SUBJECT: Reporting of Research Noncompliance and Other Select Research-related Events in VA Human Research

1. PURPOSE

This SOP establishes the procedures to be followed when research noncompliance and other select research-related events occur in human research at Minneapolis VA Health Care System (MVAHCS).

2. POLICY

It is VHA policy that all VA medical facilities that conduct VA research promptly review and report the following events: serious or continuing research noncompliance; events that may pose a genuine risk of harm to the safety, rights, or welfare of human research subjects or others as a result of participation in VA research, including their rights to privacy and confidentiality; events that may pose a genuine risk of harm to the safety, rights, or welfare of VA personnel conducting VA research; events that may compromise the care or welfare of animals used in VA research; and events that may be indicative of compromised effectiveness of the VA medical facility's research review and oversight programs. *(VHA Directive 1058.01 §4.)*

Members of the VA research community must ensure that **deaths** that are both unanticipated *and* related/possibly related to research participation are immediately reported to the IRB of record as outlined below.

Members of the VA research community must ensure that **Unanticipated Problems in Human Subjects Research Involving Risks to Subjects or Others** (UPIRTSOs), including **serious adverse events** which are both unanticipated *and* related/possibly related to research participation, are reported in writing to the IRB of record within 5 business days of becoming aware of the event.

Members of the VA research community must ensure that **apparent Serious or Continuing Noncompliance** Involving VA Non-Exempt Human Subjects Research (i.e., human research that has not received a determination of Exempt and is under the oversight of an IRB) are reported in writing to the IRB of record within 5 business days of becoming aware of the noncompliance.

Members of the VA research community must ensure that **apparent Serious or Continuing Noncompliance** Involving VA Exempt Human Subjects Research (i.e., human research that has received a determination of Exempt) are reported in writing to the research review committee (RRC) with primary oversight responsibility of the study (e.g., R&D Committee, Subcommittee on Research Safety) within 5 business days of becoming aware of the noncompliance.

3. DEFINITIONS

Adverse Event (AE): An Adverse Event (AE) is any untoward physical or psychological occurrence in a human subject participating in research, whether considered related to the subject's participation in research or not.

Exempt Human Subjects Research: Exempt human subjects research is research involving human subjects determined to be exempt, as applicable, under 38 C.F.R. 16.104 of the 2018 Federal Policy for the Protection of Human Subjects ("2018 Common Rule") or under 38 C.F.R.

16.101(b) of the pre-2018 Common Rule. For most exempt human subjects, the research review committee (RRC) with primary oversight is the R&D Committee (RDC).

Non-Exempt Human Subjects Research does not meet the exempt criteria above, and the research review committee (RRC) with primary oversight is the IRB of record.

Local Research: Local research is research approved by the reporting VA medical facility (MVAHCS or SCVAHCS) regardless of whether it is conducted on-site or at another institution such as the VA medical facility's academic affiliate (i.e., University of Minnesota).

Noncompliance: Noncompliance is any failure to adhere to applicable requirements for overseeing, reviewing, approving, or conducting VA research set forth in law, regulation, policy, or study agreements (such as reliance agreements, memoranda of understanding, data use agreements), including any failure to conduct research in accordance with a VA study protocol approved by a research review committee.

Research Review Committee: A research review committee (RRC) is any committee or subcommittee designated by a VA medical facility to review, approve and provide oversight of VA research, regardless of whether the committees are operated by a VA or a non-VA entity. Research review committees include Institutional Animal Care and Use Committee (IACUC), Institutional Biosafety Committees (IBC), Institutional Review Board (IRB) including IRBs of record outside MVAHCS, Research & Development Committee (RDC), and Subcommittee on Research Safety (SRS).

Serious Noncompliance: Serious noncompliance is any failure to adhere to requirements for conducting research that may reasonably be regarded as:

(1) Presenting a genuine risk of substantive harm to the safety, rights, or welfare of human research subjects or others, including their rights to privacy and confidentiality of identifiable private information;

(2) Presenting a genuine risk of substantive harm to the safety, rights, or welfare of research personnel who conduct research;

(3) Presenting a genuine risk of substantive harm to the health or welfare of animals used in research;

(4) Presenting a genuine risk of substantive reputational harm to VA; or

(5) Substantively compromising a VA medical facility's Animal Care and Use Program (ACUP), Human Research Protection Program (HRPP), Research Safety and Security Program (RSSP), or research information security processes.

Continuing Noncompliance: Continuing noncompliance means repeated instances of noncompliance with applicable laws, regulations, policies, agreements, or determinations of a research review committee or the prolonged persistence of noncompliance occurring after its identification, awareness, or implementation of a corrective action intended to effectively resolve the noncompliance.

Information Security and Privacy Incidents Involving VA Research: Any apparent information security or privacy incidents related to VA research, including any inappropriate access, loss, theft, noncompliant storage, transmission, removal or destruction of PHI or other VA research information deemed to be sensitive; theft, loss or noncompliant destruction of

equipment containing PHI or other VA research information deemed to be sensitive; or uses and disclosures of PHI for research without legal authority (e.g., without a valid authorization or waiver of authorization).

Related AE, Death, or Problem: A related AE, death, or problem is an AE, death, or problem that may reasonably be regarded as caused by, or possibly caused by, participation in the research.

Serious Adverse Event (SAE): A serious adverse event (SAE) in human subjects research is an untoward occurrence, whether or not considered related to a subject's participation in research, that results in death, a life-threatening experience, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, congenital anomaly or birth defect, or that requires medical, surgical, behavioral, social or other intervention to prevent such an outcome. ***For purposes of VHA Directive 1058.01, an unanticipated/unexpected SAE that is also related or possibly related to participation in human subjects research constitutes a UPIRTSO.***

Unanticipated or Unexpected: Unanticipated and unexpected refer to an event or problem in human research that is new or greater than previously known in terms of nature, severity, or frequency, given the procedures described in protocol documents and the characteristics of the study population.

Unanticipated Problem in Human Subjects Research Involving Risks to Subjects or Others: An unanticipated problem involving risks to subjects or others (UPIRTSO) in human subjects research is an incident, experience or outcome that is: unexpected, *and* related or possibly related to participation in the research, *and* indicative of the research placing subjects or others at substantively greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized. ***NOTE:*** *This description is adapted from guidance published by the HHS Office for Human Research Protections (OHRP). See https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html.*
For purposes of VHA Directive 1058.01, an unanticipated/unexpected SAE that is also related or possibly related to participation in human subjects research constitutes a UPIRTSO.

4. RESPONSIBILITIES

Investigators: The investigator is responsible for timely reporting of apparent serious and/or continuing noncompliance, local unanticipated and related/possibly related serious adverse events, deaths, and apparent UPIRTSOs to the research review committee (RRC) with primary oversight over the study, and for implementing any actions necessary to prevent an immediate hazard to subjects. Reporting timelines are detailed below.

Institutional Review Board of Record: The IRB of record is responsible for determining if there is a need for action to prevent an immediate hazard to subjects; for determining whether the reported event constitutes serious and/or continuing noncompliance, or an actual UPIRTSO; for identifying remedial actions if needed; and for notifying local leadership and national oversight groups as appropriate.

Associate Chief of Staff for Research & Development: The ACOS/R&D or equivalent is responsible for promptly reviewing and reporting events as specified in this directive, and

alerting, or designating an individual to alert, the VA medical facility Director and ORO by email or telephone within 1 business day after receiving the initial oral notification of a local research death of a human subject or a human death associated with VA animal or laboratory research and providing relevant information as requested.

VA Facility Director: The facility director is responsible for ensuring prompt reporting of events to VA and other pertinent federal agencies (e.g., FDA, OHRP) as applicable, and is the Institutional Official (IO). The Facility Director must notify, or designate an individual to notify, the appropriate ORO workgroup(s) within five (5) business days after receiving written notification of any situation that is reportable to ORO under this directive.

5. SERIOUS ADVERSE EVENTS OCCURRING AT SITES OTHER THAN MVAHCS

Investigators are asked to not report individual serious adverse events occurring at other sites in multi-site trials. These events are assessed by a designated monitoring entity (e.g., Data & Safety Monitoring Board/Data Monitoring Committee, coordinating or statistical center, study sponsor). In lieu of reporting individual adverse events occurring at other sites, the conclusions of the designated monitoring entity are to be submitted to the MVAHCS IRB as Notifications when MVAHCS IRB is the IRB of record for the MVAHCS investigator.

6. REPORTING OF DEATHS THAT ARE BOTH UNANTICIPATED *AND* RELATED/POSSIBLY RELATED TO RESEARCH PARTICIPATION

VA personnel, including WOC (without compensation) and Intergovernmental Personnel Act (IPA) appointees, must ensure **oral** notification of the IRB of Record immediately upon becoming aware of any local research death that is both unanticipated AND related/possibly related to the research. VA personnel must also ensure that follow-up written notification is provided to the appropriate IRB of Record within one (1) business day of becoming aware of such a death.

a) The ACOS/R&D, or designee, must alert the VA medical facility Director and appropriate ORO workgroup by email or telephone within one (1) business day after receiving the initial oral notification and provide relevant information as requested.

b) Within one (1) business day after receiving written notification of the death, the IRB Chair or another qualified IRB voting member must assess and document whether any actions are warranted to eliminate apparent immediate hazards to subjects and, if so, initiate those actions.

c) The IRB must review the death and the determination of the IRB Chair or qualified IRB member-reviewer at its next convened meeting not to exceed 30 days from the date of written notification, and must determine and document that:

   (1) The death was both unanticipated **and** related or possibly related to the research; *or*

   (2) There is insufficient information to determine whether the death was both unanticipated and related or possibly related to the research, and what information is needed; *or*

   (3) The death was not unanticipated and/or the death was not related or possibly related to the research.

d) If the IRB is unable to make a determination on the matter within 30 calendar days of the convened IRB's initial review due to insufficient information or due to a lack of sufficient time to complete its review, the IRB must notify the VA medical facility Director, the RCO, and the ACOS/R&D in writing no later than five (5) business days after the determination was due.

The VA medical facility Director, or designee, must notify the appropriate ORO workgroup within five (5) business days after receiving the IRB's written notification that it is unable to make a determination.

e) Regardless of the IRB determination above, the convened IRB must also determine and document whether any protocol or informed consent modifications are warranted. If modifications are warranted, the convened IRB must determine and document whether or not investigators must notify or solicit renewed/revised consent from previously enrolled subjects; and if so, when such notification or consent must take place and how it must be documented.

f) The IRB must notify the VA facility Director and the ACOS/R&D of its determinations within 5 business days of making those determinations.

g) The VA facility Director must report the determinations to ORO within 5 business days after receiving the IRB's notification of a determination.

7. REVIEW OF UNANTICIPATED AND RELATED/POSSIBLY RELATED SERIOUS ADVERSE EVENTS AND UNANTICIPATED PROBLEM INVOLVING RISKS TO SUBJECTS OR OTHERS

a) An unanticipated and related/possibly related SAE or an apparent UPIRTSO occurring in MVAHCS research must be reported to the IRB of record within 5 business days of becoming aware of the event.

b) Within 5 business days of receiving a report, the IRB Chair or a qualified IRB member-reviewer must determine and document whether any actions are warranted to eliminate apparent immediate hazards to subjects. If any actions are identified, the IRB must initiate those actions.

c) The convened IRB must review the incident and the immediate hazard assessment of the IRB Chair or qualified IRB member-reviewer at its next meeting, not to exceed 30 calendar days after the date of the written notification, and must determine and document that:

(1) The incident was serious **and** unanticipated **and** related or possibly related to participation in the research and indicative of the research placing subjects or others at substantively greater risk of harm than was previously known or recognized (i.e., whether the incident represents an actual UPIRTSO); *or*

(2) There is insufficient information to determine whether the incident was unanticipated and related or possibly related to participation in the research; *or*

(3) The incident was not unanticipated and/or the incident was not related or possibly related to participation in the research (i.e., not a UPIRTSO).

d) The IRB must determine if the event also constitutes serious and/or continuing non-compliance, and document as indicated in the section of this document "**REPORTING OF APPARENT SERIOUS OR CONTINUING NONCOMPLIANCE**".

e) If the IRB is unable to make a determination on the matter within 30 calendar days of the convened IRB's initial review due to insufficient information or due to a lack of sufficient time to complete its review, the IRB must notify the VA medical facility Director, the RCO, and the ACOS/R&D in writing no later than five (5) business days after the determination was due. The VA medical facility Director, or designee, must notify the appropriate ORO workgroup within five (5) business days after receiving the IRB's written notification that it is unable to make a determination.

f) Regardless of the determination, the convened IRB must also determine and document whether any protocol or informed consent modifications are warranted. If modifications are warranted, the convened IRB must determine and document whether or not investigators must notify or solicit renewed/revised consent from previously enrolled subjects; and if so, when such notification or consent must take place and how it must be documented.

g) The IRB must notify the VA facility Director and the ACOS/R&D in writing within 5 business days after its convened meeting if the IRB determines that the incident, experience, or outcome constitutes an actual UPIRTSO.

h) The VA facility Director must report the situation to ORO within 5 business days after receiving the IRB's notification of a serious determination.

8. REPORTING OF *LOCAL* SERIOUS ADVERSE EVENTS WHICH ARE NOT UNANTICIPATED AND/OR RELATED/POSSIBLY RELATED

Adverse events in non-Exempt research which are serious but are not unanticipated (see definition above) ***and/or*** are not related/possibly related to the research are reported to the IRB at continuing review. MVAHCS IRB continuing review forms direct how these events are to be reported.

NOTE: *Decision charts related to reporting SAEs and problems involving risks to subjects or others are provided on the ORO website at:*
https://www.va.gov/ORO/Docs/Guidance/1058_01_Decision_Chart_Rsch_Death_SAE_Problem_09_14_2015.pdf

9. REPORTING OF APPARENT SERIOUS OR CONTINUING NONCOMPLIANCE

a) VA personnel must ensure that the appropriate IRB of Record is notified, in writing, within five (5) business days after becoming aware of any apparent serious or continuing noncompliance with applicable laws, regulations, policies, and agreements pertaining to non-exempt human subjects research. This includes, but is not limited to, serious or continuing noncompliance with the Common Rule, local VA medical facility policies and SOPs related to human subjects research, IRB-approved protocols, and the requirements or determinations of the IRB.

> *Note:* Any apparent information security or privacy incidents related to VA research, including any inappropriate access, loss, theft, noncompliant storage, transmission, removal or destruction of PHI or other VA research information deemed to be sensitive; theft, loss or noncompliant destruction of equipment containing PHI or other VA research information deemed to be sensitive; or uses and disclosures of PHI for research without legal authority (e.g., without a valid authorization or waiver of authorization) may fall under this category.

b) In response to the written notification, the IRB of Record must:

   a. Review the written notification at its next convened meeting, not to exceed 30 calendar days after the date of written notification. Incidents covered by this paragraph may call for immediate attention and require the IRB to convene an emergency session prior to its next scheduled meeting.

   b. Determine and document within 60 calendar days of the convened IRB's initial review:

      i. whether or not serious and/or continuing noncompliance occurred; and if so,

ii. what, if any, remedial actions are needed to resolve present noncompliance or prevent future noncompliance.

c) The IRB must determine if the event also constitutes a UPIRTSO, and document as indicated in the section of this document "**REVIEW OF UNANTICIPATED AND RELATED/POSSIBLY RELATED SERIOUS ADVERSE EVENTS AND UNANTICIPATED PROBLEM INVOLVING RISKS TO SUBJECTS OR OTHERS**".

c) If the IRB determines that serious and/or continuing noncompliance occurred, it must notify the VA medical facility Director, the RCO, and the ACOS/R&D in writing of its determinations within five (5) business days after making those determinations.

d) The VA medical facility Director, or designee, must report the IRB's determinations to the appropriate ORO workgroup within five (5) business days after receiving the IRB's written notification.

10. REPORTING OF OTHER EVENTS INVOLVING VA HUMAN RESEARCH PROTECTION PROGRAMS REPORTABLE TO ORO

(a) The IRB must notify the VA medical facility Director, the RCO, and the ACOS/R&D in writing within five (5) business days of becoming aware of any of the following, after which the VA medical facility Director, or designee, must notify ORO within five (5) business days:

(1) The suspension or early termination of a non-exempt VA human research study by the IRB or IO due to the study not being conducted in accordance with applicable regulations, policies, agreements, or IRB requirements or due to concerns about the safety, rights, or welfare of human subjects or others, if such suspension or termination is not otherwise reportable per the requirements of the paragraphs above.

Note: The notification of suspension or early termination of a non-exempt VA human research study by the IRB or IO must include a statement of the reason for the IRB's or IO's action.

(2) Any change in the status (e.g., expiration, restriction, suspension or termination) of the facility's FWA.

(3) The termination or non-renewal of the HHS-OHRP registration of any IRB relied upon by the VA medical facility for review and oversight of VA research.

(4) Failure of a VA medical facility to achieve or maintain full accreditation of its HRPP if such accreditation is sought by the VA medical facility.

11. EXEMPT HUMAN RESEARCH

(a) Reporting of any of the above events in Exempt human research requires reporting to the Research Review Committee (RRC) with primary oversight of the project (e.g., R&D Committee, Subcommittee on Research Safety) on the same timelines as noted above.

12. FOLLOW-UP RESPONSIBILITY: Human Research Protection Program

13. REFERENCES

VHA Handbook 1058.01, version 10/22/2020

VHA Directive 1200.05(2), version 01/07/2019

ORO flowchart: Reporting Systemic Deficiencies and Noncompliance in VA Research (03/12/2021), Reporting_of_Systemic_Deficiencies_and_Noncompliance_in_VA_Research.pdf

ORO flowchart: Reporting Human Deaths, Unanticipated Problems and Accident, Injury, Illness or Exposure in VA Research (03/12/2021), Reporting_Human_Deaths_Unanticipated_Problems_and_Accident_Injury_Illness_and_Exposure_in_VA_Research.pdf