



MCW Office of Research Standard Operating Procedure

REQUIREMENTS FOR REPORTING TO THE IRB

Unit: Human Research Protections Program (HRPP), Office of Research

Applies to: Faculty and Staff involved in human research

PURPOSE:

Federal regulations (45 CFR 46.108(a)(4) & 21 CFR 56.108(b)) require written procedures for ensuring *prompt* reporting of certain events to the IRB, appropriate institutional officials, any supporting department or agency head (or designee), and OHRP. The purpose of prompt reporting is to ensure that appropriate steps are taken in a timely manner to protect subjects from avoidable harm.

When conducting clinical investigations of drugs, including biological products, under 21 CFR part 312 and of medical devices under 21 CFR part 812, an investigator's responsibilities include the following:

- To prepare and submit the following complete, accurate, and timely reports (§ 812.150 & 312.64):
 1. Any *unanticipated adverse device/drug events* occurring during an investigation
 2. Any *deviation from the investigational plan* made to protect the life or physical well-being of a subject in an emergency

This policy seeks to define events which meet the prompt reporting criteria to the MCW IRB and those that require reporting to the MCW IRB with the Continuing Progress Report (CPR).

DEFINITIONS:

Prompt reporting: Within 5 calendar days of when the Principal Investigator (PI) learns of the event.

Unanticipated Problem Involving Risks to Subjects or Others (UPIRSO): Any incident, experience, or outcome that meets **all** of the following criteria:

1. Unanticipated (in terms of nature, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, Instructions for Use/Device Manual and/or Investigator's Brochure; 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) or test article; 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.

Adverse event: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of any project procedure or treatment, regardless of whether it is considered related to the project procedure or treatment.

Serious adverse event: An adverse event that (1) results in death, (2) is life-threatening, (3) requires inpatient hospitalization or prolongation of existing hospitalization, (4) results in persistent or significant disability/incapacity, (5) results in a congenital anomaly/birth defect, or (6) is an important medical event that jeopardizes the subject or requires medical intervention to prevent one of outcomes listed above.

A serious adverse event could occur at an external site or a site under the purview of the MCW IRB.

Unanticipated adverse event: An adverse event that is not consistent in nature, frequency, or severity with the current IRB protocol, investigator's brochure, device manual/instructions for use, or consent form.

Unanticipated adverse device effect: An unanticipated adverse device effect means any serious adverse event caused by or associated with a device, if that event was not previously identified in nature, severity, or degree of incidence in the project protocol, or consent form, or the investigational plan or investigational device exemption (IDE) application or any unanticipated serious problem associated with a device and related to the rights, safety or welfare of research subjects.

Protocol deviation: A protocol deviation involves changes to the project design/procedures that are considered to be an exception to the approved protocol.

Significant protocol deviation: Significant protocol deviations are those that increase the risk to participants or others, decrease potential benefits of the project, undermine the scientific integrity of the project, or occur more than once.

Planned protocol deviation: Any temporary protocol deviation acknowledged by the IRB prior to its initiation. Any permanent change to the protocol constitutes an amendment that must be submitted to the IRB for approval prior to initiation.

Non-Compliance with IRB Policies and Procedures: Failure to comply with regulations or MCW IRB Policies and Procedures or failure to follow the requirements or determinations of the IRB.

Serious Noncompliance: An IRB determination when there is an action or omission taken by an investigator that shows disregard or violation of federal regulations or institutional policies applicable to human subject research that demonstrably increases risks to human subjects, adversely affects the rights and welfare of human subjects, or compromises the integrity/validity of the research.

- The IRB does not have to find that harm has occurred, or was likely to occur, to make a determination of serious noncompliance
- Failure to obtain IRB approval of human subjects research when required under HRPP or applicable laws and regulations constitutes serious noncompliance.
- Multiple instances of noncompliance that are deemed not-serious individually may constitute serious noncompliance when considered collectively.
- The IRB may consider mitigating factors such as corrective action, that play a role in the determination of whether the event increased risk, decreased potential benefits or negatively affected the integrity/validity of the research. If despite

these factors, the event's occurrence meets the definition of serious noncompliance, then the event should be categorized as such.

Continuing noncompliance: An IRB determination when there is a pattern of repeated noncompliance that continues after initial discovery, including inadequate efforts to take corrective actions within a reasonable timeframe. Examples include a pattern of behavior that evidences a lack of attention to research or knowledge of the regulations or institutional policies HRPP, or the protection of research participants or that is likely to continue without intervention.

- Continuing noncompliance also includes failure to respond to a request to resolve an episode of noncompliance

PROCEDURE:

Events which meet MCW's Prompt Reporting Criteria:

1. With respect to each research project an Investigator is conducting, they must ensure that the following problems, events and/or new information involving risk to research participants or others are reported to the IRB no later than 5 calendar days after becoming aware of the problem, event or information. The MCW HRPP has categorized these events as follows:
 - a. Any Adverse Events (internal or external) that meet all of these criteria:
 - i. Unexpected
 - ii. Possibly, probably, or definitely related to the research
 - iii. Suggests the research places research participants or others at a greater risk of physical or psychological harm than was previously known or recognized.Examples include but are not limited to the following:
 - Unanticipated adverse events (either occurring internally or at an external site) which meet the criteria above
 - Serious Adverse Event(s) that meet the criteria above
 - New information that might affect adversely the safety of the participants or the conduct of the project
 - Any change significantly affecting the conduct of the project or increasing the risk to participants
 - New findings that result in premature closure of a project or are related to an unanticipated problem involving risks to subjects or others
 - b. Follow-up reports to initially reported Adverse Events which meet all of the above criteria. If the follow-up report does not contain significant new information and additional follow-up reports are expected, they should be grouped into a single reportable event submission.
 - c. Unanticipated Problems or any incident, experience, or outcome that meets all of the following criteria:
 - i. unexpected with reference to procedure/risks defined in initial IRB application
 - ii. possibly, probably, or definitely related to participation in the research project, and
 - iii. Suggests the research places subjects or others at greater risk of harm than was previously known or recognized.Examples include but are not limited to the following:
 - Breach of privacy or confidentiality including lost or stolen project records that contain private identifiable subject information.
 - Any other problem that the investigator considers to be unanticipated and indicates that subjects or others are at increased risk of harm.

- Incarceration of a subject in a protocol not approved to enroll prisoners.
 - Complaint of a subject when the complaint indicates unexpected risks or cannot be resolved by the research team.
- d. Safety Notice/Report from Sponsor or Central Site if report describes new information regarding risks or unanticipated problems involving risks.
Examples include but are not limited to the following:
 - Sponsor imposed suspension for risk.
 - Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
 - Any safety reporting requirements specified by the IRB as a condition of approval.
 - A paper is published from another project that shows that the risks or potential benefits of the research might be different from those initially presented to the IRB.
 - Suspension or Termination of the project by the Sponsor
- e. Report from a Data Safety Monitoring Board (DSMB) or Equivalent if the report describes new information regarding risks or unanticipated problems involving risks.
Examples include but are not limited to the following:
 - An interim analysis or safety monitoring report indicates that the frequency or magnitude of harms or benefits might be different from those initially presented to the IRB.
- f. External Audit Reports which identify activities that increases risk to subjects or others, compromises the integrity of the research or is out of compliance with MCW HRPP policies and procedures.
Examples include, but are not limited to the following:
 - FDA Inspection reports
 - FDA 483 Citation
 - HHS audits
 - Sponsor & CRO Monitoring Reports
- g. Internal Routine Review or Audit Reports which identify activities that increases risk to subjects or others, compromises the integrity of the research or is out of compliance with MCW HRPP policies and procedures.
Examples include but not limited to the following:
 - MCW QA/QI Routine Review Final Reports
 - MCW QA/QI For-Cause Audit Reports
 - MCW Corporate Compliance Audits
- h. Significant Protocol Deviation
Examples include but are not limited to the following:
 - Any departure from the protocol (deviation or violation) that harmed subjects or others; that indicates subjects or others might be at increased risk of harm; or that compromises the integrity of the research data.
 - Any change made to the research without prior IRB approval in order to eliminate apparent immediate harm
- i. Planned Protocol Deviation which increases the risk to participants or others, decrease potential benefits of the project, or undermines the scientific integrity of the project.
Examples include but are not limited to the following:
 - Enrolling a subject who does not meet eligibility criteria
 - Not performing a specific screening procedure for a patient as indicated in the protocol
- j. Non-Compliance with IRB Policies and/or Procedures

Examples include but are not limited to the following

- Any allegation of non-compliance with protocol requirements (including protocol deviations or violations) or IRB policies.
2. If an Investigator determines the event, problem or information meets the immediate reporting criteria; they should complete and submit a Reportable Event Form via eBridge for the project. If the event applies to several projects, a Reportable Event Smart Form should be submitted for each project which is affected.
 - If an Investigator does not have enough information to determine if the event met all of the above criteria, it is recommended to report the event to the IRB and if possible update the reportable event with additional information later.
 3. If an event occurs when an Investigator is unreachable or unavailable to submit the Reportable Event Smart Form via eBridge, the project team should complete the following steps to ensure IRB notification:
 1. Contact the IRB Coordinator assigned to the project to report the event
 2. "Print" the printable version of the Reportable Event Smartform to pdf and save the pdf document
 3. Submit to the IRB Coordinator the saved pdf Reportable Event Smart Form via email as an attachment for documentation purposes
 4. Scan the email with the pdf attachment and upload the scanned document to the Reportable Event workspace (Section 98) as documentation that the IRB was notified of this event within the required timeframe
 5. Ensure that the PI is notified to review and submit the Reportable Event Smart Form via eBridge as soon as possible

Exceptions to the reporting timeframe

In times of pandemic or natural disaster, reports of significant protocol deviations (1.h) and noncompliance with MCW IRB policies and procedures (1.j) do not require immediate reporting. The IRB will issue guidance based on the event to prioritize reporting and reviewing events that pose risk to subjects.

IRB Review:

1. When a new reportable event is received via eBridge by the IRB, the HRPP office will review the event submission and attached documentation for completeness and determine the type of IRB review (Expedited Review or Convened Committee) after evaluating if the event could be an unanticipated problem involving risks to subjects (UPISRO) or others or be considered serious or continuing noncompliance.
 - a. For Reportable events which were submitted promptly, but determined to not meet the above criteria, the IRB Coordinator II will return the Reportable event to the Investigator with the following comment in eBridge:
 - i. Based on staff review, it appears the reportable event submitted to the IRB does not meet the "prompt reporting" criteria. It is recommended for the Investigator to withdraw the event and submit it at the time of Continuing Progress Reporting. If the Investigator wishes for the Reportable Event to be reviewed at this time, please include additional information or the rationale for why it is being reported to the IRB.
 - ii. In the situation that additional rationale is provided, the IRB Office will use its discretion in determining if the reportable event will be reviewed.
2. The IRB Chair or Committee will review the event and any applicable materials from the main project submission (e.g. Protocol, consent form, etc.) and determine if the

event meets the UPIRSO criteria or represents Serious or Continuing noncompliance.

3. The IRB Chair or Committee will consider the following during the review of the reportable event:
 - a. A process to have any adverse events or outcomes from the reportable event reported to the IRB
 - b. Considers informing current participants of the termination or suspension.
 - c. Whether procedures for withdrawal of enrolled participants take into account their rights and welfare (e.g., making arrangements for medical care outside of a research project, transfer to another researcher, and continuation in the research under independent monitoring).
4. Once the IRB Chair or Committee's review is complete, the Investigator will receive either an acknowledgement letter of the event or a request for modifications.
 - a. The acknowledgement letter may include additional requests for action such as submitting an amendment, providing additional follow-up reports or informing participants of the event.
 - b. Investigators must respond to the IRB Committee's request for additional information or changes within the identified timeframe as stated in the letter or no later than 30 days.
5. If IRB Committee determines the event meets the criteria either as an UPIRSO, or represents a Serious noncompliance or Continuing noncompliance, HRPP staff will follow *Staff: Communication with Federal Agencies* to notify and report to outside regulatory agencies including but not limited to DHHS or FDA as required by the federal regulations and MCW IRB policies.

Events which do not meet MCW's Prompt Reporting Criteria

1. Events which do not meet MCW prompt reporting criteria as outlined in this procedure should be reported to the IRB with a project's continuing progress report (CPR) as detailed below. The CPR form prompts Investigators to provide information regarding all related adverse events in summary format to provide the IRB a full picture of what has occurred since the initial approval or most recent CPR.
2. The IRB expects only the following to be reported:
 - a. **Adverse Events for Single-site Projects:** This summary should include all internal serious adverse events that were considered related and unexpected.
 - b. **Adverse Events for Multi-site Projects:** This summary should include all internal and external serious adverse events that were considered related and unexpected.
 - c. **Protocol Deviations:** A summary of all protocol deviations.
 - d. **Other Unanticipated Problems:** A summary of all unanticipated problems involving risks to subjects or others, unless included in the summary of adverse events.
 - e. **Monitoring Committee Report (DSMC, DSMB, etc.):** Report(s) commensurate with the data and safety monitoring plan approved by the IRB.

REFERENCES:

45 CFR 46.108(a)(4)
21 CFR 56.108(b)
21 CFR 312
21 CFR 812
21 CFR 812.150
21 CFR 312.64

SUPPORTING DOCUMENTS:

Effective Date: 12/19/2025
Version number: 10.0
Previous Version/date: 9.0, 07/01/2022
Responsible Office: HRPP Office
Approval Date: 12/18/2025

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