.3 Does the information represent Serious Noncompliance?

3.2.1.4 Does the information represent Continuing Noncompliance?

3.2.1.5 Does the information represent an Unanticipated Problem Involving Risks to Subjects or Others?

3.2.1.6 Does the information require Suspension or Termination of IRB Approval?

3.2.2 If additional information is needed to answer the six questions:

3.2.2.1 Send stipulations letter

3.2.2.2 Upon receipt of PI responses, review as per 3.1.1.1.

3.2.3 If the answer to each of the six questions is "no":

3.2.3.1 Send out notification for PI.

3.2.3.2 Respond as needed to Complainant

3.2.4 If the information represents Noncompliance that is neither Serious Noncompliance, nor Continuing Noncompliance, evaluate any submitted corrective and preventative action (CAPA) plan.

3.2.4.1 Work with the research team to develop a sufficient CAPA plan (see SOP 1401, section 3.2.5).

3.2.4.2 If the research team develops a sufficient CAPA plan, send out the notification of the finding of Noncompliance for the submitter.

3.2.4.3 If the research team cannot develop a sufficient CAPA plan, consider the Noncompliance to be Continuing Noncompliance and refer to the Chair and Vice Chair of the IRB Safety Committee for review by the convened IRB.

3.2.5 If the information potentially represents Serious Noncompliance, Continuing Noncompliance, an Unanticipated Problem Involving Risks to Subjects or Others, or requires Suspension or Termination of IRB Approval,

3.2.5.1 Consider if any immediate actions are necessary to protect the rights and welfare of participants. In situations where subjects may be in imminent serious harm, suspension of IRB approval may be initiated by the Chair or SWAG, after which the study must be reviewed by the convened IRB to either uphold or lift the suspension. Notify the IRB Safety Committee of the New Safety Information.

3.2.5.2 If appropriate, coordinate with other UNC offices or parties about the New Safety Information, as applicable (e.g. University Counsel, UNC Hospitals Risk Management, Research Integrity Officer, Privacy Office).

3.2.6 If SWAG is uncertain about what the information represents, it will refer the information to the IRB Safety Committee.

3.3 In preparation for the IRB Safety Committee Meeting,

3.3.1 The IRB Analyst will:

3.3.1.1 Prepare the agenda and identify the materials required for the review (e.g., New Safety Information, master protocol, consent documents, recruitment materials, investigator brochure, email correspondence with the investigator, IND safety report, etc.) no later than 7 calendar days prior to the meeting.

3.3.1.2 Assign the New Safety Information to a Presenter.

3.3.1.3 Notify the Administrative Assistant that the agenda and materials required for the review are accessible.

3.3.1.4 Confirm quorum.

3.3.2 The Administrative Assistant will:

3.3.2.1 Confirm attendance for the meeting and report attendance to the IRB Analyst.

3.3.2.2 Distribute the agenda, the report of New Safety Information, and other information required for the review no later than 7 calendar days prior to the meeting.

3.3.3 The Presenter will:

3.3.3.1 Review the New Safety Information.

3.3.3.2 Request additional information as needed directly from the PI.

3.3.3.3 Complete SUPPLEMENT 1: Safety Committee Review Worksheet

3.3.3.4 Email completed worksheet and communicate any deferrable issues to the IRB Analyst 3 business days prior to the meeting.

3.3.4 The Safety Committee Members will:

3.3.4.1 Review the New Safety Information and Complete SUPPLEMENT 1: Safety Committee Review Worksheet. Communicate any deferrable issues to the Presenter no later than 3 business days prior to the meeting.

3.3.5 The IRB Chair or Vice Chair will:

3.3.5.1 Review all New Safety Information on the agenda.

3.3.5.2 The Chair will invite the PI to the meeting to answer questions or clarify information as needed.

3.4 At the IRB Safety Committee Meeting,

3.4.1 The Presenter will:

3.4.1.1 Present the New Safety Information and proposed CAPA.

3.4.1.2 Lead the committee through a discussion of considerations and proposed determination(s) using SUPPLEMENT 1: Safety Committee Review Worksheet. If applicable, make a motion for Serious Noncompliance, Continuing Noncompliance, an Unanticipated Problem Involving Risks to Subjects or Others, a Suspension of IRB Approval or a Termination of IRB Approval.

3.4.2 The Chair or Vice Chair will:

3.4.2.1 Lead the meeting.

3.4.2.2 Call for motions.

3.4.2.3 Call for a vote.

3.4.3 The IRB Analyst will document in sufficient detail the determinations, actions, requested changes, and recommendations by the IRB Safety Committee as specified in SOP 1001, Documentation and Records.

3.5 Following the review by the IRB Safety Committee,

3.5.1 The IRB Analyst will:

3.5.1.1 Prepare the notification letter to the PI.

3.5.1.1.1 The notification includes the determination, the rationale for the determination, and any actions requested and recommended by the committee. It also states that the investigator may request that the convened IRB reconsider its determination based on new information not available or considered at the time of the determination. See 3.8 for additional information.

3.5.1.1.2 Prepare stipulations.

3.5.1.1.3 Copy the OHRE Director and the Institutional Official on the notification letter if the information is determined to represent Serious Noncompliance, Continuing Noncompliance, an Unanticipated Problem Involving Risks to Subjects or Others, a Suspension of IRB Approval or a Termination of IRB Approval.

3.5.1.1.4 Copy the PI's Department Chair, Division Chair, Director, and/or Dean on the notification letter if the information represents Serious Noncompliance, Continuing Noncompliance, a Suspension of IRB Approval, or a Termination of IRB Approval.

3.5.1.1.5 Copy the Director of the Office of Clinical Trials (or designee) if the information represents Serious Noncompliance, Continuing Noncompliance, an Unanticipated Problem Involving Risks to Subjects or Others, a Suspension of IRB Approval, or a Termination of IRB Approval AND the study is sponsored.

3.5.1.1.6 Prepare and distribute the minutes to the IRB Safety Committee Chair (or Vice Chair, when applicable) for review.

3.5.1.1.7 Review PI responses to stipulations from IRB Safety Committee and notify Chair or Vice Chair when their review is completed.

3.5.2 The Chair or Vice Chair will:

3.5.2.1 Review summary of determinations, actions, requested changes, and recommendations prepared by the IRB Analyst during the meeting.

3.5.2.2 Send out the PI notifications and stipulations.

3.5.2.3 Review PI responses to stipulations and either confirm they are adequate or resend stipulations, as needed, until resolved.

3.5.3 The Compliance Manager will:

3.5.3.1 Draft report to the appropriate federal agencies of Serious Noncompliance, Continuing Noncompliance, an Unanticipated Problem Involving Risks to Subjects or Others and Suspension or Termination of IRB Approval in consultation with the IRB Chair and Director of OHRE. The appropriate federal agency is:

3.5.3.1.1 OHRP, when research is federally funded.

3.5.3.1.2 FDA, when the research is FDA-regulated.

3.5.3.1.3 Other federal agencies, when the research is overseen by those agencies and they require reporting separate from OHRP.

3.5.3.2 Send the draft report to The Office of University Counsel and the Institutional Official for review.

3.5.3.3 Send draft report to the PI for review of the study description, event details, timeline and CAPA for accuracy.

3.5.3.4 If UNC is the IRB of record for another institution with an IRB, and the New Safety Information involves investigators or subjects at that institution, provide the relying institution a reasonable opportunity to review and comment on the report.

3.5.3.5 For Unanticipated Problems Involving Risks to Subjects or Others, the Compliance Manager will include following elements in the report:

3.5.3.5.1 Title of the research project and/or grant proposal in which the problem occurred;

3.5.3.5.2 Name of the principal researcher on the protocol;

3.5.3.5.3 Number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement);

3.5.3.5.4 A detailed description of the New Safety Information; and

3.5.3.5.5 Actions the institution is taking or plans to take to address the problem (e.g., revise the protocol, suspend participant enrollment, terminate the research, revise the informed consent document, inform enrolled participants, increase monitoring of participants, etc.).

3.5.3.6 For Serious or Continuing Noncompliance, the Compliance Manager will include the following elements in the report:

3.5.3.6.1 Title of the research project and/or grant proposal in which the noncompliance occurred;

3.5.3.6.2 Name of the principal researcher on the protocol;

3.5.3.6.3 Number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement);

3.5.3.6.4 A detailed description of the noncompliance; and

3.5.3.6.5 Actions the institution is taking or plans to take to address the noncompliance (e.g., educate the researcher, educate all research staff, suspend the protocol, suspend the researcher, conduct random audits of the researcher or all researchers, etc.).

3.5.3.7 For suspension or termination, the Compliance Manager will include the following elements in the report:

3.5.3.7.1 Title of the research project and/or grant proposal that was suspended or terminated;

3.5.3.7.2 Name of the principal researcher on the protocol;

3.5.3.7.3 Number of the research project assigned by the IRB that was suspended or terminated and the number of any applicable federal award(s) (grant, contract, or cooperative agreement);

3.5.3.7.4 A detailed description of the reason for the suspension or termination; and

3.5.3.7.5 The actions the institution is taking or plans to take to address the suspension or termination (e.g., investigate alleged noncompliance, educate the researcher, educate all research staff, require monitoring of the researcher or the research project, etc.)

3.5.3.8 Copy the following individuals on the report:

3.5.3.8.1 Institutional Official

3.5.3.8.2 Director of OHRE

3.5.3.8.3 IRB Chair

3.5.3.8.4 PI

3.5.3.8.5 Office of University Counsel

3.5.3.8.6 PI's Department Chair, Division Chair, Director, and/or Dean, if the New Safety Information represents Serious Noncompliance, Continuing Noncompliance, a Suspension of IRB Approval, or a Termination of IRB Approval.

3.5.3.8.7 Other relevant parties at the discretion of the Institutional Official and Director of OHRE

3.5.3.9 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.

3.5.3.9.1 The report is described as a preliminary report when it concerns an Unanticipated Problem Involving Risks to Subjects or Others, 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 Safety Committee.

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

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

3.7 As required by regulations, any decision of the IRB with respect to research involving human subjects is final. However, the investigator may request that the convened IRB reconsider its determination regarding UPIRSO, noncompliance, and/or corrective actions on the basis of new information that was not available or considered at the time the determination was made. No other circumstances warrant a reconsideration. The investigator petition must be made within 10 calendar days of notification of the Safety Committee'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 The IRB Compliance Manager, the Director of OHRE, Chair or Vice Chair, and the Institutional Official will review all responses received from federal agencies. All correspondence will be maintained on file in the OHRE.

## 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 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.

4.3 Allegation of Noncompliance: An unproven assertion of "Noncompliance."

4.4 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.

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

4.6 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.

4.7 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(b)(5)

5.2 FDA Regulations: 21 CFR §56.108(b)

## 6 RELATED DOCUMENTS

6.1 SUPPLEMENT 1: Safety Committee Review Worksheet

**SUPPLMENT 1: Safety Committee Review Worksheet**

*This worksheet is used by IRB members to consider determinations and actions in response to New Safety Information.*

| **Study #:** | **PI Name:** |
|---|---|
| **Name of Reviewer:** | **Date of Completion:** |

**UNANTICIPATED PROBLEM INVOLVING RISK SUBJECTS OR OTHERS (UPIRSO)**

**If all (3) criteria apply, the new safety information is considered an UPIRSO:**

☐ 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.

☐ Related or possibly related to a participant's participation in the research.

☐ Serious or suggests that the research places (or could have placed) participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Notes:

**SERIOUS NONCOMPLIANCE**

**If one of the criteria below apply, the new safety information is considered Serious Noncompliance:**

☐ Non-compliance that adversely and significantly affects the rights of participants

☐ Non-compliance that adversely and significantly affects the welfare of participants

Notes:

**CONTINUING NONCOMPLIANCE**

**If one of the criteria below apply, the new safety information is considered Continuing Noncompliance:**

☐ 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.

☐ Repeated instances of noncompliance within one study or across multiple studies that has a high likelihood of resulting in Serious Noncompliance.

Notes:

| **Range of possible considerations for UPIRSO, SERIOUS or CONTINUING NONCOMPLIANCE:** | | **Check all that apply** |
|---|---|---|
| 1.1 | Should the research be suspended?<br>Scope of the suspension (i.e., all or parts of the research?): | ☐ |
| 1.2 | Should the research be terminated?<br>Scope of the termination (i.e., all or parts of the research?): | ☐ |
| 1.3 | Should current participants be notified when such information may relate to participants' willingness to continue to take part in the research? | ☐ |
| 1.4 | Does the research protocol require modification? (e.g., additional monitoring of participants) | ☐ |
| 1.5 | Does the consent form require modification? | ☐ |
| 1.6 | Should current participants be re-consented? | ☐ |

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| 1.7 | Should participants who have completed the study be provided with additional information? | ☐ |
| 1.8 | Should the continuing review schedule be modified? | ☐ |
| 1.9 | Is additional monitoring of the research required? | ☐ |
| 1.10 | Is additional monitoring of the consent process required? | ☐ |
| 1.11 | Should the Principal Investigator receive additional mentoring or training?<br>(i.e., training with OHRE compliance manager, repeat CITI training, eROC modules, observe IRB meeting, IT Security training, etc.) | ☐ |
| 1.12 | Should other members of the research team receive additional mentoring or training? | ☐ |
| 1.13 | Is referral to other organizational entities required? | ☐ |
| 1.14 | Recommendations for the Vice Chancellor for Research: Are limitations (e.g. prohibition on use of data collected as part of protocol noncompliance) on the investigator's use of research data recommended? | ☐ |
| 1.15 | Recommendations for the Vice Chancellor for Research: Are correction to publication or retraction of publication recommended? | ☐ |
| 1.16 | Recommendations for the Vice Chancellor for Research: Is the investigator required to disclose that the data were collected unethically/outside protocol? | ☐ |
| 1.17 | Recommendations for the Vice Chancellor for Research: Should the data be destroyed? | ☐ |
| 1.18 | Are additional resources to support the research recommended/required? | ☐ |
| 1.19 | Is additional information needed to obtain a final decision? | ☐ |

**Note. The IRB cannot retroactively approve use of data collected without UNC approval (including secondary use of the data).**

## PI's Proposed CAPA

☐ Acceptable

☐ Acceptable with modification as specified:

☐ Unacceptable

## Suspension

☐ Temporary withdrawal of approval of all research activities

☐ Temporary withdrawal of approval of some research activities as specified:

## Termination

☐ Permanent withdrawal of approval

| **Range of possible considerations for SUSPENSION and TERMINATION:** | | **Check all that apply** |
|---|---|---|
| 1.1 | Are there any actions needed to protect the rights and welfare of currently enrolled participants?<br>Suggested actions: | ☐ |
| 1.2 | Is there a need for medical care arrangements outside of research study? | ☐ |
| 1.3 | Should participants be transferred to another researcher? | ☐ |
| 1.4 | Should participants be transferred to another research site? | ☐ |
| 1.5 | May participants continue in the research under independent monitoring? | ☐ |
| 1.6 | How will current participants be informed of the termination or suspension? | ☐ |

| | | |
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| | Suggested methods of notification: | |
| 1.7 | If suspension, what actions should be taken by the Investigator in order for the suspension to be lifted?<br>Suggested actions: | ☐ |