

Grand Valley State University Institutional Review Board (IRB)	
Title: <i>Reportable Events: Protocol Deviations, Unanticipated Problems and Adverse Events</i>	
Section: 1020.	This policy and procedure supersedes those previously drafted
Approved by HRRC: 02/14/2012 Revised by HRRPPC: 04/24/2018 Revised by HRRPPC: 11/27/2018 Revised by IRBPPC: 03/31/2020 Revised by IRBPPC: 09/29/2020 Revised by IRBPPC: 01/26/2021	Approved by RIO/HRPA: 02/16/2012 Revisions approved by AIO/RIO: 05/12/2018 Revisions approved by AIO/RIO: 12/19/2018 Revisions approved by AIO/RIO: 04/06/2020 Revisions approved by AIO/RIO: 10/2/2020 Revisions approved by AIO/RIO: 03/01/2021
Effective Date: 03/01/2021	
Related documents: 120: <i>Compliance with Applicable Laws and Regulations</i> 341: <i>Unapproved Research</i> 710: <i>Assessing Risk to Research Participants</i> 720: <i>Assessing Risk to Vulnerable Participants</i> 730: <i>Collection, Management and Security of Research Information</i> 1010: <i>Modifications to Approved Protocols</i> 1030: <i>Research Noncompliance</i> 1040: <i>Post-Approval Compliance Review</i> 1050: <i>Suspension or Termination of Research Activities</i> 1060: <i>Closures of Approved Research Studies</i> 1070: <i>Responding to Concerns and Complaints About Human Subjects Research Activities</i>	

## **Policy**

It is the Principal Investigator’s responsibility to ensure all reportable events, including protocol deviations, unanticipated problems, and serious adverse events, associated with the conduct of a human subjects research study are appropriately assessed for level of risk and reported to the IRB within the appropriate timeframe for the type of event identified as outlined in this policy. Reportable events that are or may be unanticipated problems involving risks to subjects or others require review by the IRB. Additional reporting requirements may be subsequently directed by the IRB.

## **Definitions**

1. **Risk:** The probability of harm (physical, social, emotional, or economic) occurring as a result of participation in a research study. Both the probability and magnitude of possible harm may vary from minimal to significant. A low probability of a severe harm is low risk; a high probability of a minor harm also is low risk. See *IRB Policy 710: Assessing Risk to Research Participants*, *IRB Policy 720: Assessing Risk to Vulnerable Participants*, and *IRB Policy 730: Collection, Management, and Security of Research Information* for further details.
2. **Event or Problem:** An incident, experience, or outcome that occurs during the conduct of a research study that may require reporting to the GVSU IRB, another reviewing IRB, the Office for Human Research Protections (OHRP), the Food and Drug Administration (FDA), and/or a research sponsor.

3. *Protocol deviation*: Any change, divergence, or departure from an IRB-determined exempt protocol or IRB-approved non-exempt protocol that is not implemented or intended as a systematic change; or any other, unplanned, instance of protocol noncompliance. The deviation may be accidental or due to negligence and is considered minor if it does not have a major impact on the participant's rights, safety, or well-being, or the completeness, accuracy, and reliability of the study. This may also include failure to comply with federal laws and regulations, GVSU's policies and procedures, and standards of professional conduct and practice. Protocol deviations are a form of noncompliance (See *IRB Policy 1030: Research Noncompliance* for further details regarding noncompliance).
4. *Protocol violation*: A divergence from an IRB-determined exempt protocol or IRB-approved non-exempt protocol that materially reduces the quality or completeness of the data, makes the informed consent form inaccurate, and/or impacts a participant's safety, rights, or welfare.
5. *Unanticipated adverse device effect (UADE)*: Any incident, experience, or outcome that meets either of the following criteria:
  - a. 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 (including a supplementary plan or application), or
  - b. Any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
6. *Unanticipated problem (UP)*: Any incident, experience, or outcome that meets all of the following criteria:
  - a. 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;
  - b. 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
  - c. 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.
7. *Adverse Event (AE)*: Any untoward or unfavorable occurrence in a human subject, including any abnormal sign (e.g., 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. AEs encompass both physical and psychological harms.

8. *Serious Adverse Event (SAE)*: Any adverse event that occurs to research participants or study team members that results in death; is life threatening, or places the participant at immediate risk of death from the event as it occurred; requires or prolongs hospitalization; causes persistent or significant disability or incapacity; causes a prolonged or permanent harm that is psychological, social, legal, or financial; or is another condition which investigators judge to represent significant hazards.
9. *Related to the research*: Some aspect of the research study (e.g., research procedure, data collected from research study, etc.) that is directly related to the event or problem. “Directly” means possibly, probably, or definitely related to the study procedure, study drug, the device, or participation in the study.

## **Procedures**

1. Researcher reporting requirements are as follows:
  - a. Members of the research team must immediately report the occurrence of an unanticipated problem, unanticipated adverse device effect or serious adverse event to the Principal Investigator (PI). Upon learning of the incident, the PI is required to determine the classification of the event, taking into consideration the risk to participants, and the expectedness and severity of the incident.
  - b. Regardless of the review level of the protocol (exempt, expedited, or full), the PI must submit a written notification to the IRB within seven (7) calendar days of first learning of any unanticipated problem, unanticipated adverse device effect or adverse event that may impact participant safety, confidentiality, information security, or privacy, or any conduct of human subjects research without IRB approval. This includes, but is not limited to, the following types of events:
    - i. Unanticipated problems involving risks to participants or others (see the Appendix for assistance in determining when an adverse event represents an unanticipated problem that needs to be reported to the IRB).
    - ii. Serious adverse events
    - iii. Conduct of human subjects research without IRB approval (See *IRB Policy 341: Unapproved Research*)
    - iv. Protocol violations
      1. Consent and/or authorization issues, including:
      2. Failure to obtain consent and/or authorization from participants
      3. Enrolling participants using a consent which does not include all known risks, or continuation of subject participation without notification of newly identified risks
      4. Use of outdated informed consent or HIPAA/FERPA authorization which is missing substantive content that may affect the participant’s willingness to participate
      5. Minor deficiencies in informed consent or HIPAA/FERPA authorization process or documentation that affect ten (10) or more participants, or 10% of the total sample population, whichever is smaller, within a one-year period.

- v. Participant complaints that indicate an unexpected risk and/or affect the rights and welfare of human subjects
  - vi. Incidents that may compromise information security, subject privacy, and/or confidentiality (e.g., data breach)
  - vii. Data and Safety Monitoring Board (DSMB) reports, interim analyses, or other oversight committee/monitoring reports that state there is a concern about the risk/benefit profile of the study, or that temporarily halt research activities.
- c. If the adverse event is related to the research and includes a fatality or hospitalization, the PI must **immediately** notify the ORCI, IRB Chair, and the Research Integrity Officer (RIO).
- d. Any data breach occurring on a project involving General Data Protection Regulation (GDPR)-covered research must be reported to the appropriate university GDPR compliance official (Vice Provost for Research Administration) and the ORCI **within 24 hours** upon identification of the breach. See *IRB Policy 120: Compliance with Applicable Laws and Regulations* for more details.
- e. In the event of a UADE where the researcher is also the sponsor-investigator, the researcher must immediately conduct an evaluation of the UADE and must report the results of the evaluation to the FDA, all reviewing IRBs, and participating investigators within 10 working days after first receiving notice of the effect.
- f. Additional reporting requirements to federal agencies, study sponsors, risk management, legal counsel, police authorities or other entities also may be required as determined and directed by the ORCI, IRB Chair, and/or university RIO.
- g. For non-exempt studies, the following events do not require immediate reporting to the IRB, but shall be reported at the time of the next continuing review, or at project closure if there are no further continuing reviews required for the study:
- i. Non-serious adverse events
  - ii. Unanticipated problems that did not impact participant safety, confidentiality, information security, or privacy
  - iii. Protocol deviations that occurred and which the PI does not believe impacted subject safety and/or affected the integrity of the data
  - iv. DSMB reports, interim analyses, or other oversight committee/monitoring reports
  - v. Other pertinent study reports as deemed necessary by the PI
- h. Protocol deviations occurring on exempt studies that do not impact participant safety, confidentiality, information security, or privacy, only require reporting to the IRB if they affect ten (10) or more participants, or 10% of the total sample population, whichever is smaller, within a one-year period. If an event or problem that requires reporting to the IRB within 7 calendar days is identified after study closure, it still must be reported to the IRB, regardless of the length of time since study closure.

- i. Per 45 CFR 46.108(a)(3)(iii), planned protocol deviations must be reviewed and/or approved by the IRB prior to implementation unless the deviation is necessary to eliminate apparent immediate hazards to the subject. Refer to *IRB Policy 1010: Modifications to Approved Protocols* for additional information.
- j. The PI shall utilize the appropriate reporting form in the ORCI's electronic database management system to document the details of the reportable event. The following documents or information must accompany the report:
  - i. Summary and outcome of the reportable event
  - ii. Steps taken to prevent recurrence
  - iii. Supporting documents such as the informed consent form, Data Safety Monitoring Board report, and/or de-identified participant progress reports

## 2. IRB Review of the Reportable Event

### a. Initial Assessment

- i. The IRB Chair, or designated IRB member, will review the reporting form to make the following preliminary determinations:
  - 1. Whether any component of the study or the study itself should be suspended or terminated and reasons for such action. Suspension or termination actions must comply with *IRB Policy 1050: Suspension or Termination of Research Activities*.
  - 2. Whether the reported event constitutes noncompliance that may be serious or continuing. Refer to *IRB Policy 1030: Research Noncompliance* for next steps.
  - 3. Whether the reported event meets the definition of an unanticipated problem.
- ii. If the information provided is insufficient to make the determinations above, the reporting form will be returned to the PI requesting additional information. The PI must respond to the request for additional information within **five business days**.
- iii. If the reviewer determines the reportable event does not meet the definition of an unanticipated problem, the rationale for this decision is documented, and a formal determination letter is provided to the PI. No further action is needed.
- iv. If the reportable event does, or might, meet the definition of an unanticipated problem, the reviewer will determine if the reportable event requires review by the convened IRB, or if expedited/exempt review is appropriate.
  - 1. Expedited/exempt review shall be limited to reportable events where only slight changes in risk have been reported, such that only minor changes in the study protocol or informed consent documents are required.
  - 2. For reportable events requiring review by the convened IRB, the IRB Chair will determine if an emergency meeting of the IRB is necessary or if the review can occur at the next scheduled meeting of the IRB.

### b. Convened IRB Review of Reportable Event Submission

- i. The IRB will first determine whether the reportable event meets the definition of an unanticipated problem.
  - 1. If the IRB determines that the reportable event does not meet the definition of an

unanticipated problem, the rationale for this decision is documented and a formal determination letter is provided to the PI. No further action is needed.

2. The IRB may table the report and request that additional facts be collected or that a further investigation be conducted if necessary for its determinations.
  3. If the IRB determines the reportable event meets the definition of an unanticipated problem, the IRB will consider the following actions:
    - Suspend or terminate IRB approval
    - Require additional information from the principal investigator with a plan for corrective action
    - Transfer research to another investigator
    - Modify the protocol
    - Modify the informed consent form or information disclosed during the consent process
    - Provide additional information to active participants whenever the information may affect their willingness to continue participation
    - Provide additional information to past participants
    - Require current subjects to re-consent
    - Increase the frequency of continuing reviews
    - Observe the research and the consent process
    - Require additional training of the investigator and/or research team
    - Allow continuation of some research activities under the supervision of an independent monitor
    - Require additional follow-up of participants
    - Require adverse events or outcomes to be reported to the IRB
    - Consider whether changes made without prior IRB review and approval were consistent with ensuring the participants' continued welfare
    - Other actions as deemed appropriate by the IRB.
- ii. Upon completion of the IRB's review, a formal determination letter will be provided to the PI.
- c. As appropriate and within a reasonable timeframe, the IRB Chair, ORCI or RIO will submit to authorities as required by regulation, law and practice, a brief written report of the reported event, the findings of any inquiries made, the IRB directed actions, if any, justification for the IRB's actions, and any continued investigation or action plans.

## **Guidance**

1. Examples of unanticipated problems and adverse events (UP/AE):
  - a. Injury, disability, incapacity, hospitalization, life-threatening experience, death, side-effects, aggressive or unusual behavior, or other problem that was potentially related to the research procedures, regardless of the severity of the event;
  - b. Harm or damage (or risk of harm or damage) to the safety, rights, or welfare of research participants, research staff, or others;
  - c. Any accidental or unintentional change to the IRB-approved protocol that involved risks or has the potential to recur;
  - d. Any change to the protocol made without prior IRB approval which was intended to eliminate apparent immediate hazard to a research participant;
  - e. Any publication in the literature, safety monitoring report, interim result, or other finding that indicates an unexpected change to the risks or potential benefits of the research;

- f. Any complaint of a participant that indicates an unanticipated risk or which cannot be resolved by the research staff;
- g. Breach of privacy, confidentiality, or data security;
- h. Loss or destruction of study data;
- i. Incorrect labeling/dosing of study medication or test article;
- j. Possible abuse disclosed in an interview and/or survey;
- k. Urgent situations that may occur as the result of unanticipated problems during the research project
- l. A preponderance of participants do not accept the explanation provided for the use of deception in a study

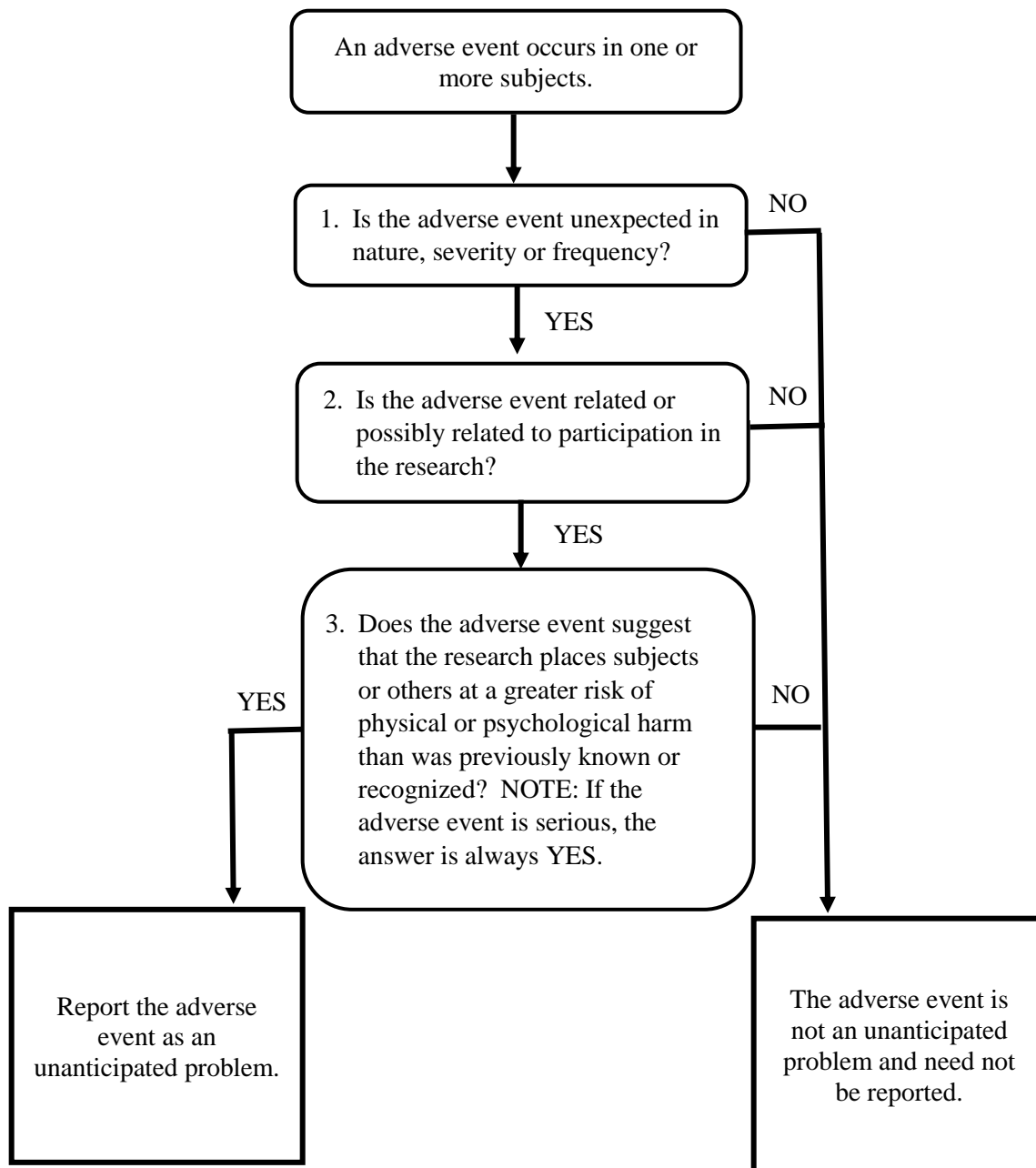
2. Examples of protocol deviations\*

- a. Enrolling a subject who does not meet eligibility criteria.
- b. Study visits outside of the protocol-defined windows.
- c. Conduct of research by individuals not listed on the protocol.
- d. Use of a consent form that was not the most recently-approved version.
- e. Enrolling more participants than approved.
- f. Failure to appropriately document consent and/or authorization.

\*Deviations may be considered major or minor, depending upon the circumstances.

**Appendix**

Determining whether an adverse event represents an unanticipated problem that needs to be reported to the IRB



Adapted from OHRP: "Unanticipated Problems Involving Risks & Adverse Events Guidance," dated January 15, 2007, <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html>