I. Purpose

This policy defines reportable events and the requirements of Principal Investigators (PI) to report all reportable events as outlined in this document **within 5 working days of research team notification of the event**. Routine informational reporting that should be included as part of an annual continuing review report rather than a separate reportable event is also outlined.

II. Responsibilities

The PI is responsible for promptly reporting any unanticipated problem that involves risks to participants or others that are **unexpected** and **related** to participation in the research study, and serious. Serious events suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

- **Unanticipated Problem**
  Any incident, experience, or outcome in any study involving human subjects that meets **ALL** of the following criteria:

  A. Is 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, informed consent document, and the PI brochure; and( b) the characteristics of the subject population being studied; **AND**

  B. Is 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.

- **Unexpected**
  An event is unexpected when its specificity and severity are not accurately reflected in the protocol- related documents, such as the informed consent document, the protocol, or the Investigator’s Brochure/Package Insert/Device Information; or the event is expected that increases in frequency and/or severity.

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• **Relatedness to Participation in the Research**

The PI is responsible for determining the relatedness of an event.

An event is related to the research procedures if in the opinion of the PI, it was more likely than not to be caused by the research procedures, or if it’s more likely than not that the event affects the rights and welfare of current participants. (In evaluating whether an event is **related** (possibly, probably or definitely) to research participation), the PI should consider whether the event:

- Is temporally related to the intervention.
- Is not produced by the subject’s clinical state.
- Is not due to environmental factors or non-research interventions.
- Follows a known pattern of response to the intervention.
- Disappears/decreases with reduction in dose or cessation of intervention.

• **Serious**

Any event that occurs during a subject’s participation in the study that meets the criteria established in the Food and Drug Administration (FDA) definitions (21 CFR 312) for both serious and unexpected. Note that events not associated with participation in the study, e.g., those that occur after screening, but before administration of a test article, would not be considered serious and unexpected (21 CFR 312.60).

- **Death**
  Report if you suspect that the death was an outcome of the adverse event, and include the date if known. **All deaths that have happened within 30 days of the last study intervention, and not related to progressive disease. Any death can be reported, if the PI feels that it is significant** no matter when it occurs.

- **Life-threatening**
  Report if suspected that the patient was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product that might have resulted in the death of the patient.

- **Hospitalization (initial or prolonged)**
  Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event.

- **Emergency room visits**
  That do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

- **Disability or Permanent Damage**
  Report if the adverse event resulted in a substantial disruption of a person’s ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient’s body function/structure, physical activities and/or quality of life.

- **Congenital Anomaly/Birth Defect**
  Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

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- **Required Intervention to Prevent Permanent Impairment or Damage (Devices)**
  Report if you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.

- **Other Serious (Important Medical Events)**
  Report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

### III. Required Reporting and Time Frames

PIs are required to report the following events **promptly, but within 5 working days from study team notification of the event** (please note, this requirement is in addition to requirement of study sponsors and/or funding agencies, which may be of a shorter duration).

*All reports will be submitted in the electronic IRB submission system.*

*Please note the following events that require reporting to the IRB:*

1) **Unanticipated problems**

2) **Serious adverse events (SAEs)**

3) **Adverse events (AEs) that are Unexpected and Related to participation in the research**

4) **IND Safety reports and Med Watch reports** that require changes to the protocol and consent must be reported within 5 business days after receipt for AEs. All other IND safety reports should be reported to the IRB as a summary at the time of continuing review.

5) **All deaths** that have occurred within 30 days of the last study intervention (study-related treatment or activity) and not related to progressive disease must be reported to the IRB. Please note, the PI may report any death that is significant, no matter when it occurs.

6) **Protocol Deviations** must be reported to the IRB as a potential unanticipated problem involving risk to the subjects or others when they:
   a) Increase risk or decrease benefits, affect the subject’s rights, safety, welfare or affect the integrity of the data;

7) **Protocol violations** that harmed participants or others or that indicates participants or others may have been placed at increased harm, must be reported to the IRB. Such violations increase risk or decrease benefit, affect the subject’s rights, safety, welfare and/or the integrity of the data, and should be reported. Examples of Reportable Violations, include, but are not limited to:

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a) Variations/errors in drug dosing/dispensing/storage
b) Use of prohibited medication
c) Enrolling subjects that do not fulfill inclusion/exclusion criteria
d) Subjects receiving any study related activity such as treatment, procedures, testing/drug administration prior to obtaining documented IRB approved consent or use of unapproved or expired consent
e) Variations in the use of a study device
f) Protocol violations identified by the sponsor monitor visits or study coordinator that may affect the safety of a subject or the integrity of study data. PIs are required to submit the report with the protocol violation

8) **Unanticipated Adverse Device Effects** that meet FDA Device Study Regulations must be reported to the IRB as soon as possible but no later than 5 working days after the PI first learns of the reportable event.

9) **Reports from Data Safety Monitoring Boards (DSMBs) and Data Monitoring Committees (DMCs)**

10) **Notification Letters** from external oversight entities. Notification letters could include enrollment suspension, enrollment closure, enrollment re-activation, audit findings, inspection findings, or any other notifications of research findings that increases risks to enrolled subjects or the need to inform current or potential subjects in the consenting process as soon as possible but no later than seven (7) days after the PI receives the report.

11) **Revised Investigator Brochures that do not include a change in risk, protocol revision, or informed consent document revision.** Investigator Brochures with a revision of the protocol or study documents must be submitted as a protocol amendment rather than reportable event, however immediate notification of the IRB within 5 days is still required if an increase in risks is identified.

12) **Information that indicates a change to the risks or potential benefits of the research.**
For example:
   a) An interim analysis or safety monitoring report indicates that frequency or magnitude of harm or benefit may be different than initially presented to the IRB.
   b) A paper is published from another study that shows the risks or potential benefits of your research may be different than initially presented to the IRB.
   c) Study placed on hold by the PI, FDA, or the Sponsor for reasons that may include safety, toxicity, and/or efficacy.

13) **A change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol**

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14) **Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research participant**

15) **Research conducted without prior GRU IRB approval**

16) **Event that requires prompt reporting to the sponsor**

17) **Loss or corruption of study data**

18) **Sponsor imposed suspension for risk**

19) **Complain of a participant when the complaint indicates unexpected risks or cannot be resolved by the research team**

20) **A breach of confidentiality**

21) **Incarceration of a participant in a protocol not approved to enroll prisoners.** To include administration of a protocol intervention to a prisoner in a protocol not approved for enrolling prisoners

22) **Any information that changes the risks or potential benefits of the research such as:**
   a) An interim analysis or safety monitoring report indicating that frequency or magnitude of harms or benefits may be different from those initially presented to the IRB.
   b) A paper is published from another study that shows that the risks or potential benefits of your research may be different from those initially presented to the IRB.

23) **Change to the protocol made without prior IRB approval intended to eliminate an apparent and immediate hazard to a research participant**

24) **Any other event that indicates participant or others might be at risk of serious, unanticipated harms that are reasonably related to the research.**

### IV. Reports at the time of continuing IRB review

Unless otherwise required by the IRB approved protocol, the PI will report the following at the time of continuing review:

- A summary of all other adverse events that have not been previously reported such as IND Safety Reports for Industry Sponsored protocols and Data Monitoring Committee (DMC) or Data Safety Monitoring Board (DSMB) Reports for multi-center studies. If the frequency and severity of these adverse events meet the criteria of an Unanticipated Problem (UAP), the PI must provide a thorough evaluation of these events to the IRB.

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V. Additional Definitions and Examples

1. **Adverse Event:** Any untoward medical occurrence associated with the use of drug in humans, including any abnormal sign (for example abnormal physical exam or laboratory finding), symptom, or disease, whether or not considered drug related, that is, any adverse event observed during a clinical trial.

2. **IND Safety Report:** A report from the Sponsor of a new toxicity identified in an investigational agent. This report is an expedited, written notification to the FDA of an adverse experience associated with the use of a study drug that is both unexpected and/or serious. PIs who are IND holders are subject to compliance with both the adverse event reporting requirements of the sponsor and the requirements of the PI.

3. **Med Watch Report:** A report from the FDA of a new toxicity identified in an approved drug that requires notification to providers who prescribe the drug. Adverse drug reactions reported through Med Watch can act as ‘signals’ which are investigated to determine their clinical significance and potential public health impact.

4. **Unanticipated Adverse Device Effect:** An unanticipated adverse device effect is any serious adverse effect on health or safety; 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 application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

5. **Protocol Deviation:** Any change, divergence, or departure from the IRB approved study procedures in a research protocol that is under the investigator’s control and that has not been approved by the IRB. Deviations may result from the actions of the study subject, investigator, or study staff.

   a. **Minor Deviations**

      Changes or alterations in the conduct of the trial which do not have a major impact on the subject’s rights, safety or well-being, or the completeness, accuracy and reliability of the study data. Examples of minor deviations include but are not limited to:

      i. a missed visit window for follow-up with no procedure required at the visit;
      ii. initials missing from one page of the consent document;
      iii. Parent or participant forgets to print name on the consent document

      if the PI identifies a trend in an increasing number of deviations which could cause potential harm or well-being to research subjects, the trend needs to be reported to the IRB.

      There may be instances of protocol waivers granted by the sponsor for a GRU PI to accrue a subject who does not meet the inclusion/exclusion criteria for enrollment. The IRB does not

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approve the protocol waiver; however, documentation of waivers must be maintained in the research records.

6. **Protocol Violation**: Any change, divergence, or departure from the IRB approved study procedures in a research protocol that **does** have a major impact on the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. The following are criteria and examples of types of protocol violations.

   a. *The violation has harmed or posed a significant or substantive risk of harm to the research subject. Examples include, but are not limited to:*
      i. A research subject received the wrong treatment or incorrect dose
      ii. A research subject met withdrawal criteria during the study but was not withdrawn
      iii. A research subject received an excluded concomitant medication.

   b. *The violation compromised the scientific integrity of the data collected for the study. Examples include, but are not limited to:*
      i. A research subject was enrolled but does not meet the protocol's eligibility criteria
      ii. Failure to treat research subjects per protocol procedures that specifically relate to primary efficacy outcomes (if it involves patient safety it meets the first category above)
      iii. Changing the protocol without prior IRB approval
      iv. Inadvertent loss of samples or data.

   c. *The violation is a breach of human subjects protection regulations, policies, or procedures on the part of the PI(s). Examples include, but are not limited to:*
      i. Failure to obtain informed consent prior to initiation of study-related activities/ procedures
      ii. Falsifying research or medical records
      iii. Performing activities, tests, or procedures beyond the individual's professional scope or privilege status (credentialing)

   d. *The violation involves serious or continuing noncompliance with federal, state, local or institutional human subjects protection regulations, policies, or procedures. Examples include, but are not limited to:*
      i. Working under an expired professional license or certification
      ii. Failure to follow federal and/or local regulations, and intramural research or hospital and clinic policies
      iii. Repeated minor deviations.

   e. *The violation is inconsistent with the GRU Human Research Protection Program's research, medical, and ethical principles. Examples include, but are not limited to:*

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i. A breach of confidentiality and/or privacy
ii. Inadequate or improper informed consent procedures.

7. Notification Letters: Correspondence from any outside oversight entity such as the FDA, a Sponsor, Contract (or Clinical) Research Organization (CRO), a DSMB, DMC providing new information indicating that there has been a change in the risks and potential benefits to subjects participating in a research study.

VI. IRB Review Responsibilities

The IRB Chair or designee reviews reports as soon as possible after receipt by the IRB Office. The IRB Chair can determine that 1) an event only needs to be presented to the IRB in a report format; 2) an event needs to be placed on the next IRB Agenda for discussion and Full Board action; or 3) an event requires immediate action to protect human subjects. If in the IRB chair’s judgment immediate action is required to protect research subjects or others such as suspension of the protocol, and communication with enrolled subjects, he/she shall immediately contact the PI and the GRU IRB Office. Information with regard to the reportable event and Chair’s action will be added to the IRB Agenda for the next convened IRB meeting.

IRB Review of reportable events at the time of continuing review: The IRB will review the overall conduct of the study, including all reportable events during the reporting period and summary information (such as collective adverse events, IND safety reports and any additional material provided as part of the continuing review report) to determine if the amount and nature of reportable events has increased the risks of participation for subjects on the protocol.

IRB actions: An IRB may take actions that include, but are not limited to, the following:

A. No change in the protocol and/or consent document(s) is necessary.
B. The protocol and/or consent documents must be changed to reflect the increased risk. The IRB will stipulate the required changes that will be submitted by the PI as an amendment for future IRB review. The IRB will decide whether current subjects should be re-consented or informed by other means depending on the nature of the study.
C. The study will be closed to new enrollment but, depending on the nature of the study, current subjects may continue in follow-up status or actively on the protocol.
D. The study must be closed. Subjects currently enrolled must be informed and safely withdrawn.

Documenting its decision(s): The IRB will document its decisions in the meeting minutes and notify the PI in writing of their decision.

Regulations and Policies:

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• DHHS regulations at 45 CFR 46.103(b)(5) and 45 CFR 46.113.
• FDA regulations at 21 CFR 56.108(b)(1), 21 CFR 56.113 and 21 CFR 312.32(c)

Guidance Documents:

• Office for Human Research Protections (OHRP) Guidance on Reviewing and Reporting Unanticipated Problems involving Risk to Subjects or others and Adverse Events, January 15, 2007 (see <http://www.hhs.gov/ohrp/policy/advevtguid.html>).

Appendix A:  For Charlie Norwood VA Medical Center (CNVAMC) Research

1. The terms “unanticipated” and “unexpected” refer to an event or problem in CNVAMC research that is new or greater than previously known in terms of nature, severity, or frequency, given the procedures described in protocol-related documents and the characteristics of the study population.

2. For unanticipated problems involving risks to participants or others, members of the CNVAMC research community are required to ensure that all unanticipated problems involving risks to participants or others in research are reported promptly to the IRB.

3. For serious unanticipated problems involving risks to participants or others, within five business days of becoming aware of any serious unanticipated problem involving risks to participants or others in CNVAMC research, members of the CNVAMC research community are required to ensure that the problem has been reported in writing to the IRB. Serious unanticipated problems involving risks to participants or others include:

   • Interruptions of participant enrollments or other research activities due to concerns about the safety, rights, or welfare of human research participants, research staff, or others.
   • Any work-related injury to personnel involved in human research, or any research-related injury to any other person, that requires more than minor medical intervention (i.e., basic first aid), requires extended surveillance of the affected individuals, or leads to serious complications or death.
   • Any VA National Pharmacy Benefits Management (PBM) Bulletins or Communications (sometimes referred to as PBM Safety Alerts) relevant to one or more of the VA facility’s research projects.
   • Any data monitoring committee, data and safety monitoring board or data and safety monitoring committee report describing a safety problem.
   • Any sponsor analysis describing a safety problem for which action at the VA facility might be warranted.
   • Any unanticipated problem involving substantive harm or a genuine risk of substantive harm, to the safety, rights, or welfare of human research participants, research staff, or others.
   • Any problem reflecting a deficiency that substantively compromises the effectiveness of the VA facility’s HRPP.
     ○ Local unanticipated serious adverse events.

4. Policies and procedures indicate that within five business days of becoming aware of any local (i.e., occurring in the reporting individual’s own facility) unanticipated serious adverse events in CNVAMC research, members of the CNVAMC research community are required to ensure that the serious adverse event has been reported in writing to the IRB.

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5. This requirement is in addition to other applicable reporting requirements (e.g., reporting to the sponsor under FDA requirements):
   a. The unfounded classification of a serious adverse event as “anticipated” constitutes serious non-compliance.
   b. IRB review of serious unanticipated problems and unanticipated serious adverse events.

6. Policies and procedures indicate that within five business days after a report of a serious unanticipated problem involving risks to participants or others, or of a local unanticipated serious adverse event, the convened IRB or a qualified IRB member-reviewer must determine and document whether the reported incident was serious and unanticipated and related to the research.

7. “Related” means the event or problem may reasonably be regarded as caused by, or probably caused by, the research.

8. If the convened IRB or the IRB reviewer determines that the problem or event was serious, unanticipated, and related to the research, the IRB chair or designee must report in writing the unanticipated problem or event within five business days after the determination to:
   a. Medical center director.
   b. Associate chief of staff for research.
   c. The Research and Development Committee.

9. The medical center director must report the problem or event to the appropriate Office of Research Oversight research officer within five business days after receiving such notification.

10. If the convened IRB or the IRB reviewer determines that the problem or event was serious, unanticipated, and related to the research, a simultaneous determination is required regarding the need for any action (e.g., suspension of activities; notification of participants) necessary to prevent an immediate hazard to participants in accordance with VA regulations.

11. All determinations of the IRB reviewer (regardless of outcome) must be reported to the IRB at its next convened meeting.

12. If it was determined that the problem or event is serious, unanticipated, and related to the research, the convened IRB must determine and document whether a protocol or consent document modification is warranted.

13. If the convened IRB determines that a protocol or consent document modification is warranted, the IRB must also determine and document:
   a. Whether previously enrolled participants must be notified of the modification.
   b. When such notification must take place and how such notification must be documented.

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Determining Whether an Adverse Event Represents an Unanticipated Problem That needs to be reported to the IRB under HHS Regulations at 45 CFR Part 46

An adverse event occurs in one or more subjects

1. Is the adverse event unexpected in nature, severity, or frequency?
   - NO
   - YES

2. Is the adverse event definitely, probably, or more likely than not related to participation in the research?
   - NO
   - YES

3. Does the adverse event suggest that the research placed subjects or others at a greater risk of physical or psychological harm than was previously known or recognized? Note: If the adverse event is serious, the answer is always “Yes”
   - YES
   - NO

Report the adverse event as an unanticipated problem under 45CFR part 46

STOP

The adverse event is not an unanticipated problem and need not be reported under 45 CFR part 46

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