



Human Research Protection Program / Institutional Review Board
Standard Operating Procedure
2018 Common Rule

**For Studies Initially Approved on
or After January 21, 2019**

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1 Unanticipated Problems Involving Risks to Subjects or Others: A type of Reportable New Information

Regulations require an organization to have written procedures for ensuring prompt reporting of “unanticipated problems involving risk to subjects or others” (UPs). At MaineHealth, these are a type of ‘Reportable New Information’ (RNI).

This section provides definitions and procedures for the reporting of UPs to the MaineHealth IRB. Investigators conducting research under the oversight of an external IRB must comply with the reporting requirements of the external IRB as well as the internal reporting requirements outlined in Section 8.3.

In conducting its review of protocol deviations, noncompliance, subject complaints, and other reportable events, the IRB will also consider whether the event or issue was caused by, contributed to, or otherwise related to an UP.

1.1 Definitions

Unanticipated problems involving risk to participants or others. Unanticipated problems involving risks to subjects or others (UPs) refer to any incident, experience, outcome, or new information that:

1. Is unexpected; **and**
2. Is at least possibly related to participation in the research; **and**
3. Indicates that subjects or others are at a greater risk of harm (including physical, psychological, economic, legal or social harm) than was previously known or recognized

UPs also encompass Unanticipated Adverse Device Effects, as defined below.

Unexpected. The incident, experience or outcome is not expected (in terms of nature, severity, or frequency) given the research procedures that are described in the study-related documents, such as the IRB-approved research protocol/research plan and informed consent documents; and the characteristics of the subject population being studied.

Related. There is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.

Adverse Event. For the purposes of these policies and procedures, an adverse event (AE) is any untoward or unfavorable 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. Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

Serious Adverse Event: An adverse event is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial

disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an 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.

Unanticipated Adverse Device Effect. An Unanticipated Adverse Device Effect (UADE) means 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 related to the rights, safety, or welfare of subjects [[21 CFR 812.3\(s\)](#)].

1.2 Procedures

1.2.1 Reporting

Unanticipated Problems are reported to the MaineHealth IRB using the “MaineHealth-Progress Report, Study Completion, Reportable New Information Form’ Wizard in IRBNet.

Adverse events (serious or not) in 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 MaineHealth IRB does not accept reports of adverse events that are not UPs.

Serious Adverse Events that (a) meet the definition of a UP, i.e., related to the study and unanticipated, and (b) either occurs at MaineHealth, or occurred at another site resulting in study-wide change to the protocol or informed consent form must be reported **within 5 business days** using the form referenced above.

If the Serious Adverse Event is, or results in, death, and (a) meets the definition of a UP, i.e., related to the study and unanticipated, and (b) either occurred at MaineHealth, or occurred at another site resulting in study-wide change to the protocol or informed consent form, then it must be reported **within 48 hours** using the form referenced above.

Investigators must report UPs to the IRB within **10 business days** of occurrence (or notification, if from outside of MaineHealth) using the form referenced above. If investigators are uncertain but believe that the event might represent an UP, a report should be submitted.

The following are examples of UPs:

1. A breach of confidentiality or loss of research data (e.g., a laptop or thumb drive is lost or stolen);
2. 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);

3. Incarceration of a research subject after enrollment on an active research study (requiring additional regulatory review to ascertain added risk to the subject as a result of incarceration)
4. 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 (e.g., tendon rupture, progressive multifocal leukoencephalopathy);
5. Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be 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 (e.g., a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control). A summary and analyses supporting the determination should accompany the report;
6. An AE that is described or addressed in the investigator's brochure, 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 investigator's brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an unanticipated problem involving risk to human subjects. A discussion of the divergence from the expected specificity or severity should accompany the report;
7. A serious AE that is described or addressed in the investigator's brochure, 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;
8. AEs involving direct harm to subjects enrolled by the local investigator which in the opinion of the investigator or sponsor, may represent an UP;
9. IND Safety Reports from sponsors that meet the criteria for an UP. Such reports must be accompanied by an analysis from the sponsor explaining why the report represents an UAP and whether it has been reported to the FDA as such;
10. Unanticipated adverse device effects (UADEs);
11. 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 investigator's brochure, 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.
12. Reports (including reports from DSMBs/DMCs) that indicate that risks are greater than previously known or that indicate that the research should be modified, suspended, or halted.
13. Sponsor or lead investigator/coordinating center-imposed suspension or termination of some or all research activities;

14. An unanticipated event related to the research that exposes subjects to potential risk but that does not involve direct harm to subjects;
15. An unanticipated event related to the research that results in actual harm or exposes individuals other than the research subjects (e.g., investigators, research assistants, students, the public, etc.) to potential risk;
16. New information that indicates increased risk, new risk(s), or decrease to potential benefit from what was previously understood. Examples include:
 - a. An interim analysis or safety monitoring report indicates that the frequency or magnitude of harms or benefits may be different than initially presented to the IRB;
 - b. A report or publication that indicates the risks, benefits, or merit of the research are different from what was previously understood.

1.2.2 Review Procedures

1. Upon receipt of the MaineHealth-Progress Report, Study Completion, Reportable New Information Form, the IRB staff pre-reviews the submission and, if needed, contacts the investigator for corrections or additional information.
2. The IRB Chair or designated reviewer receives and reviews the report and makes an initial determination as to whether the event represents an UP. If needed, the Chair or designee may request additional information from the investigator, sponsor, or others (including study committees, such as data monitoring committees, data safety monitoring boards, or steering committees).
3. If the reviewer determines that the problem does not meet the definition of an UAP, they will determine whether any additional actions are necessary to ensure the protection of human subjects. As warranted, the reviewer may refer the matter to the convened IRB for review. The results of the review will be recorded in IRBNet and communicated to the investigator.
4. If the reviewer determines that the event may be an UAP, the report will be referred for review by the convened IRB. The convened IRB will determine whether the event is a UAP and whether any additional actions, such as those outlined below, are necessary to ensure the protection of human subjects. If needed, the IRB may request additional information from the investigator, sponsor, or others (including study committees, such as data monitoring committees, data safety monitoring boards, or steering committees). The results of the review will be recorded in the IRB minutes and communicated to the investigator.
5. Based upon the circumstances, the IRB may take any of the following actions, or others, to ensure the protection of human subjects:
 - a. Requiring modifications to the protocol or plan or procedures for implantation of the research (Research Plan) as described in the application and other materials submitted to the IRB;
 - b. Revising the continuing review timetable;

- c. Modifying the consent process;
- d. Modifying the consent document;
- e. Providing additional information to current participants (e.g., whenever the information may relate to the subject's rights, welfare, or willingness to continue participation);
- f. Providing additional information to past participants;
- g. Requiring additional training of the investigator and/or study staff;
- h. Requiring that current subjects re-consent to participation;
- i. Monitoring the research;
- j. Monitoring consent;
- k. Reporting or referral to appropriate parties (e.g., the IO, Privacy Officer, Risk Management, etc.);
- l. Suspending IRB approval;
- m. Terminating IRB approval;
- n. Other actions as appropriate given the specific circumstances.

When the IRB determines that an event is an UAP, the IRB staff will follow the procedures for reporting to regulatory agencies, sponsors, and organizational officials in Section 22. When appropriate, a preliminary report may be submitted while more information is obtained to inform the determination or actions.