Adverse Event Management and Problem Reporting		
VCU/VCUHS CLINICAL RESEARCH STANDARD OPERATING PROCEDURES		
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1. PURPOSE

This Standard Operating Procedure describes the policies and procedures for adverse event (AE) management and reporting in clinical research. The scope of this SOP includes the recognition, identification, management, documentation, and reporting of any AEs that occur in the course of a clinical research study at VCU, VCUHS, and all affiliated and participating sites.

2. REQUIREMENTS

All AEs (including events identified as serious adverse events) shall be managed according to the requirements of the protocol and per applicable regulations, policies of the Institutional Review Board (IRB) of record and in a manner that ensures the protection of research participants and the collection of quality data.

3. DEFINITIONS

Adverse event (AE) – An adverse event (AE) is any untoward medical occurrence in a human subject participating in research. The event is undesirable and unintended, but is not necessarily "unanticipated" (rendering it also reportable to the IRB) unless the frequency or severity causes the event to be unanticipated. Adverse events include abnormal laboratory findings, a symptom, or disease temporally associated with the use of an investigational agent, or the progression of disease, whether or not related to the medicinal (investigational) product.

Serious adverse event (SAE) – A serious adverse event (SAE) is any adverse event, defined above, whether or not related to the investigational product, which meets any ***one*** *of the six* criteria:

1. Results in death,
2. Is life-threatening,
3. Requires inpatient hospitalization or prolongation of an existing hospitalization,
4. Results in persistent or significant disability/incapacity,
5. Results in a congenital anomaly/birth defect
6. Is an important medical event that when based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Unanticipated Problem (UP) – The Office of Human Research Protections (OHRP) considers unanticipated problems to include any incident, experience, or outcome that meets ***ALL*** of the following criteria:

A. Was 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. Was related or possibly related to participation in the research (in OHRP's 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); 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.

Unanticipated Adverse Device Effect (UADE) - The FDA defines an unanticipated adverse device effect as - "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 any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (21 CFR 812.3(s)).

4. PROCESS

A. Preparation

- The investigator and appropriate members of the research team should be familiar with the safety information about the investigational product. Safety information is available in study documents such as the investigator's brochure, package inserts, and safety reports provided by the sponsor.
- The investigator should review the protocol and study procedure manual (if any) about the requirements of recording and reporting of AEs for the particular trial. Some studies require toxicity grading (e.g., National Cancer Institute) in the management of AEs.
- An AE is assessed and reported by the investigator from the time that the investigational product is administered/applied. However, some studies require AE assessment starting from initiation of screening procedures for capturing AEs related to protocol-specific procedures.
- Refer to the protocol to determine when AE assessments are no longer required.

B. Assessing, Identifying, Managing, and Documenting AEs

- Participants should be assessed at each visit, or study assessment, for AEs that may have occurred since the previous visit or assessment, ensuring that the following are appropriately investigated:
    - Spontaneous reports of adverse events by subjects

- Observations of adverse events by clinical research personnel
- Reports by family members or medical care providers
- Event documentation in medical records or progress notes that may be AEs
- Reports of participant death during the protocol-defined follow-up period, whether considered treatment-related or not
- Tests and procedure results

- When an AE is probable, all appropriate resources shall be directed toward ensuring the safety and well-being of the participant.
- Steps to be followed:
    1. Critical elements when determining and documenting an AE
        a. Severity
        b. Seriousness
        c. Probable relationship to the investigational product
    2. Identify the status of each AE as:
        a. New
        b. Ongoing, or
        c. Resolved
    3. Consider and document any possible related symptoms, and/or abnormal diagnostic/procedure results that can be appropriately grouped together under a specific AE.
    4. Document any interventions used to address the AE including any AE-related study modification such as dosing or treatment schedule.
    5. Reference reporting timeline requirements as defined by the study's IRB of record and/or protocol.
    6. Follow all AEs until resolution or stabilization, per the protocol and good clinical practice, and document accordingly. If necessary for the immediate well-being of the participant, the Principal Investigator may, after consultation with the sponsor, elect to break any blind associated with the study, see SOP CR-CO-500 Blinding - Codes and Code Breaking. Therapeutic intervention measures shall be taken as outlined in the protocol. For deviations from the protocol necessary to protect the life or well-being of the subject in an emergency, refer to the VCU HRPP Investigator Manual (HRP-103), and see CR-RE-340.2a: Protocol Deviations and Violations. The participants shall have clinical assessments (frequency to be determined by the principal investigator or designee, unless dictated by the protocol) until the AE has stabilized or resolved.
    7. Ensure that all information regarding AEs is recorded immediately in a source document and in the appropriate case report form, as required by the protocol.
    8. IRB Reporting: The investigator and research staff should be familiar with and take steps to be compliant with ***IRB reporting*** policies for all AEs which meet the requisite reporting requirements of “unanticipated problems” or “unanticipated adverse device effect”, through a Reportable New Information (RNI) submission

a. If there is any further action required by the IRB or regulatory body after reviewing the safety reports, the investigator should inform the sponsor.
b. Refer to the policy of the IRB of record to determine reporting requirements to submit

9. Sponsor Reporting: The sponsor should be provided with any and all information related to an AE occurrence in accordance with the study protocol's reporting requirements. If applicable, the form provided by the sponsor should be completed. As much of the following information should be included as possible:
    a. Protocol name and number
    b. Possible test articles: investigational product/devices, comparator, or placebo
    c. Lot number and expiration date
    d. Study subject number/identification
    e. Demographic data
    f. Nature of the event
    g. Severity of the event (may be classified in the protocol). Probable relationship of the AE to the investigational product
    h. Date (and time) of AE onset
    i. Date (and time) of AE resolution, if available
    j. Dose, frequency, and route of administration of the investigational product
    k. Start and stop dates (and times for IV infusions, as applicable) of test article administration
    l. Concomitant medication and therapies
    m. Clinical assessment of the participant at this time
    n. Results of any laboratory and/or diagnostic procedures, treatments, autopsy findings
    o. Follow-up plan
    p. Outcome

C. Serious Adverse Events
- Serious Adverse Events (SAEs) should be classified as expected or unexpected, per protocol.
- Report SAEs to the sponsor, the principal investigator, the ethics committee or institutional review board (if applicable), and the FDA (if applicable) as required by the protocol and in accordance with any other applicable procedures/policies.
- SAEs that occur during the study period (specified in the protocol) and that are considered to be possibly related to the investigational product or research procedures should be treated, documented, and reported immediately to all parties (e.g, sponsor, ethics board or institutional review board (if applicable), the FDA (if applicable), and entire study team).

D. Multi-Center Studies

For multi-centered trials, the sponsor will send external SAE reports (e.g. MedWatch, Suspected Unexpected Serious Adverse Reaction (SUSARs), etc,) to each investigator participating in trial testing of the same investigational product. The investigator should acknowledge receipt of the external SAE reports to the Sponsor. The external SAE reports are submitted to the IRB in accordance with:

- VCU HRPP Policies and Guidance
- Policies of any applicable IRB of Record

E. Investigator-held IND/IDE studies

Studies that are conducted under a VCU investigator-held IND/IDE are also subject to FDA reporting requirements for an AE. The FDA's reporting requirements may vary from the IRB of record's reporting requirements. All safety reports should be submitted on the 3500A form (MedWatch Form).

- Drugs/Biologics: Initial reporting of any suspected AE's that are considered serious and unexpected and are suspected to be associated with the use of the investigational product must be reported within 15 *calendar* days of the event. Unexpected fatal or life-threatening AEs suspected to be associated with the use of the investigational product must be reported within 7 *calendar* days of the event. Follow up reporting related to a previously reported AE must be reported within 15 calendar days of the additional relevant information becoming available. Any AEs that are not serious, unexpected, fatal or life-threatening should be reported with the submission of the annual report.
- Devices: Initial reporting of an unanticipated AE caused/associated with a device must be reported to the FDA and reviewing IRB within 10 *working* days of the event.

F. Unanticipated Problems

It is the principal investigator's responsibility to determine if an AE is a potential unanticipated problem (UP) to be reported to the IRB of record in accordance with the IRB of record's governing policy

5. REFERENCES

A. Code of Federal Regulations

- 21 CFR 50.25 – Elements of Informed Consent
- 21 CFR 56.108 – IRB Functions and Operations
- 21 CFR 56.115 – IRB Records
- 21 CFR 312.32 – IND Safety Reports
- 21 CFR 312.33 – Annual Reports
- 21 CFR 312.44 – Termination
- 21 CFR 312.64 – Investigator Reports
- 45 CFR 46.116 – General Requirements for Informed Consent

B. FDA

- IRB Continuing Review After Clinical Investigation Approval Information Sheet
- Investigator Responsibilities – Protecting the Rights, Safety and Welfare of Study Subjects – Information Sheet
- Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs – Improving Human Subject Protection – Information Sheet
- Safety Reporting Requirements for INDs and BA/BE Studies – Information Sheet
- MedWatch Forms for FDA Safety Reporting

C. OHRP Guidance: Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events: OHRP Guidance (2007)"

D. ICH Harmonised Tripartite Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A

E. Good Clinical Practice
- ICH E6: Harmonized Tripartite Guideline for GCP
    - Section 3 - Institutional Review Board/Independent Ethics Committee (IRB/IEC)
        - Section 3.1 - Responsibilities
        - Section 3.2 - Composition, Function and Operation
        - Section 3.3 - Procedures
        - Section 3.4 - Records
    - Section 4 - Investigator
        - Section 4.3 - Medical Care of Trial Subjects
        - Section 4.4 - Communication with IRB/IEC
        - Section 4.5 - Compliance with Protocol
        - Section 4.10 - Progress Reports
        - Section 4.11 - Safety Reporting
        - Section 4.12 - Final Report(s) by Investigator

F. IRBs
- HRPP Policies and Guidance; HRPP Toolkit
    - HRP-001; SOP: Definitions
    - HRP-103; Investigator Manual
    - HRP-103p; pSite Investigator Manual
    - HRP-814; Form: Site Reportable New Information
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- National Cancer Institute CIRB Policies
- WCG Guide for Researchers Advarra
- IRB Handbook for Investigators, Institutions, Sponsors, and Sponsors' Representatives -

(Requires login through Advarra's CIRBI system)
- Other external IRB Policies

- VCU Clinical Research Standard Operating Procedures
- CR-CO-500 Blinding - Codes and Code Breaking
- CR-RE-340.2a- Protocol Deviations and Violations

Review/Revision History CR-RE-300		
Version No.	**Effective Date**	**Description**
CR-RE-300.3	07-15-2024	• Update definition of UADE • Emphasized working vs calendar days • Clarified IRB reporting • Updated references • Links updated • Formatting edits
CR-RE-300.2a	07-01-2020	• Links updated
CR-RE-300.2	07-01-2020	• Biennial review performed • Minor formatting edits • Reference links updated
CR-RE-300.1	11-01-2017	• Original