

- i. The responsibility of Faculty of Medicine Investigators to abide by applicable institutional policies, CHS policies, ethical standards, and applicable federal and state laws
- ii. The responsibility of Faculty of Medicine Investigators to conduct the research in accordance with the CHS-approved protocol
- iii. The publishing rights of the Faculty of Medicine Investigator, within Faculty of Medicine guidelines.
- iv. What medical care, if any, will be provided to participants in the event of a study related injury and how a participant will receive or be reimbursed for such care.
- v. What compensation or payments, if any, will be provided to participants who incur a study related injury
- vi. The responsibility of the Sponsor to promptly report to the Investigator any findings that could:
 - a. Affect the safety of participants
 - b. Affect the willingness of participants to continue with the research
 - c. Influence the conduct of the study
 - d. Alter the CHS approval
- vii. Mechanisms to communicate to participants any study results which may affect their safety or medical care.

13. Adverse Events and Unanticipated Problems

In the course of a research project, various problems arise some of which may affect the research participants in varying degrees of severity. It is important that the CHS be aware of any problems that arise so that a determination can be made by the CHS whether such problems are anticipated or unanticipated and involve risks to participants or others with resultant corrective actions. Investigators must contact the CHS office via phone or email as soon as possible but not more than 48 hours after learning of a problem within their research program. All calls and emails are handled confidentially by CHS staff. The convened CHS will decide, as described below, which of the problems are anticipated or unanticipated involving risks to participants or others and subsequently determine whether any corrective actions need to be taken including, in extreme cases, suspension of the research with notification to participants.

Definitions and examples are provided below. However, the Investigator must report the following to the CHS as soon as possible, but in all cases not more than 48 hours:

- Any adverse event (any harm experienced by a participant regardless of whether the event was internal (on-site) or external (off-site) and regardless of whether the event meets the FDA definition of “serious adverse event”) which in the opinion of the Investigator are both **unexpected and related**.
 - **“Unexpected”** is defined as an event whose specificity and severity are not accurately reflected in the human studies application, protocol, consent form, current investigational brochure or medical device/medication package insert.

- **“Related to the research procedures”** is defined as an event which in the opinion of the Investigator, was more likely than not to be caused by the research procedures or if it more likely than not affects the right and welfare of current participants.
- Information that indicates a change to the risk or potential benefits of the research , such as
 - An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits might be different from those initially presented to the CHS;
 - A paper is published from another study that shows that the risks or potential benefits of the research might be different from those initially presented to the CHS.
- Breach of confidentiality.
- Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Change to the protocol taken without prior CHS review to eliminate an apparent immediate hazard to a research participant.
- Incarceration of a participant in a protocol not approved to enroll prisoners.
- Any event that requires prompt reporting to the sponsor
- Sponsor imposed suspension for risk.
- Complaint of a participant when the complaint indicates unexpected risks or which cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional change to the CHS approved protocol) that harmed participants or others or that indicates participants or others may be at risk of increased harm.
- Unanticipated Adverse Device effect: any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem , or death was not previously identified in nature, severity ,or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.
- **Serious Adverse Event (SAE):** (used interchangeably with Adverse Event (AE) in many settings) is defined as any adverse event occurring that results in any of the following outcomes:
 - Death;
 - A life threatening adverse drug experience;
 - In-patient hospitalization or prolongation of existing hospitalization;
 - Persistent or significant disability/incapacity;
 - Prolonged hospitalization;
 - Congenital anomaly/birth defect;
 - Any important medical event that may not result in death, be life-threatening, or require hospitalization may still be considered a serious adverse event when , based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. .
- **Unanticipated Problem involving Risks to Participant or Others** is defined as a problem that is (1) unforeseen and (2) indicates that participants or others are at increased risk of harm. The majority of the studies reviewed by CHS involve social and behavioral research and thus, these events may be sometimes difficult to determine. As stated above,

all problems should be reported to the CHS office for evaluation by the CHS staff, CHS Chair or CHS.

13.1. When and How to Report Events to the CHS

The CHS adheres to 45 CFR § 46.103(b)(5)(i) and 21 CFR § 56.108(b)(1), which require IRBs to have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the federal department or agency head of any unanticipated problems involving risks to research participants or others.

Investigators should report any research problems involving human participants or research staff via telephone or email immediately but not more than 48 hours after learning of the problem (as defined above). After the initial contact with the CHS Office, Investigators are required to file an Unanticipated Problem/Adverse Event form (Appendix 52) and/or a separate written report to the CHS office, as well as to study sponsor or FDA (if applicable), *within five working days of the event* unless otherwise specified (depending on the severity of the event) by the CHS office.

13.1.1. When there is a Data Safety Monitoring Board or Committee (DSMB/C)

DSMB/Cs (see Section 10.1.3) can be relied upon by the CHS to review SAEs happening at other study sites in a clinical trial, but the CHS must still receive and review reports of local adverse events. If a study has a DSMB/C, the Investigator should submit the data safety monitoring report to the CHS office as soon as it is available. DSMB/C reports should include a statement indicating that the data have been reviewed, the date of review and a summary of specific findings of the research study.

13.2. CHS Review of Reported Problems

The CHS Staff will consult with the CHS Chair and work with the Investigator upon notification of a reported problem (Appendix 52). The CHS Chair will review the report and determine whether the problem 1) is unforeseen; and 2) indicates that participants or others are at increased risk of harm. If both criteria are met, then the problem is considered an unanticipated problem involving risks to participants or others and requires review by the convened CHS. If the CHS Chair believes that the situation is urgent, the CHS staff or Chair will contact the Investigator to request that he/she voluntarily place the study on hold while the CHS Chair reviews the problem more thoroughly and determines whether the problem can wait until the next convened CHS meeting, or whether it requires an emergency CHS meeting.

If the problem is anticipated, or does not involve increased risk of harm to participants or others, the Chair will review the event and indicate whether any action is required of the Investigator, or to the protocol, consent process or documents. In these circumstances, if the study is reviewed via expedited procedures, the Chair or his/her designee may review these changes via expedited procedures, or, if the changes require convened CHS review, procedures will be followed as outlined in Section 6.

The Chair may:

- Determine whether the problem: is unanticipated; and involves risks to participants and/or others.
- Require additional information from the Investigator;
- Require additional information from any additional reviewing IRBs;
- Contact other CHS members or experts in the field for consultation as to the degree or level of risk;
- Request review of the unanticipated problem at the next convened meeting (if the risk upon discovery is considered not an immediate significant risk to other participants);
- Call an emergency meeting, if the problem and risk is such that a study and/or study procedures need to be suspended. In such cases, the CHS office may handle all communication to the Investigator, the Institutional Official and federal agencies; funding sponsors will be notified by SPA or OTD, as appropriate and as outlined below in section 13.3.1.

If an event is reviewed by the convened CHS, the CHS shall determine appropriate action in response to the report including one or more of the following:

- Decide that no further action is necessary and that the research may continue as designed (whether previously temporarily halted or not).
- Require further investigation by a member or outside expert designated by the Chair prior to the next convened CHS meeting.
- Require modification to the study/protocol and/or procedures necessary to minimize risks to participants.
- Require that additional information regarding risks be given to past participants and determining when this information should be given.
- Require notification of current participants when such information might relate to the participants willingness to continue to take part in the research.
- Require modification to the consent process and/or form to accurately reflect the nature, frequency or severity of the event.
- Require re-consenting current participants in the study.
- Require modification of the continuing review schedule.
- Require assessment by Quality Assurance Coordinator including monitoring of research procedures and consent process.
- Suspend the study procedures including any new enrollment of participants, or suspend the study approval altogether.
- Terminate the study approval.
- Referral to other institutional office as appropriate.

13.3. Document Distribution

The following documents are provided to the CHS prior to review of an unanticipated problem involving risks to participants or others:

- Event report(s) – including any previous events related to the study
- CHS Application and protocol, if separate documents
- Continuing Review Application from current review period, including progress report and CHS initial applications, if necessary

- DSMB report, if applicable
- The associated grant is provided to the Chair and is brought to the CHS meeting.
- Any other materials of relevance or requested by the CHS

13.3.1. Notification of CHS Determinations to Investigator, Institutional Officials, and Regulatory Agencies

The CHS staff will notify the Investigator as soon as possible (ordinarily within three working days of report receipt) of the level of review required for the reported problem, as well as any additional information that may be needed by the Chair or convened CHS to perform a thorough review.

The CHS staff shall send the Investigator written notice of any action taken by the Chair or CHS and the reasons for that action, ordinarily within five working days of the CHS meeting but notification may be sooner depending on the severity of the event or the specifics of the CHS determination. However,

- If the CHS determines that a study needs to be suspended or terminated immediately, the Investigator will be notified by phone or email immediately after the meeting.
- In cases where enrollment in the study had been temporarily halted and the halt has been lifted, the Investigator will be notified immediately after the meeting by phone or email. Email messages will be sent with a “receipt confirmation” affixed to the message so that the CHS staff will know that the Investigator received the message.

The CHS is required to report to OHRP “any unanticipated problems involving risks to subjects or to others”, and thus the ORSP Director will forward decisions of the CHS within five working days to the Director of Compliance at OHRP and to the following other agencies or institutional officials, as appropriate:

- The Investigator’s Faculty of Medicine Department Head (and any additional Department Heads where the Investigator holds multiple professional appointments)
- The Faculty of Medicine Institutional Official. The IO will contact any additional institutional authorities, such as the Dean of the Faculty of Medicine, the President of the University, the Associate Provost for Research, the representative from the Office of the General Council, and Risk Management and Audit Services;
- The Sponsored Research Administration representative (where grants are supporting the research), and the Office of Technology Development (where corporate/company contracts are supporting the research). SPA or OTD will notify the study sponsor.
- Any additional University departments involved in the conduct of the research;
- Any additional IRBs and institutions involved in the research (for multi-site studies, subcontracts, IRBs and institutions relying on CHS review);
- The FDA, when the research is FDA-regulated; and
- Any additional federal agencies involved when the research is subject to those agencies.

Suspensions and terminations of research will be handled and managed as outlined in Section 15 of this policy document.