CARILION CLINIC INSTITUTIONAL REVIEW BOARD
Standard Operating Guidelines

Title: 2.9: Review of Research: REPORTING UNANTICIPATED PROBLEMS, INCLUDING ADVERSE EVENTS	
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Primary Sponsor: Human Research Protections Office	**Approved By:** Director of the Human Research Protections Office

Objective:

To clarify when unanticipated problems, including adverse events, must be reported to the Carilion Institutional Review Board (IRB), and to identify the process for reporting them.

General Description:

Researchers need to be aware that certain unanticipated problems must be reported to the IRB within a specific timeframe. The Food and Drug Administration (FDA) and the Office for Human Research Protections (OHRP) both have guidelines with regard to what must be reported. While it is essential to report all unanticipated problems that meet the requirements of being reportable, it is also important to avoid excess documentation by reporting those that are not reportable. This guideline will help clarify what must be reported to the IRB under both sets of regulations for all studies, including specific requirements for drug studies and device studies.

Definitions:

Adverse Event – any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom, or disease, associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. It can be physical or psychological. The vast majority of adverse events are not unanticipated problems, and do not have to be reported to the IRB.

Related or Possibly-Related Adverse Event – any adverse event caused or at least partially caused by the procedures in the research

Serious Adverse Event – any adverse event that:
- Results in death
- Is life-threatening (places subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect; or
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

Unexpected Adverse Event – any adverse event that occurs in one or more of the subjects and 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 the study related documents or 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 subjects experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

Procedure:

Unanticipated Problems that Must be Reported to the IRB

Unanticipated Problems Involving Drugs:

The following adverse drug experiences should be reported to the IRB as unanticipated problems:

- Any unexpected and related or possibly related adverse event that places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized, especially serious adverse events.
- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- A series of adverse events that, on analysis, is both unanticipated and a problem for the study. There would be a determination that the series of adverse events represents a signal that the adverse events were not just isolated occurrences and were significant to the rights and welfare of the subjects.
- An adverse event that is described or addressed in the investigator's brochure, protocol, or informed consent documents, or expected to occur in study subjects at an anticipated rate (e.g., expected progression of disease, occurrence of events consistent with background rate in subject population), but that occurs at a greater frequency or a greater severity than expected.
- Any other adverse event that 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 assure the protection of human subjects.

In a multicenter study, the sponsor receives adverse event information from all study sites and is in a better position to analyze the significance of adverse event information and make determinations about whether an adverse event is an unanticipated problem. While it is the investigators' responsibility to report all unanticipated problems to the IRB, for multicenter studies, the investigator may rely on the sponsor's assessment and provide to the IRB a report of the unanticipated problem prepared by the sponsor. If the investigator knows that the sponsor has reported the unanticipated problem directly to the IRB, the investigator would not have to provide the IRB with a duplicate copy of the report received from the sponsor. To report an adverse event that the investigator has determined represents an unanticipated problem, a Promptly Reportable Information Form must be completed and submitted in the Carilion IRB electronic submission system PRIS3M within seven days of the investigator learning of the event.

Regardless of whether the adverse event is determined to be an unanticipated problem, the investigator must also ensure that it is reported to a monitoring entity (the sponsor, an independent medical monitor, a DSMB/DMC, etc.), if required under the monitoring provisions described in the protocol. If the investigator determines that an adverse event is not an unanticipated problem, but the monitoring entity determines that it is an unanticipated problem,

the monitoring entity should report this determination to the investigator, and such reports must be promptly submitted by the investigator to the Carilion IRB.

For any report of an adverse event that does not meet the definition of an unanticipated problem, the investigator should maintain a copy of the report and documentation of the basis for the determination, but not provide a copy of the report to the IRB. An example of an adverse event that does not need to be reported to the IRB includes:

- A subject is enrolled in a trial to test a new medication for patients with severe congestive heart failure. During the study, the subject experiences worsening heart failure. This is not a reportable AE because it is expected that subjects with severe heart failure will experience a worsening of that condition.

Unanticipated Problems Involving Devices:

An unanticipated adverse device effect is:

- Any serious, unexpected and related or possibly related adverse event.
- 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
- Any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects
- Any other adverse event that 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; or 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 assure the protection of human subjects.

Investigators are required to submit to the IRB and the sponsor a report of any unanticipated adverse device effect (UADE) occurring during an investigation as soon as possible, but in no event later than seven business days after the investigator first learns of the effect. Sponsors must then conduct an immediate evaluation of a UADE and report the results of this evaluation to the FDA, all reviewing IRBs, and all participating investigators within seven business days after the sponsor first receives notice of the effect.

Regardless of whether the adverse event is determined to be an unanticipated problem, the investigator must also ensure that it is reported to a monitoring entity (the sponsor, an independent medical monitor, a DSMB/DMC, etc.), if required under the monitoring provisions described in the protocol. If the investigator determines that an adverse event is not an unanticipated problem, but the monitoring entity determines that it is an unanticipated problem, the monitoring entity should report this determination to the investigator, and such reports must be promptly submitted by the investigator to the Carilion IRB.

For any report of an adverse event that does not meet the definition of an unanticipated problem, the investigator should maintain a copy of the report and documentation of the basis for the determination, but not provide a copy of the report to the IRB. An example of an adverse event that does not need to be reported to the IRB includes:

- A subject is enrolled in a study to compare a new device used in total knee surgery. Following the surgery, the subject is given an autologous blood transfusion. This is not a reportable AE because the necessity of the blood transfusion was not unexpected.

Unanticipated Problems Not Involving Adverse Events:

Unanticipated problems that must be reported to the IRB are defined as any incident, experience, or outcome that meets all of the following criteria:

- 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;
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- 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.

Upon becoming aware of an adverse event that does not involve a drug or device, the investigator should assess whether the adverse event represents an unanticipated problem by referring to the above criteria. If the investigator determines that the adverse event does represent an unanticipated problem, the investigator must report it to the Carilion IRB using the Carilion IRB electronic submission system PRIS3M within seven days of the investigator learning of the event.

Some types of unanticipated problems are not adverse events, such as unanticipated problems that involve social or economic harm instead of physical or psychological harm, or unanticipated problems that place subjects or others at risk of harm, but no harm occurs. Examples of this include:

- An unencrypted laptop that contains identifiable, sensitive information about subjects is stolen from an investigator
- A subject receives an overdose of an experimental agent, but no apparent harm occurs to the subject
- Subjects are enrolled in a study and it is later discovered that they have received an investigational product that was obtained from donors who were not appropriately screened for potential viral contaminants

Upon becoming aware of any other incident, experience, or outcome that is not related to an adverse event, but still may be an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem. If it does represent an unanticipated problem, the investigator must report it to the IRB within seven days of the investigator learning of the event.

For multicenter research protocols, if a local investigator at one institution proposes changes to the protocol or informed consent document in response to an unanticipated problem, the investigator should consult with the study sponsor regarding the proposed changes because changes at one site could have significant implications for the entire research study.

Interactions that Should Occur between IRBs and Data Safety Monitoring Boards (DSMBs)/Data Monitoring Committees (DMCs) with Regard to Adverse Events and Unanticipated Problems

Whenever a DSMB/DMC determines that an AE represents an unanticipated problem, the DSMB/DMC or study sponsor should report the event(s) to the investigators and IRBs at each participating study site. The procedure for ensuring this should be described in a monitoring

plan in the IRB-approved protocol. If the DSMB/DMC determines that adverse events are occurring at the expected frequency and severity level and has no concerns regarding the safety of human subjects, then only a periodic report to that effect should be sent to investigators and IRBs at each participating study site. The reports generated by DSMBs/DMCs should be submitted to the IRB within seven business days of receipt in the investigator's office.

Items the IRB Will Consider at the Time of Initial Review with Respect to Adverse Events and Unanticipated Problems

Before any research is approved, the IRB should consider the spectrum of adverse events that might occur in subjects. The IRB must review sufficient information regarding the risk profile of the proposed research study, including the type, probability, and expected level of severity of the potential adverse events that may result from the research. The investigator should describe how the risks of the research will be minimized.

Additionally, given the expected risks of the research, the IRB must ensure that the research includes, if appropriate, an adequate plan to monitor adverse events and unanticipated problems that may occur in subjects enrolled in research. The IRB is not the appropriate entity to monitor research. The monitoring plans for research must address the following items:

- The type of data or events that are to be captured under the monitoring plan
- Who will be responsible for monitoring the data collected
- The time frames for reporting adverse events and unanticipated problems to the monitoring entity
- The frequency of assessments of data or events captured by the monitoring plan
- Definition of specific triggers or stopping rules that will dictate when some action is required
- The procedures for review of scientific literature and data from other sources that may inform the safety or conduct of the study
- Procedures for communicating to the IRB, the study sponsor, and other appropriate entities the outcome of the reviews by the monitoring entity

References:
SOG 6.4 Conduct of Research: NON-COMPLIANCE, SUSPENSION, TERMINATION, UNANTICIPATED PROBLEM
SOP HRP 112: Promptly Reportable Information, New Information