Adverse event:

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 <u>all</u> 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

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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 the event to prioritize report 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 it 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. Whether procedures for withdrawal of enrolled participants take into account their rights and welfare (e.g., making arrangements for medical care outside

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