Adverse Events (AE) and Unanticipated Problems

Information that may impact the risk/benefit ratio should be promptly reported to and reviewed by the Institutional Review Board (IRB) to ensure adequate protection of the welfare of participants. Based upon such information the IRB may need to reconsider its approval, require modifications, or revise the continuing review time period. If there is a question regarding whether or not to report an adverse event or problem to the IRB, investigators are encouraged to err on the side of "over-reporting."

Definitions

Adverse Event (AE): 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. Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although, they can occur in the context of social and behavioral research.

Serious Adverse Event (SAE): Any adverse event that meets any of the following conditions: (1) results in death; (2) is life-threatening (places the subject at immediate risk of death from the event as it occurred); (3) requires inpatient hospitalization or prolongation of existing hospitalization; (hospitalization for a protocol-specified activity or for an elective, pre-planned procedure is not considered an SAE.) (4) results in persistent or significant disability/incapacity; (5) results in a congenital anomaly or a birth defect; or (6) based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention. Serious adverse events should be reported to the IRB and will be reported to the Vice President of Research.

Unanticipated Problem or Unanticipated Problems 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 a subject's 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) related to the research than was previously known or recognized.

Types of events that require reporting

The following problems should be reported to the IRB within two days of awareness. These events are explained in greater detail further in this policy.

- On-site adverse events that are unexpected, related to the research, and involve new or increased risks to participants or others
- Off-site adverse events that have been determined to be unanticipated problems (explanation below) involving risks to participants or others
- Changes made to the research protocol without IRB approval in order to remove immediate hazards to participants
- Any new information that may adversely affect the safety of participants or the conduct of the study
- Other unanticipated events, incidents, or problems related to the research that indicate that participants may be a new or increased risk:
    - Any event that requires reporting to the sponsor
    - Any accidental or unintentional change to the IRB-approved protocol that involves risk or has the potential to recur.
    - Any publication in the literature, safety monitoring or DSMB report, interim result, or other finding that indicates an unexpected change in the risk/benefit ratio or indicates possible new risks previously unidentified.
    - Any complaint from a participant that indicates an unexpected risk, regardless of the status of the participant's enrollment

Unanticipated Problems

An unanticipated problem must meet three criteria to be considered reportable to the IRB:

(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 (in this guidance document, 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

(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.

Unanticipated problems that do not meet ALL THREE criteria DO NOT need to be reported immediately to the IRB. These criteria apply regardless of whether the event is internal or external (at another site).

Some unanticipated problems are not adverse events but affect the safety or welfare of participants. Examples of unanticipated problems that are not adverse events that require reporting to the IRB due to their serious nature and relatedness to the research include:

1. Breach of privacy or confidentiality, including lost or stolen confidential information that might involve risk to that individual or others;

2. Receipt of the wrong dose of a study medication without evidence of harm;

3. Contaminated study drug (put subjects at risk of harm);

4. Publication in the literature, safety monitoring report, including a Data and Safety Monitoring Report, interim result, or other finding that indicates an unexpected change to the risk - benefit assessment;

5. Accidental or unintentional change to the IRB-approved protocol that involves risks or has the potential to recur;

6. Complaint from a subject or family member that indicates an unanticipated problem;

7. Laboratory or medication errors that may involve risk to that individual or others;

8. Change in FDA labeling because of adverse consequences or withdrawal from marketing of a drug, device, or biologic used in a research protocol;

9. Disqualification or suspension of an investigator;

10. Sponsor imposed suspension of the study or study enrollment for risk;

11. Change in the status of a subject that might affect their eligibility to remain in the study, require their withdrawal from the study or require the IRB to re-review the research in order to make determinations that adequate protections are in place to protect vulnerable populations. Examples include: (a) Incarceration within a penal institution or detention facility; (b) Pregnancy at any time during participation in a research study; (c) Transfer of a child from their parents/guardians to foster care (ward of the state);

12. Other events that are unanticipated and indicate the potential for increased risk of harm to subjects or others

Action letters

Action Letters are considered to be serious adverse events. Any Action Letter received should be reported to the IRB within two days of awareness. Action Letters should be reported with the same procedure used for reporting serious adverse events.

Adverse device effect

An adverse device effect is 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 or severity, or degree of incident in the investigational plan or

application, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of participants.

Adverse device effects should be reported to the IRB.

Investigator responsibilities for reporting adverse events/unanticipated problems

How to report

It is the investigator's responsibility to keep the IRB informed of all serious adverse events and unanticipated problems that meet the criteria listed above. Serious adverse events and/or unanticipated problems should be reported to the IRB within two days of awareness using the AE Report Form. It is also the investigator's responsibility to keep the IRB informed of all local protocol deviations associated with a protocol, including changes made to the research without prior IRB approval in order to eliminate apparent immediate harm to participants.

The Adverse Event Report Form includes:

- General study information
- When and where the event occurred
- An assessment of the seriousness and likelihood that the event is study-related
- A description of the event
- An assessment by the investigator regarding whether or not the event is listed in the informed consent form or if the consent form needs to be revised, or if subjects should be re-consented in order to inform them of the possibility of this event

To assist in determining if a serious adverse event/ unanticipated problem should be reported immediately, please consult the OHRP guidance at:

https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html

Investigators are to complete the Adverse Event Report Form when reporting serious adverse events or unanticipated problems to the IRB. The form is used to document the investigator's opinion so that the IRB can make an accurate assessment of whether the risk/benefit ratio has been significantly affected or if changes to the protocol and/or informed consent document are appropriate. The IRB Chair or full board may request additional information from the investigator.

Review of Adverse Events / Unanticipated Problems

For off-site, external AEs

Adverse events and unanticipated problems occurring at external sites where Woman's is the IRB of record will be submitted and reviewed using the same procedures for on-site events. For

multi-site studies where Woman's is the IRB of record, Woman's uses the SMART IRB Standard Operating Procedures (SOPs) and adverse event submissions will be reviewed in accordance to the guidelines set by these SOPs. According to the SMART IRB SOPs, reports of serious adverse events, deviations, significant subject complaints, and other events specifically requiring reporting to the Reviewing IRB (Woman's) in accordance with Reviewing IRB policies and procedures will be submitted to and reviewed by the Reviewing IRB.

Adverse events occurring at Woman's where Woman's is the relying institution will be submitted according to the IRB Reliance Agreement with the reviewing institution. These events may also be submitted to the Research and Development Committee (R&D) and Woman's IRB for subject safety concerns.

For on-site AEs

For these types of events occurring at Woman's, the Adverse Event Subcommittee will conduct a review of the submitted adverse event/unanticipated problem. The Adverse Event Report Form, adverse event reviewer form, current study consent form, and current study protocol (if necessary) will be distributed to the members of the subcommittee via courier.

This subcommittee will determine if the event is an unanticipated problem involving increased risk to participants or others. The IRB Chair will determine if the adverse event / unanticipated problem should be reported to the IRB at the next meeting of the full board or should be reported in summary format at continuing review.

If the Adverse Event Subcommittee recommends immediate action, a letter will be sent to the investigator outlining any necessary requirements. The IRB Chair, with input from the Adverse Event Subcommittee, can approve any action including, but not limited to, changes to the protocol or consent process, temporary suspension or termination of the study, or other actions needed to protect participants and/or eliminate immediate hazards to participant safety effective immediately. Any actions taken by the IRB Chair in such cases will be reviewed at the next convened meeting of the full board and further actions may be taken as necessary. If additional changes are required by the full board, an additional letter will be sent to the investigator. On-site AEs may require reporting to the sponsor and required agencies (OHRP, FDA).

Adverse events / unanticipated problems deemed to have no significant increased risk to participants may be reported to the IRB at the next continuing review, as determined by the IRB Chair. Adverse events / unanticipated problems deemed to have significant increased risk to participants will be reviewed by the AE subcommittee, including the IRB Chair. The following actions may be taken:

- Report the adverse event / unanticipated problem at the next continuing review
- Report the adverse event / unanticipated problem at the next convened IRB meeting

- Report the adverse event / unanticipated problem at the next convened IRB meeting and implement changes to the study immediately for participant safety
- Report the adverse event / unanticipated problem at the next convened IRB meeting and immediately suspend the study temporarily until the board can review the event

Adverse events / unanticipated problems involving more than minimal risk to participants or others that are placed on the agenda for the next convened meeting will be reviewed by all IRB members and the following documents will be distributed to all members for review prior to the meeting:

- Adverse Event Report Form
- Current consent form
- Reviewer form

After review of the adverse event / unanticipated problem by the full board, the IRB may consider a range of actions:

- suspending the study
- terminating the study
- notifying current participants of the event when such information may affect their willingness to continue to take part in the research
- requiring current participants to re-consent to participation with new information
- modifying the protocol and/or consent process
- notifying past participants of additional information
- modifying the continuing review schedule
- implementing or modifying the monitoring of the research
- monitoring the consent process
- referral to other organizational entities
- notifying regulatory agencies (OHRP, FDA)

Reporting to Agencies

The investigators are responsible for the accurate reporting, documentation, investigation, and follow-up of all possible study-related adverse events and local protocol deviations. The Organizational Official will be notified of any serious adverse events or unanticipated problems.

Investigators and/or the Human Protections Administrator are responsible for informing sponsors and government agencies (e.g., FDA for research that is FDA-regulated and OHRP when the research is covered by HHS regulations) of any adverse events and local protocol deviations, as appropriate. All unanticipated problems should be reported to FDA or OHRP, as appropriate, within one month of the IRB's receipt of the report of the problem from the investigator.

OHRP notes that, in some cases, the requirements for prompt reporting may be met by submitting a preliminary report to the IRB, appropriate institutional officials, the supporting HHS agency head (or designee), and OHRP, with a follow-up report submitted at a later date when more information is available. Woman's IRB does not need to report to regulatory agencies already made aware of the event through reporting by the investigator or the sponsor.

Adverse events or anticipated problems should not be reported to these agencies if the research is not regulated by HHS or FDA.

Delinquent reporting

Delinquent adverse event reporting and failure to report an adverse event within the required timeframe may constitute grounds for termination of the study. If an investigator is delinquent in reporting an adverse event or protocol deviation, a letter of reprimand will be sent to the investigator informing him or her of the reporting requirements. If it is a first offense, the letter will inform the investigator that a second delinquent report for that study may result in a closure to future enrollment. If there is a second offense, the full board will review the report and may choose to terminate study approval. The IRB Chair can require any actions (including temporary suspension of patient enrollment and/or the study) needed to protect participants and/or eliminate immediate hazards to participant safety effective immediately pending full IRB review.

AEs when a Data Safety Monitoring Board is involved

Investigators must identify, if any, the Data and Safety Monitoring Board (DSMB) to the IRB that will be reviewing interim results, and include a brief description of the monitoring plan as well as procedures for transmitting the DSMB's summary/statistical reports to the IRB. Investigators for multi-site trials with DSMBs are expected to forward to the IRB within 2 days (or no later than Monday if awareness occurred on Friday) summary reports of adverse events that reveal unexpected non-serious and serious adverse events and other unexpected findings that affect the risk/benefit ratio. Such reports should also be referenced in the Summary section of the progress report at the time of continuing review and closure of the study. The reporting of adverse events in the form of DSMB summaries is in addition to, and does not replace, other reporting requirements of the IRB.

Human gene transfer

Human gene transfer is the deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA, into human subjects. For human gene transfer protocols, investigators must report any serious adverse event, anticipated or unanticipated, promptly to the IRB and other applicable agencies (example, OHRP, FDA, National Institutes of Health/Office of Biotechnology Activities).

DATE	REVISIONS
4/6/22	Added the Human Protections Administrator may also be responsible for reporting Unanticipated Problems to federal agencies