

THE NORTH SHORE MEDICAL CENTER Institutional Review Board (IRB) POLICIES AND PROCEDURES	IRB Policy Number: 020.0
Title: <i>Unanticipated Problem and Adverse Event Reporting</i>	Page: 1 of 5
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I. PURPOSE

This policy defines the requirements for reporting of unanticipated problems involving risks to subjects or others (including adverse events) to the North Shore Medical Center Institutional Review Board (NSMC IRB).

This policy complies in part with the regulatory requirement in 45 CFR 46.103(b)(5) which states, "each IRB shall follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Department or Agency head of any unanticipated problems involving risks to subjects or others." The Food and Drug Administration regulations include the same requirement [21 CFR 56.108(b)(1)]. Federal regulations at 45 CFR 46.113 and 21 CFR 56.113 state, "IRBs shall have the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or has been associated with unexpected serious harm to subjects." Investigators covered by this policy are required to report unanticipated problems to the NSMC IRB, as described in this document.

II. SCOPE

All investigators conducting human research who use the NSMC IRB are subject to this policy.

III. DEFINITIONS

Adverse event: 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 [OHRP's Guidance on Unanticipated Problems and Adverse Events, January 15, 2007].

External event: From the perspective of one particular institution engaged in a multicenter clinical trial, external events are those experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial [modified from OHRP's Guidance on Unanticipated Problems and Adverse Events, January 15, 2007]. These are typically reports received 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.

Internal events: From the perspective of one particular institution engaged in a multicenter clinical trial, internal events are those experienced by subjects enrolled by the investigator(s) at that institution [modified from OHRP's Guidance on Unanticipated Problems and Adverse Events, January 15, 2007].

Possibly related to the research: There is a *reasonable possibility* that the adverse event, incident, experience or outcome may have been caused by 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)). A *reasonable possibility* is defined as more likely than not related to the research procedures or, in other words, there is a > 50% likelihood of the event having been caused by the procedures involved in the research [Partners Human Research Committee].

Serious:

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

- results in death;
- is life threatening (places the subject at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- 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).[OHRP's Guidance on Unanticipated Problems and Adverse Events, January 15, 2007]

Other serious events: any significant economic or social harm associated with the subject's participation in research that, for example, results in the following:

- criminal or civil liability;
- damage to financial standing, employability, insurability, reputation, or are stigmatizing [Partners Human Research Committee].

Unanticipated problem involving risks to subjects or others: any incident, experience, or outcome that meets ALL of the following criteria:

1. **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 subject population being studied;
2. **Related or possibly related** to participation in the research; and
3. Suggests that the research places subjects or others at a **greater risk of harm** (including physical, psychological, economic, or social harm) than was previously known or recognized.

When the incident, experience, or outcome involves any untoward or unfavorable medical occurrence in a human subject, the incident is considered an adverse event.

For examples of adverse events that represent unanticipated problems and need to be reported, refer to [Appendix D](#) of the OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events. For examples of adverse events that do not represent unanticipated problems and do not need to be reported, refer to [Appendix C](#).

Some incidents, experiences or outcomes involving harm to subjects do not constitute adverse events but may meet the definition of unanticipated problems. Examples include:

- Participant complaints
- Laboratory errors
- Medication errors
- Procedural errors
- Unauthorized disclosure of confidential information
- Lost or stolen confidential information
- Disqualification of investigators
- Suspension of investigators

For examples of unanticipated problems that do not involve adverse events and need to be reported under the HHS regulations at 45 CFR 46, refer to [Appendix B](#) of the OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events [OHRP's Guidance on Unanticipated Problems and Adverse Events, January 15, 2007].

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:

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
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 [OHRP's Guidance on Unanticipated Problems and Adverse Events, January 15, 2007].

IV. ASSESSMENT OF EVENT AS AN UNANTICIPATED PROBLEM

Some adverse events experienced by subjects enrolled in research studies will meet the criteria for unanticipated problems involving risks to subjects or others and must be reported to the NSMC IRB. However, the vast majority of adverse events, serious and non-serious, occurring in the context of research are expected in light of the known toxicities and side effects of the research procedures or are expected due to the natural history of subjects' underlying diseases and conditions. **Unless these adverse events meet the criteria for an unanticipated problem, they do not need to be reported to the NSMC IRB.**

Sponsors are required to notify the FDA and all participating investigators of any adverse experience *associated with the use of the drug* that is both serious and unexpected or any finding from tests in laboratory animals that suggests a significant risk for human subjects. Consequently sponsors notify investigators of any adverse event that the reporting investigator classifies as possibly related or that they classify as possibly related even when the sponsor's assessment indicates that the event was more likely caused by progression of the subject's underlying disease, an intercurrent illness, or lack of drug effect. OHRP advises that it is neither useful nor necessary under the HHS regulations at 45 CFR part 46, 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. Individual adverse events should only be reported to investigators and IRBs at all institutions when a determination has been made that the events meet all criteria for an unanticipated problem. For external adverse events, the NSMC IRB requires that our participating investigators review the sponsor's safety report and report only those adverse events that, in their opinion, are unexpected, more likely than not related to participation in the research, and suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

Per OHRP guidance, an incident, experience or outcome that meets the three criteria for an unanticipated problem will 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. **Accordingly, reports of EXTERNAL unanticipated problems should only be submitted to the NSMC IRB if they meet all three criteria AND changes to the protocol and/or consent document or implementation of other corrective action are warranted.** When changes to the protocol and/or consent or implementation of other corrective actions are not warranted in order to protect the safety, welfare, or rights of subjects or others, then the external event likely does not meet the criteria of an unanticipated problem and does not require prompt reporting to the NSMC

IRB. Principal Investigators will be required to provide justification when reporting external unanticipated problems without recommendation of changes to the protocol and/or consent document or implementation of other corrective action.

For ***INTERNAL*** events, the NSMC IRB requires prompt reporting when the event meets all three criteria for an unanticipated problem regardless if a change to the protocol/consent or other corrective action is warranted.

V. PROMPT REPORTING OF UNANTICIPATED PROBLEMS TO THE NSMC IRB

A. Criteria for Prompt Reporting:

Internal Unanticipated Problem: Unexpected + possibly related + serious or non-serious event

External Unanticipated Problem: Unexpected + possibly related + serious or non-serious event + requires change in protocol/consent process or documentation or implementation of other corrective action

B. Timeframe for Prompt Reporting

i. **SERIOUS** Unanticipated Problems Involving Risks to Subjects or Others

All **SERIOUS** unanticipated problems meeting the above criteria must be reported to the NSMC IRBAs soon as possible, but in no event later than **10 working days (14 calendar days)** from the date the investigator first became aware of the event. Changes made in approved research to eliminate and apparent immediate hazard to subjects must be reported within 24 hours.

Note for External Events: When the research is no longer being actively conducted at sites that relied on the NSMC IRB for review, report ONLY those events that may impact the health, welfare or safety of subjects who were enrolled by sites that originally relied on the NSMC IRB for review. For example, submit reports of secondary malignancies or problems with implanted devices.

ii. **NON-SERIOUS** Unanticipated Problems Involving Risks to Subjects or Others

All unanticipated problems meeting the above criteria that are **NOT serious** must be reported to the NSMC IRB **within 20 working days (30 calendar days)** from the date the investigator first became aware of the problem or event.

Investigators are required to complete and submit the NSMC IRB Unanticipated Problem/Adverse Event Reporting Form and attach any necessary relevant documentation.

C. IRB Actions

All reports of unanticipated problems will be added to the agenda for the next convened meeting of the NSMC IRB following report receipt. The IRB Chairman may elect to call an emergency IRB meeting as necessary. All IRB members will receive all submitted materials related to the unanticipated problem and the study file will be available at the meeting for reference and review. The convened IRB will assess whether the affected research protocol still satisfies the requirements for IRB approval, in particular, whether risks to subjects are still minimized and reasonable in relationship to the anticipated benefits. In response to the unanticipated problem, the convened IRB may suspend or terminate the research, require notification of current participants when information may relate to participants willingness to continue to take part in the research, request modification of the protocol, informed

consent, continuing review schedule, notification to past participants, and/or monitoring of the research or consent process.

Reports of internal events determined to meet the criteria of an unanticipated problem will also be reported to NSMC's Chief Medical Officer (designated Institutional Official), the IRB Administrative Liaison and OHRP and/or FDA as required by regulations within 30 days of the convened IRB meeting.

Unanticipated problems that are submitted to the IRB but are found by the IRB Chair or designated reviewer, to not meet the IRB's reporting requirements, will be returned to the investigator without being reviewed or acknowledged by the IRB.

VI. REQUIREMENTS FOR REPORTING ADVERSE EVENTS AT CONTINUING REVIEW

At continuing review, the NSMC IRB must ensure that the criteria for IRB approval under HHS regulations at 45 CFR 46.111 and, when applicable, FDA regulations at 21 CFR 56.111 continue to be satisfied. Investigators are required to provide a summary of any unanticipated problems that occurred since the last continuing review.

Investigators participating in multicenter clinical trials subject to monitoring by the sponsor, a coordinating or statistical center, or a Data Safety Monitoring Board/Data Monitoring Committee are required to submit a copy of the current monitoring group report with the continuing review submission. Investigators responsible for monitoring their own investigator-initiated research are required to submit a report of all adverse events.

VII. Related Policies, Regulations, and References:

1. DHHS Regulations: [45 CFR 46.103\(b\)\(5\)](#); [45 CFR 46.111](#); [45 CFR 46.113](#)
2. FDA Regulations: [21 CFR 56.108\(b\)\(1\)](#); [21 CFR 56.111](#); [21 CFR 56.113](#); [21 CFR 312.32\(c\)](#)
3. [Office for Human Research Protections \(OHRP\) Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, January 15, 2007.](#)
4. [FDA Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting — Improving Human Subject Protection](#)
5. [Office for Human Research Protections \(OHRP\) Guidance on Continuing Review](#); and [FDA Information Sheet for "Continuing Review After Study Approval"](#)