



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 46.103(b)(5) & 21 CFR 56.108(b)) require written procedures for ensuring *prompt* reporting of unanticipated problems 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

Events which meet the prompt reporting criteria must be reported to the MCW IRB within 5 calendar days.

Events which do not meet the prompt reporting criteria may be reported to the MCW IRB with the Continuing Progress Report (CPR).

DEFINITIONS:

Prompt reporting: Within 5 calendar days of when the 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.

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.

External serious adverse event: An adverse event that occurs at any outside location and does not involve an MCW research subject 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.

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: Violates federal regulations or institutional policies regarding informed consent or research conduct and impact subjects' rights, welfare and/or safety or affect the scientific integrity of the project.

PROCEDURE:

Events which meet MCW's Prompt Reporting Criteria:

1. With respect to each research project an Investigator is conducting, he or she must ensure that the following problems, events and/or information involving risk to research participants or others are reported to the IRB not 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
- Unanticipated adverse device effect
- External Serious Adverse Events that meet the criteria above
- A series of adverse events 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

- 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 IRB policies & procedures (1.j) do not require immediate reporting. The IRB will issue guidance based on the the event to prioritize reporting and reviewing events that pose risks 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.
2. The IRB Chair or Committee will review the event and determine if it meets the UPIRSO criteria or represents serious or continuing noncompliance.
 - a. The IRB Chair or Committee will also review the following documents in conjunction when making their determination if the event meets the UPIRSO criteria or represents serious or continuing noncompliance:
 - i. The Protocol, if applicable
 - ii. The Consent Form, if applicable
 - iii. Investigator Brochure, Device Manual or other safety materials, if applicable
3. the IRB Chair or Committee will consider the following during the review of the reportable event:
 - a. 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).
 - b. Considers informing current participants of the termination or suspension.
 - c. A process to have any adverse events or outcomes from the reportable event reported to the IRB
4. Once the IRB’s review is complete the Investigator will receive either an acknowledgement letter of the event or a request for modifications. 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. 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 the event is a UPIRSO or serious 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. Any Reportable Event which does 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). The CPR form prompts Investigators to provide information regarding all reportable events in summary format to provide the IRB a full picture of what has occurred since the initial approval or most recent CPR.
2. All Reportable Events including any which were immediately reported in accordance with this procedure must be submitted with a CPR. This information should be submitted in a summary worksheet (such as excel) and be clearly labeled (e.g., "Internal Adverse Events", "External Adverse Events", etc.). Guidance for these summary reports is outlined below:
 - a. **Internal Adverse Events for Projects where MCW is the Only Site or Central Coordinating Site:** This summary should include all internal adverse events, regardless of severity (serious and non-serious), expectedness (anticipated and unanticipated), and relatedness (may or may not be related to the project). The summary should demonstrate that the nature, frequency, and severity of these events are monitored on a continuous basis. There should be ongoing consideration as to whether particular events are expected and related to the project. A simple list of events is not an acceptable summary.
 - b. **Internal Serious Adverse Events for Multi-site Project:** For projects in which the sponsor or central site is responsible for monitoring adverse events, a summary of all serious adverse events reported from this site to the sponsor or central site must be submitted.
 - c. **External Serious Adverse Events:** If this is a multi-site project, the IRB expects a summary of serious adverse events from the sponsor or central coordinating center. **The summary should include a statement or indication related whether these events do or do not reflect a change to the overall risk benefit ratio of the project. A summary is desired, but not required from the central site or sponsor.**
 - d. **Protocol Deviations:** A summary of all protocol deviations, significant and less than significant.
 - e. **Other Unanticipated Problems:** A summary of all unanticipated problems involving risks to subjects or others, unless included in the summary of adverse events.

REFERENCES:

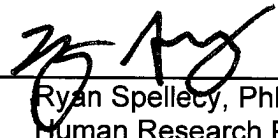
45 CFR 46.103(b)
21 CFR 56.108(b)
21 CFR 312
21 CFR 812
21 CFR 812.150
21 CFR 312.64

SUPPORTING DOCUMENTS:

Staff: Communication with Federal Agencies

Effective Date: 03/16/2020
Version number: 9.0
Previous Version/date: 8.0, 06/15/2018
Responsible Office: HRPP Office
Approval Date: 03/13/2020

Approved By
HRPP Authorized Official:



Ryan Spellecy, PhD, Director,
Human Research Protections Program (HRPP)
Assistant Provost for Research
Office of Research
Medical College of Wisconsin