12.0 Research Related Events and Unanticipated Events

Unanticipated event is a broad term to include research related events that were unexpected.

Deviations, Violations, Exceptions, AE/SAEs, and UPIRTSOs must be reported as a Research Related Event and on the Research Related Event Reporting form.

PIs must promptly report the following research-related events to the WVU IRB if they occur under the auspices of West Virginia University:

1. Adverse events involving direct harm to participants, which in the opinion of the principal PI, meet the criteria for an unanticipated problem involving risk to participants or others.
2. An unanticipated event related to the research that exposes participants to potential risk, but that does not involve direct harm to participants.
3. An unanticipated event related to the research that exposes individuals other than the research participants (e.g., PIs, research assistants, students, the public, etc.) to potential risk.
4. Information that indicates a change to the risks or potential benefits of the research that directly impacts the approved research project. These should be accompanied by an amendment to the WVU approved research project.
   For example:
   i. An interim analysis or safety monitoring report indicates that the frequency or magnitude of harms or benefits may be different than initially presented to the WVU IRB
   ii. A paper is published from another project that shows that the risks or potential benefits of your research may be different than initially presented to the WVU IRB
5. A breach of confidentiality.
6. Incarceration of a participant in a protocol not approved to enroll prisoners.
7. Change to the protocol, without WVU IRB review, to eliminate an apparent immediate hazard to research participants.
8. A complaint from a participant when the complaint indicates unexpected risks or cannot be resolved by the research team.
9. Protocol deviations or violations (meaning an accidental or unintentional change to the approved protocol) that harmed participants or others, or that indicates participants or others may be at increased risk of harm.
Major Protocol Deviations or Protocol violations must be reported within five (5) days of the PI being made aware.

10. Sponsor imposed suspension for risk for the WVU IRB approved project.
11. Any other event that indicates participants or others might be at risk of serious, unanticipated harms that are related to the WVU IRB research project.

12.0.1 Exceptions

An enrollment exception is the sponsor’s prospective approval for the enrollment of a research participant that fails to meet currently approved protocol inclusion criteria or falls under protocol exclusion criteria. Enrollment exceptions only apply to a single individual. Such requests should be rare and justified in terms of serving the best interests of the potential project participant.

It is the responsibility of the PI to submit an amendment. The WVU IRB will review the submitted amendment at a convened meeting. The submission must have documentation of Sponsor justification and approval.

These exceptions must be approved by the sponsor and the IRB of Record before being implemented. Exceptions may not increase risk or decrease benefit, affect the participant’s rights, safety, welfare, or affect the integrity of the resultant data.

12.0.2 Deviations

The IRB recognizes that deviations to approved protocols may occur. It is the responsibility of the Principal PI to notify the IRB if the deviations may expose participants to increased risk or fewer benefits, or if the deviation compromises the integrity of the project.

A protocol deviation or violation occurs when there is a variance in a research project between the protocol and the activities being performed. Protocol deviations may be minor or major, as defined below.

12.0.2.1 Minor Protocol Deviations

A deviation is considered minor if it meets all three of the below criteria:

The deviation has no substantive effect on the risks or benefits to the individual research participant; and

The deviation has no substantive effect on the value of the data collected; and
The deviation did not result from the willful or knowing misconduct on the part of the PI(s) or project staff.

12.0.2.2 Major Protocol Deviations

Major deviations, also referred to as protocol violations, must meet one of the following four criteria:

- The deviation has harmed or posed a significant risk of substantive harm to the individual research participant and increased the risk/benefit ratio; or
- The deviation has compromised the scientific integrity of the data collected for the project; or
- There is evidence of willful or knowing misconduct on the part of the PI(s) or project staff; or
- The PI(s) or project staff demonstrated other serious or continuing noncompliance with federal, state, or local research regulations.

Minor Deviations are reported at the time of continuing review. In contrast, Major Protocol Deviations are reported within five (5) days of the occurrence of the event or within five days of the PI becoming aware of the event.

12.0.3 Adverse Events/Serious Adverse Events

12.0.3.1 Adverse Events - An untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

12.0.3.1 Serious Adverse Events - Any adverse event temporally associated with the participant’s participation in research that meets any of the following criteria:

- results in death;
- is life-threatening (places the participant at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the participant’s health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

To meet the requirement for immediate reporting to the WVU IRB, the event must have occurred at the local site or a site under auspicious of the WVU IRB and meet ALL of the following criteria:

- Unexpected
12.0.4 Unanticipated adverse device effect (UADE)
For studies of medical devices, the investigational device exemption regulations define an unanticipated adverse device effect as “any serious 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 any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants” (21 CFR 812.3(s)). UADE reporting applies to both significant and non-significant risk (NSR) device studies.

12.0.5 Complaints
As part of its commitment to protecting the rights and welfare of human participants in research, WVU reviews all complaints and allegations of non-compliance and takes any necessary action to ensure the ethical conduct of research.

All PIs and other project personnel involved in human participants’ research are required to comply with all laws and regulations governing their research activities, as well as with requirements and determinations of the IRB. Project personnel includes the Principal PI and any staff member directly involved with participants or the informed consent process.

Complainants may choose to remain anonymous.

12.0.6 Confidentiality/Data Breach
The acquisition, access, use, or disclosure of protected health information or protected research-related data that was disclosed in a manner not permitted, which compromises the security or privacy of the protected health information or otherwise protected data.
12.1 PI Reporting Requirements

PIs must report unanticipated events to the IRB promptly. If the event requires immediate intervention to prevent serious harm to participants or others, the PI must report the event within five (5) days of receiving notice of the event. In like fashion, PIs must report all other unanticipated events occurring at the local research site to the WVU IRB as soon as possible, but no later than five (5) business days from the date of the event or from the date the PI is notified of the event.

Additionally, problems occurring within thirty (30) days after participants’ active participation or treatment must be reported according to the above schedule.

PIs are not required to report deviations from other sites unless a WVU PI serves as the managing PI for a multi-centered project. The IRB reserves the right to request more frequent reporting and/or the submission of an action plan, depending on the nature of the deviations or violations. Major protocol deviations will be reviewed by the full Committee review upon determination by the IRB Reviewer.

Repetitive deviations, either minor or major, may be ruled by the IRB to constitute non-compliance, possibly resulting in the suspension of IRB approval.

Reporting Forms

Research Related Event Form

Unanticipated Event forms are to be completed for those events that qualify as a research-related event, as listed above. SAEs, Major Deviations/Violations, and UPIRTSOs are to be reported to the IRB within five (5) days of the occurrence of the event or the PI becoming aware of the event. Minor Deviations or AE’s that do not meet the requirement for immediate reporting are to be reported at the time of continuing review. Events that meet all of the following three criteria will be discussed at a convened IRB meeting:

➢ The problem/event was unanticipated
➢ The problem/event was at least possibly related to the research procedures
➢ The problem/event may reflect the new or increased risk to participants

PIs or the project team must report possible unanticipated events to the HRPP, in writing, using the Research Related Event Form, Deviation/AE Summary Form (as applicable), or Complain Form.

The report should contain the following:

• Detailed information about the possible unanticipated problems, including relevant dates.
• Any corrective action planned or already taken, to ensure that the possible unanticipated problems are corrected and will not occur again.
• An assessment of whether any participants or others were placed at risk as a result of the event or suffered any physical, social, or psychological harm and any plan to address these consequences.
• Any other relevant information.
• Any other information requested by the HRPP.

A report of a possible unanticipated event that involves risks to participants or others will be immediately forwarded by HRPP staff to the IRB Chair if the HRPP staff believes that immediate intervention may be required to protect participants or others from serious harm. Upon receipt of a report of a possible unanticipated problem or complaint from someone other than the PI or project staff, the IRB Director will notify the PI on the project when appropriate.

Reporting Major Deviations
PIs are required to report major protocol deviations that occur only at a WVU affiliated research site(s). This includes external sites if the WVU PI is the lead PI on a multi-site project. Major deviation reports must be filed with the OHRP and IRB within five (5) business days of their occurrence, or within five (5) business days of the PI becoming aware of the occurrence. This submission to the IRB should be made through the Notify IRB Action that can be found on the Protocol Actions tab of the approved protocol.

Reporting AE/SAEs
To meet the requirement for immediate reporting to the WVU IRB, the event must have occurred at the local site or a site under auspicious of the WVU IRB and meet ALL of the following criteria:

• Unexpected
• Related or Possibly Related
• Serious

ALL SAEs at the local site resulting in death must be reported to the WVU IRB within five (5) days of the event or the PI becoming aware of the event.

If related or possibly related to the project, events resulting in hospitalization or prolonged hospitalization must be reported to the WVU IRB within five (5) days of the event or the PI becoming aware of the event.
Deviations or AE Summary Report

If an SAE/AE or deviation does not meet the criteria for immediate reporting (within five days) to the IRB for review, those events should be reported at the time of continuing review in a summary form, including the dates of each event and the outcome.

Reporting Minor Deviations and Exceptions

Unanticipated Event forms are to be completed for those events that qualify as a protocol deviation or violation. Minor Deviations must be filed with the WVU OHRP at the time of continuing review. The Chair or designated IRB reviewer may choose to place any deviation or violation on the agenda of the next convened IRB meeting for discussion. The PI may be asked to appear at that meeting to answer any questions or clarify issues for the IRB.

AE/SAEs

All AEs or SAEs occurring at the local site or a site under the auspices of WVU must be reported at the time of continuing review is summary form.

Complaint Concern Form

A complaint form can be found on the OHRP Website. Complaints and or concerns can also be reported to WVU anonymously via the WVU Ethics Reporting online system found on the OHRP website. The Chair and/or the WVU OHRP Director will promptly handle (or delegate staff to handle), and, if necessary, investigate all complaints, concerns, and appeals received by the IRB. This includes complaints, concerns, and appeals from PIs, research participants, and others.

The identity of any entity bringing a complaint, concern, and/or allegation of non-compliance to the attention of OHRP using the form from the website will be kept confidential to the greatest extent possible.

All complaints, written or verbal (including telephone complaints), and regardless of point of origin, may be recorded on a complaint form and emailed to the IRB address. The complaint will then be reviewed by WVU OHRP and forwarded to the IRB Chair, WVU OHRP Director and others are appropriate.

Upon receipt of the complaint, the Chair and/or the Director will make a preliminary assessment of whether the complaint warrants immediate suspension of the research project. If a suspension is warranted, the procedures in SOP Section 3 will be followed. If the complaint meets the definition of non-compliance, it will be considered an allegation of non-compliance and processed accordingly. If the complaint meets the definition of an unanticipated problem involving risk to participants or others (UPIRTSO) or other unanticipated events, it will be handled accordingly.
The IRB Chair and/or OHRP Director shall contact the complainant to acknowledge that the complaint has been received and is being investigated, providing a follow-up contact.

**Monitoring Reports**

PIs are required to report results of audits, inspections, or monitoring visits conducted by sponsors or other external entities through the Notify IRB Action in the WVU+kc system. Reports submitted by the Data Safety Monitoring Board can also be submitted as a Notify IRB Action.

### 12.2 IRB Review Procedures

**IRB Procedures for Handling Reports of Unanticipated Events**

The IRB is charged with making three specific determinations following reporting of an unanticipated event that meets the criteria for reporting to the WVU IRB.

The IRB must determine if the reported information constitutes a reportable event as given below:

- Unanticipated problems involving risk to participants or others (UPIRTSO)
- Non-Compliance
- Suspension or Termination of IRB Approval of a research protocol

**Unanticipated problems involving risk to participants or others (UPIRTSO)** – A UPIRTSO is an unanticipated problem involving risks to participants or others, refer to any incident, experience, outcome, or new information that:

- Is unexpected or *unanticipated* at the time of its occurrence *and* is:
- not already described as potential risks in the approved research protocol or consent document
- not listed in the PI Brochure
  - not due to an underlying disease
  - occurring at an increased frequency or at an increased severity than expected
  - Is *related* or possibly related to participation in the research, *and*.
- Indicates that participants or others are at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

**Non-Compliance**

Non-compliance – Any action or activity associated with the conduct or oversight of research involving human participants that fails to comply with either the research plan as approved by a designated IRB or federal regulations.
or institutional policies governing human participant research. Non-compliance may be minor or sporadic, or it may be serious or continuing. Note: Once a finding of non-compliance is proven, it must be categorized as serious or continuing, not serious and not continuing or minor or sporadic.

PIs and their project staff are required to report instances of potential Non-Compliance. The Principal PI is responsible for reporting any possible non-compliance by project personnel to the IRB. Common reports to the IRB that are not serious or continuing are typically protocol deviations. However, any individual or employee may report observed or apparent instances of noncompliance to the WVU IRB. In such cases, the reporting party is responsible for making these reports in good faith, maintaining the confidentiality, and cooperating with WVU IRB and/or institutional review of these reports.

If an individual, whether PI, project staff, or other, is uncertain whether there is cause to report noncompliance, he or she may contact the IRB Chair directly to discuss the situation informally or submit a complaint form to the IRB email address.

Reports of non-compliance must be submitted to the OHRP within ten working days of discovery of the noncompliance. The report must include a description of the noncompliance and the personnel involved.

**Review of Unanticipated Events by IRB Staff and Chair**

The following are the steps that will be taken by HRPP Staff and the IRB Chair or designated member, upon receipt of a possible Unanticipated Event Form from a Principal PI.

1. Upon receipt of the Unanticipated Event Form, the IRB support staff checks the form for completeness. If any applicable sections of the form are incomplete or have been answered unsatisfactorily, the IRB staff will return the form to the PI or the designated contact person via the electronic submission system.

2. The IRB chairperson and/or another experienced member(s) designated by the IRB Chair receives and reviews the report of the event(s) considered to be an unanticipated problem. The IRB Chair (or designee) will make the final determination as to whether the event is to be regarded as an unanticipated event. At that point, the event will be referred to as the convened board for discussion.

3. Based on the information received from the PI, the IRB Chair or designee may suspend research to ensure the protection of the rights and welfare of participants. Suspension directives made by the IRB Chair (or designee) must be reported to a meeting of the convened IRB.

4. The IRB, the IRB Chair, or the designee has authority to require submission of more detailed, contextual information from the PI, sponsor, project coordinating center, or the DSMB/DMC about any adverse event occurring in a research protocol as a condition of the continuation of the IRB’s approval of the research.
5. If the reviewer finds either of the following to be true, the reviewer will find that the problem is not an Unanticipated Event and the form is filed in the protocol record, the determination is communicated to the PI, and no further action is taken.

➢ The problem was foreseen; or
➢ No participants or others were harmed, and participants or others are not at increased risk of harm.
➢ If the reviewer considers that the problem is an unanticipated problem, but that the risk is no more than minimal, the reviewer will review:
   ➢ The currently approved protocol;
   ➢ The currently approved consent document;
   ➢ Previous reports of unanticipated problems involving risks to participants or others; and
   ➢ The PI’s brochure (if applicable).

6. After reviewing all of the materials, the reviewer will request appropriate actions, depending on the nature of the risk involved. This includes modification of the protocol or the consent form, if applicable. The results of the review will be recorded in the protocol record and communicated to the PI. All events determined to be an UPIRTSO will be reported to the relevant regulatory agencies and institutional officials, according to the procedures in this section.

All reported unanticipated events related to research where the risk is more than minimal that meet the requirements for immediate reporting will be reviewed at a convened IRB meeting.

**IRB Review of Research Related Events**

The protocol information, the currently approved consent document, previous reports of unanticipated problems involving risks to participants or others, the PI’s brochure (if one exists), the unanticipated event form, and recommendations from the IRB Chair or designee, when appropriate, are available to board members.

After a review of the protocol and research related event report, the convened IRB will make findings and recommendations based on the following considerations:

➢ Whether the reported event is an unanticipated problem involving risks to participants or others (UPIRTSO), according to the definition in this policy.
➢ Whether suspension or termination of approval is warranted.
➢ Whether the event constituted Non-Compliance, either serious or continuing, or minor or sporadic.
➢ A failure to follow any of the regulations and policies outlined in this document or failure to follow the determinations of the IRB, which, in the judgment of the convened IRB, increases risks and decreases potential benefits to research participants is considered serious non-compliance. Research conducted without prior IRB approval or participation of participants in research activities without their prior consent (in studies where consent was not explicitly waived by the IRB) is considered serious non-compliance.
➢ Whether further reporting to Institutional and/or federal officials is required.
➢ The appropriate action, in response to the submitted report.
➢ Whether the PI’s corrective action plan is appropriate or additional information is needed.

If the IRB finds that the event is not a reportable event, according to the definition, the IRB may recommend the following actions:

- No action is required.
- Requiring modifications to the protocol.
- Revising the continuing review timetable.
- Modifying the consent process.
- Modifying the consent document.
- Providing additional information to current participants (i.e. whenever the information may relate to the participant’s willingness to continue participation).
- Providing additional information to past participants.
- Requiring additional training of the PI and/or project staff.
- Other actions appropriate for the local context.

If the IRB finds that the event is an unanticipated problem involving risks to participants or others (UPIRTSO), according to the definition in the policy, the IRB may recommend any of the following actions:

- Requiring modifications to the protocol.
- Revising the continuing review timetable.
- Modifying the consent process.
- Modifying the consent document.
- Providing additional information to current participants (e.g. whenever the information may relate to the participant’s willingness to continue participation).
- Providing additional information to past participants.
- Requiring additional training of the PI and/or project staff.
- Reconsidering approval.
- Requirement that current participants re-consent to participation.
- Monitoring of the research.
- Monitoring of the consent process.
- Referral to other organizational entities (e.g., legal counsel, institutional official).
- Suspending the research.
- Terminating the research.
- Other actions appropriate for the local context.
If a report suggests that participant safety is at risk, the IRB may immediately suspend or terminate the research. Any suspension or termination of research by the IRB must be promptly reported to the Institutional Official, the Director of OHRP, OHRP, and FDA (if FDA-regulated) through the Institutional Official. This should be done in writing.

If, after reviewing a report, the IRB finds that the event is an UPIRTSO, a Serious or Continuing Non-Compliance or that suspension or termination of approval is warranted, the IRB will:

1. Notify the PI in writing of its findings, with copies to the Chair of the PI’s department and/or research unit, other affected units, and the PIs supervisor; and
2. Report its findings and recommendations to the Institutional Official for further reporting to the appropriate federal officials (ORO, OHRP, and FDA).

Review of Allegations of Non-Compliance

All allegations of non-compliance will be reviewed by the IRB Chair (or designee), who will review:

➢ All documents relevant to the allegation.
➢ The last approval letter from the IRB.
➢ The last approved IRB application and protocol.
➢ The last approved consent document.
   ➢ The grant, if applicable.
   ➢ Any other pertinent information (i.e. questionnaires, DSMB reports, etc.)

The IRB Chair or designee will review the allegation and make a determination as to the validity of the allegation. They may request additional information, an investigation, and/or an audit of the research in question.

When the Chair or designee determines that non-compliance did not occur because the incident was within the limits of an approved protocol for the research involved, the determination is reported to the PI and, if applicable to the reporting party. The determination will be communicated to the Institutional Official, in cases where the IO and any other parties had been notified at the outset.

If in the judgment of the IRB Chair or designee, the reported allegation of non-compliance is valid, the non-compliance will be processed according to Section 10.3.2.

If, in the judgment of the IRB Chair or designee, any allegation or findings of non-compliance warrants suspension of the research before completion of any review or investigation, to ensure the protection of the rights and welfare of participants, the IRB Chair may suspend the research as described in Section 3.9. A subsequent review by the IRB will occur.

The Chair may determine that additional expertise or assistance is required to make these determinations and may form an ad hoc committee to assist with the review and fact-gathering process. When an ad hoc committee assists in the
review process, the Chair is responsible for assuring that minutes of the meeting are generated and kept to help support any determinations or findings made by the ad hoc committee.

Review of Findings of Non-Compliance

Non-Compliance is Determined Not Serious or Not Continuing
When the Chair or designee determines that non-compliance occurred but does not meet the definition of serious or continuing non-compliance, the determination is reported to the PI and the reporting party (if applicable) following the determination by the convened IRB.

The Chair or designee will either accept the submitted corrective action plan or will work with the PI to develop a corrective action plan to prevent future non-compliance. If, however, the PI refuses to implement a corrective action plan, the matter is referred to a convened meeting of the IRB.

Non-Compliance is Determined Serious or Continuing
If in the opinion of the Chair or designee, a non-compliance has occurred and potentially meets the definition of serious or continuing non-compliance, the report is referred for review by the IRB at the next convened available meeting.

The Chair may use discretion and call an emergency IRB meeting should the circumstances warrant such an urgent meeting.

All findings of serious or continuing non-compliance referred to the IRB will be reviewed at a convened meeting. All IRB members will have access to:

- All documents relevant to the allegation.
- The last approval letter from the IRB.
- The last approved IRB protocol.
- The last approved consent document.
- At this stage, the IRB may:
  - Find that there is no issue of non-compliance.
  - Find that there is non-compliance that is neither serious nor continuing and that an adequate correction plan is in place.
  - Find that there is serious or continuing non-compliance and approve any changes proposed by the Chair and/or ad hoc committees.
  - Find that there may be serious or continuing non-compliance and direct that a formal inquiry (see Section 10.3.3) be held.
  - Request additional information.
Inquiry Procedures

A determination may be made by the convened IRB that an inquiry is necessary based on several issues that may include but are not limited to:

- Participants’ complaint(s) that rights were violated.
- Report(s) that the PI is not following the protocol as approved by the IRB.
- Unusual and/or unexplained adverse events in a project.
- Repeated failure of the PI to report the required information to the IRB.

A subcommittee is appointed consisting of IRB members, and non-members if appropriate, to ensure fairness and expertise. The subcommittee is given a charge by the IRB, which can include any or all of the following:

- Review of the protocol(s) in question.
- Review of the sponsor audit report(s) of the PI, if appropriate.
- Review of any relevant documentation, including consent documents, case report forms, participant’s investigation and/or medical files, etc., as they relate to the PI’s execution of her/his project involving human participants.
- Interview of appropriate personnel if necessary.
- Preparation of either a written or oral report of the findings, which is present to the full IRB at its next meeting;
- Recommend actions if appropriate.

Final Review

The results of the inquiry will be reviewed at a convened IRB meeting where the IRB will receive a report from the subcommittee. If the results of the inquiry substantiate the finding of serious or continuing non-compliance, the IRB’s possible actions could include, but are not limited to:

- Request or revise a corrective action plan from the PI.
- Verification that participant selection is appropriate and observation of the actual informed consent process.
- An increase in data and safety monitoring of the research activity.
- Request a directed audit of target areas of concern.
- Request a status report after a determined number of participants receive the intervention.
- Modify the continuing review cycle.
- Request additional PI and staff education.
- Notify current participants, if the information about the non-compliance might affect their willingness to continue participation.
- Require modification of the protocol.
- Require modification of the information disclosed during the consent process.
- Require current participants to re-consent to participation.
- Suspend the project (see below).
- Terminate the project (see below).

In cases where the IRB determines that the event of noncompliance also meets the definition of an unanticipated problem involving risks to participants or others, the policy and procedure for review of such events will also be followed.
The PI is informed of the IRB determination, and the basis for the determination in writing and is given a chance to respond. If the IRB determines that the non-compliance was serious or continuing.

**NOTE:** The IRB must reach a determination that serious or continuing noncompliance did (or did not) occur within 30-45 days after receiving a report of apparent non-compliance. Remedial actions involving a specific project or research team must be completed within 90-120 days after the IRB’s determination.

Remedial actions involving programmatic noncompliance must be completed within 120-180 days after the IRB’s determination, unless remediation requires substantial renovation, fiscal expenditure, hiring, legal negotiations, etc.