LOUIS STOKES CLEVELAND DVA MEDICAL CENTER
Medical Research Service
Standard Operating Policy and Procedure (SOP)

Effective Date: June 1, 2017

SOP Title: Research Personnel Notification of Pharmacy Benefits Management Drug Safety Alerts and Adverse Drug Events Related to Interventional Human Subjects Research Studies

SOP Number: HSP-021

SOP Version: .02

1. PURPOSE: This policy will ensure that the investigators, Associate Chief of Staff for Research and Development (ACOS for R&D), Administrative Officer for Research and Development (AO for R&D), and Institutional Review Board (IRBs) are notified as soon as possible about all Department of Veterans Affairs (VA) Pharmacy Benefits Management (PBM) Services alerts. This early notification of the ACOS for R&D, AO for R&D, investigator, and Chiefs of Pharmacy Services will allow for a timely assessment of risks to research subjects and, when indicated, modifications in research protocols, informed consent, and prompt notification of research participants to ensure the highest level of protections for these research subjects

2. POLICY: Each VA facility conducting human subjects research must establish standard operating procedures (SOPs) that ensure rapid notification of investigators, ACOS for R&D, AO for R&D, IRBs, and Research and Development Committees of relevant National PBM Bulletins and National PBM Communication Drug Safety Alerts. These SOPs must, when required, ensure appropriate notification of research subjects involved, and appropriate modifications to the research protocol and informed consent to ensure the highest level of protections for the research subjects.

3. DEFINITIONS:

a. **Adverse Drug Event (ADE).** An ADE is an injury from the use of a drug. Under this definition, the term ADE includes harm caused by the drug (adverse drug reactions and overdoses) and harm from the use of the drug including dose reductions and discontinuation of drug therapy. An ADE is a response to a drug which is noxious and unintended and which occurs at doses normally used in people for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function. It can be a causal or suspected link between a drug or adverse drug reaction. However, causality or association of the drug to the adverse drug reaction does not have to be established in order to report an adverse drug reaction or adverse drug event.

b. **Adverse Drug Reaction (ADR).** A response to a drug which is noxious and unintended and which occurs at doses normally used in people for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

(1) **Observed ADR.** Defined in the Computerized Patient Record System (CPRS) as a reaction that is "directly observed or occurring while the patient was on the suspected causative agent." Observed refers to a newly noted adverse outcome, typically within the past 3 months. Although the term implies that the provider of record made the diagnosis, the fact that a provider may not have visually observed an ADR does not preclude reporting as observed.

(2) **Historical ADR.** An event that occurred greater than 3 months prior to or that reportedly occurred in the past at another healthcare setting. It is defined in the system as "reported by the patient as occurring in the past: no longer requires intervention."

(3) Allergy. An adverse drug reaction mediated by an immune response (e.g. rash, hives).

(4) Side Effect. A side effect is an expected and known effect of a drug that is not the intended therapeutic outcome. The term side effect tends to nominalize the concept of injury from the drug. It is recommended that the term should generally be avoided in favor of ADR.

(5) Mild ADE Severity. An event that requires minimal therapeutic intervention such as discontinuation of drugs.

(6) Moderate ADE Severity. An event that requires active treatment of adverse reaction or further testing or evaluation to assess extent of non-serious outcome.

(7) Serious ADE Severity. An event is serious when the patient outcome is: death, life-threatening, hospitalization (initial or prolonged), disability or permanent damage, congenital anomaly or birth defect, required intervention to prevent permanent impairment or damage, other serious or important medical events. It may result in an organ threatening situation, significant or permanent disability, requiring interventions to prevent permanent impairment or damage, or prolonged hospitalization or death.

c. **Comparator Drug.** A comparator drug is an agent that the investigational drug is being compared to in a clinical trial. A comparator drug may be the current standard of care for the disease state being studied.

d. **Investigational Drug.** An investigational drug is a chemical or biological drug that is used in a clinical investigation. An investigational drug can be a new chemical compound which has not been released by the FDA for general use, or an approved drug that is being studied for an approved or unapproved use, dose, dosage form, or administration schedule, under an Investigational New Drug (IND) application, in a controlled, randomized, or blinded clinical trial.

e. **National PBM Bulletin.** A National PBM Bulletin is a Drug Safety Alert that includes standard sections: Issue, Background, Recommendations, and References. It is disseminated by PBM to the Drug Safety Alert Mail Group within 10 business days of

receipt of notification from the FDA or other credible source, once sufficient evidence has been collected. The recommended actions in a National PBM Bulletin include provider notification as well as actions to be carried out by the provider. When warranted, recommended actions include patient notifications by phone call, in person or by letter. Confirmation that actions have been completed will be required.

f. **National PBM Communication.** A National PBM Communication is a Drug Safety Alert that does not include standard sections, but is warranted to further clarify and/or emphasize what is noted in the drug-related safety information. It is disseminated by PBM to the Drug Safety Alert Mail Group within 10 business days of receipt of notification from the FDA or other credible source, once sufficient evidence has been collected. The recommended actions in a National PBM Communication include provider notification and when warranted, patient notifications by phone call, in person or by letter. Confirmation that actions have been completed will be required.

g. **Study-related Drugs.** Any specific molecular entity that is related to a study outcome and is specifically mentioned in the research informed consent documents.

4. RESPONSIBILITES:

a. Facility Director. The facility Director is responsible for disseminating all Drug Safety Alert documents within the facility, confirming document dissemination and follow-up action to the VISN Director when required, ensuring that the VA Investigator or clinician documents in CPRS any observed ADEs that occurred or were recognized in association with any FDA-approved drug or biologic used in a research study, ensuring that all VA investigators or clinicians involved in direct patient care receive employee health care orientation training on entering ADEs into CPRS and VA ADERS of any FDA approved drug or biologic, and ensuring participation of research staff with appropriate departments or groups involved in the ADE process for the coordination of ADE reporting and risk assessments.

b. Chief of Staff (COS). The COS is responsible for disseminating all Drug Safety Alerts and related materials to the Associate Chief of Staff (ACOS) for Research and Development (R&D), verifying that all required actions have been completed including mailing of patient or subject letters, and the appropriate documentation of all actions has been completed, reporting to the facility Director that all research subjects have been notified when notification is required.

c. Facility Chief, Pharmacy Service. In addition to those responsibilities found in VHA Handbook 1108.04, the Chief of the facility's Pharmacy Service is responsible for, maintaining current records of all pharmaceutical products that are being used as either investigational drugs or comparator drugs, designating a research pharmacist to serve as liaison to the facilities research program in areas such as; the use of a study related drugs, evaluation of the impact of the research on the Pharmacy Service, and review of the research protocol and serving as a subject matter expert for the IRB when necessary.

d. ACOS for R&D and AO for R&D. The ACOS for R&D is responsible for Disseminating Drug Safety Alerts and related materials to all Principal Investigators (PIs) who have authority to practice at the VA medical facility, Communicating the Drug

Safety Alert information to their respective Institutional Review Board (IRB); and Communicating to the facility COS that all required actions were completed within the designated timeframe.

e. **IRB responsibilities include but are not limited to** review and determination of actions related to National PBM Bulletins and National PBM Communication Drug Safety Alerts that involve VA approved research at LSDVAMC.

f. **The R&D Committee is responsible for** Reviewing the findings of the IRB and making any other appropriate recommendations. Communicating these recommendations to the investigator and the IRB. Documenting all recommendations and communications with the investigator and the IRB.

5. PROCEDURE:

a. **ACOS for R&D and AO for R&D will** Review all National PBM Bulletins or National PBM Communications as soon as they are received and determine whether the specific pharmaceuticals addressed in National PBM Bulletins or National PBM Communications are being used in any of the facility's human research protocols. This is done using ProIRB, (the IRB electronic record management system), where the list of drugs is maintained. If the pharmaceutical is being used in a protocol, the ACOS for R&D and AO for R&D will:

(1) Contact the investigator (verbally and in writing) as soon as possible and always within 5 working days and forward a copy of the National PBM Bulletin or National PBM Communication to the IRB with the name of the study involved.

(2) Determine in conjunction with the investigator, the Pharmacy Service, or other qualified individual, if the report contains information that may indicate an increased risk or potential risk to research subjects, or require changes to any part of the research protocol and informed consent. NOTE: If a notification recommends discontinuing an investigational drug, a comparator drug, or a drug that is named in the research informed consent, the Office of Research and Development (ORD) must approve any such recommendation. ORD's decision must be conveyed to the IRB and the investigator.

(3) If notification of research subjects is required, will notify the COS that all research subjects have been notified and that the notification of the research subjects was appropriately documented. If all research subjects were not notified, the COS will be informed in writing that they have not and why they were not notified.

(4) If the ACOS for R&D is not a physician, will ensure that the COS or designee is consulted regarding any determinations that are made regarding the VA-PBM safety alerts.

b. **Investigator.** Each investigator will:

(1) Determine in consultation with the ACOS for R&D, the Chief, Pharmacy Service, or other qualified individuals, whether the information in the National PBM Bulletin or National PBM Communication represents apparent immediate harm or potential increased risk to research subjects. If it is determined that there is increased risk or possible harm to research subjects: A list of research subjects who may be at risk will be compiled.

(2) A*pparent Immediate Harm to the Subjects*. If it is determined that there may be a apparent immediate harm to subjects, will notify the IRB Chair as soon as possible but within 3 working days of the becoming aware of the apparent immediate harm and take the following actions:

(a) The protocol and informed consent documents will be appropriately amended immediately.

(b) Modifications in the amendment may be instituted prior to IRB approval to eliminate apparent immediate harm to the research subjects. If they are instituted, the IRB Chair must be notified of the actions taken and the amended protocol and consent must be submitted to the IRB as required by VHA policy. NOTE: PBM notification letter will be sent to the investigators, IRB, and Data Monitoring Committee (DMC). The DMC will convene within 5 days if practicable, and will submit a summary of their findings to the IRB within 24 hours of the meeting.

(3) *Possible Increased Risk to Research Subjects*. Will notify the IRB Chair of the possible increased risk to the subject within 5 working days of becoming aware of the risk. The notification will be in the form of a memorandum or other document that discusses the new information, the risk to the subjects, and a proposed action plan. The proposed plan may include amendments to the protocol and the informed consent. NOTE: If the PBM alert includes a notification letter for all patients and subjects, the letter must be submitted to the IRB for approval prior to sending it to the subjects unless there is apparent immediate harm to the research subject.

(4) Initiating all modifications approved or required by the IRB in a timeframe required by the IRB. The implementation of these modifications must be documented in the research record and as appropriate, in the subject's medical record. The modifications or changes may include, but are not be limited to, notification of the subjects by letter or phone call, amendments to the informed consent that must be signed by the subjects, additional laboratory testing or safety monitoring, or unscheduled subject visits.

(5) Responding to FDA Withdrawal of Marketed Drugs. If a research investigational drug, comparator drug, or other drug named in the research informed consent is withdrawn from the market by FDA no new study subjects may be entered into the study. Those subjects already entered into the study must be notified to stop taking the drug, noting how the drug should be stopped, and if any additional follow-up is required.

(6) Documenting ADE. All ADEs in research subjects must be entered into CPRS and VA ADERS as required by VITA Directive 2008-059. All other requirements in that directive must also be followed.

c. **IRB:**

(1) Apparent Immediate Harm to Subjects. Upon receiving information notification may represent apparent immediate harm to subjects, the IRB Chair (or designee, as appropriate) must determine and document what steps are required to protect the human subjects from harm. NOTE: Depending on the apparent immediate harm and the urgency to take immediate steps to prevent or reduce the magnitude of harm, the investigator may have already implemented some actions. Any actions taken by the investigator must be reported to the IRB within 3 working days.

(2) If the IRB Chair (or designee, as appropriate) determines that specific immediate actions have not been but must be implemented, the IRB Chair (or designee as appropriate) will communicate these determinations to the investigator in a timeframe consistent with the potential for apparent immediate harm to the subject. This will also be communicated in writing to the full IRB.

(3) Upon making its determinations, the IRB Chair (or designee as appropriate) will also notify the investigator, the R&D Committee Chair, the ACOS for R&D, the COS, and the Facility Director what steps will be taken based on the apparent immediate harm to the subjects. The IRB Chair will direct the investigator to initiate the required steps and the timeframe in which they must be implemented.

(4) Possible Increased Risk to Subjects. The IRB will review and take action on the information submitted by the investigator. The information may include an amendment to the protocol or the informed consent. During its review the IRB must determine:

(a) If the new information provided in the notification represents increased risk to the research subjects.

(b) What, if any, communication must be sent to the research subjects (current and/or former research subjects) and in what time frame.

(c) What, if any, information must be discussed with the research subjects (current and/or former research subjects) in person and in what time frame.

(d) What, if any, changes must be made to the informed consent document and the protocol.

(e) What research protocol amendments must be made to address the risk or amend the safety plan for the study.

(f) If the amended protocol and informed consent submitted by the investigator contain all required actions or if the IRB must identify additional changes.

(5) The IRB's determinations will be conveyed in writing to the investigator in a time frame that is appropriate to the possible increased risk posed by the pharmaceutical. The notification will include a timeframe for all actions. Copies of the written communication will be filed in the IRB's records.

6. REFERENCE: VHA Directive 1069, National Pharmacy Benefits Management (PBM) Drug Safety Alert Distribution, VHA Directive 1070 Adverse Drug Event Reporting and Monitoring

7. RESCISSION: May 31, 2020

8. FOLLOW UP RESPONSIBILITY: Administrative Officer Research