DEPARTMENT OF VETERANS AFFAIRS
South Texas Veterans Health Care System
San Antonio, Texas 78229-4404

Research Service Policy Memorandum 12-70

November 14, 2012

RESEARCH STANDARD OPERATING PROCEDURES (SOP)
Handling of National PBM Drug Safety Alerts

1. **PURPOSE:** To outline the procedures for dissemination of National PBM Drug Safety Alerts related to interventional human subjects research studies at the STVHCS to investigators, UTHSCSA IRB, R&D Committee, and when appropriate, to research participants. This SOP will also establish the training elements for investigators with regard to the reporting, monitoring, and surveillance of adverse drug events (ADEs) from FDA approved investigational drugs.

2. **POLICY:**

   a. The procedures for dissemination and reporting of drug-related safety information is a key component of the protection of human subjects in research and is critical to the function of the Human Research Protection Program (HRPP) at the STVHCS. In accordance with VHA Directive 2007-072, this SOP covers dissemination of PBM drug safety alerts received in the R&D office from the STVHCS Pharmacy Department and will ensure rapid notification of investigators, ACOS for R&D, Deputy ACOS for R&D, UTHSCSA IRB, and R&D Committee of relevant National PBM Bulletins and National PBM Communication Drug Safety Alerts. When required, it will also ensure appropriate notification of research subjects involved, and appropriate modifications to the research protocol and informed consent. If a PBM bulletin or drug safety alert meets the criteria of an Unanticipated Problems Involving Risk to Subjects and Others (UPIRSO), Unanticipated Adverse Device Effects (UADE), or adverse event (AE) related to a human subjects research study, the monitoring and reporting of these events will be in accordance with Research SOP for UPIRSO, UADE, and AE Reporting and the UTHSCSA UPIRSO and UADE Policy (http://research.uthscsa.edu/irb/policy/UPIRSO Policy and Procedure.doc).

   b. Definitions:

      (1) **Adverse drug event (ADE):** The STVHCS adheres to the broad definition of ADE found in VHA Directive 2008-072 where an ADE is defined as "an injury from the use of a drug". Under this definition, the term includes harm caused by the drug (adverse drug reactions and overdoses) and harm from the use of the drug. 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. .

(2) **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.

(a) **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.

(b) **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) **Unanticipated Adverse Device Effect (UADE):** See definition in the UTHSCSA IRB glossary at: http://research.uthscsa.edu/irb/GLOSSARY OF OIRB TERMS.doc

(4) **Unanticipated Problems Involving Risk to Subjects and Others (UPIRSO):** See definition in the UTHSCSA IRB glossary at: http://research.uthscsa.edu/irb/GLOSSARY OF OIRB TERMS.doc

(5) **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.

(6) **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

(7) **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.

(8) **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.

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

3. ACTION:

a. Principal Investigator:

(1) The Principal Investigator is responsible to review all PBM Bulletins and Communications that may represent an UPIRSO or UADE; determine whether the content represents a possible UPIRSO or UADE; and promptly report possible UPIRSOs and UADEs to the IRB according to the UTHSCSA UPIRSO and UADE Policy (http://research.uthscsa.edu/irb/policy/UPIRSO Policy and Procedure.doc) .

(2) The timeline for reporting UPIRSOs and UADEs by the principal investigator to the IRB is specified in the UTHSCSA UPIRSO and UADE Policy (http://research.uthscsa.edu/irb/policy/UPIRSO Policy and Procedure.doc). UPIRSOs based on PBM Bulletins and Communications will have the following shortened reporting time frames:

(a) Apparent immediate harm to the subjects. If it is determined that there may be an apparent immediate harm to subjects, the IRB must be notified within 3 working days of the investigator becoming aware of the apparent immediate harm.

(b) Possible increased risk to research subjects. The IRB must be notified within 5 working days of the investigator becoming aware of the possible increased risk to research subjects.

(3) The Principal Investigator may implement actions necessary to eliminate immediate hazards, if necessary, without prior IRB approval. Any actions taken by the investigator must be reported to the IRB within 3 working days.

(4) Protocol and informed consent modifications and IRB responsibilities related to a reported UPIRSO as a result of a PBM Bulletin or Communication will be handled as described in the UTHSCSA UPIRSO and UADE Policy (http://research.uthscsa.edu/irb/policy/UPIRSO Policy and Procedure.doc).

(5) The Principal Investigator is responsible for initiating all modifications that are approved or required by the IRB in a timeframe required by the IRB.

(6) If a study related drug is withdrawn from the market by FDA, the Principal Investigator will ensure no new subjects will be entered into the study and all subjects already entered into the study will be notified to stop taking the drug, noting how the drug should be stopped, and if any additional follow-up is required.

(7) The Principal Investigator is responsible for documenting in CPRS any observed ADEs that occurred or were recognized in association with any FDA-approved drug or biologic used in a research study.

b. IRB:

(1) The IRB will receive, review, and make a determination whether a Report of Possible UPIRSO or UADE submitted by a principal investigator as a result of a PBM Bulletin or Communication meets criteria as an UPIRSO or UADE according to the UTHSCSA UPIRSO and UADE Policy (http://research.uthscsa.edu/irb/policy/UPIRSO Policy and Procedure.doc).

(2) The IRB will consider whether additional actions or safeguards should be taken by the principal investigator, the sponsor, the study coordinating center, or DSMB/DMC to protect subjects so that the study still satisfies the requirements for continued approval by the IRB.

(3) If the UPIRSO report indicates the affected research protocol no longer satisfies the requirements for IRB approval under IRB policy the UTHSCSA Suspension or Termination of Research Policy (http://research.uthscsa.edu/irb/policy/Suspension or Termination Policy and Procedure.doc) will be initiated.

(4) Upon making its determinations, the IRB Chair or designee will notify the investigator and present the information to the full IRB board in accordance with the UTHSCSA UPIRSO and UADE Policy (http://research.uthscsa.edu/irb/policy/UPIRSO Policy and Procedure.doc)

(5) UPIRSOs or UADEs determined by the IRB will also be reported to the ACOS for R&D, or his/her designee in accordance with Research SOP for UPIRSO, UADE, and AE Reporting.

(6) The IRB Chair or designee has the independent authority to determine if a PBM Communication presents apparent immediate risk to subjects and meets criteria as an UPIRSO or UADE.

(7) All IRB deliberations and requirements will be recorded in the IRB records.

c. Facility Chief, Pharmacy Service.

(1) The Chief of Pharmacy Service will forward to the ACOS for R&D and the Deputy ACOS for R&D all PBM Bulletins and Communications received through the Drug Safety Alert Mail Group or the Safety Notices (PBM) Mail Group.

(2) The ACOS for Research will ensure the Research Pharmacy maintains current records of all pharmaceutical products that are being used as either investigational drugs or comparator drugs.

(3) The Chief of Pharmacy Service will ensure all ADEs for research subjects entered into CPRS by Principal Investigators are entered into VA ADERS as per the local pharmacy policy on ADERS.

(4) Additional responsibilities are in accordance with VHA Handbook 1108.04 and Research SOP Handling of Investigational Drugs and Devices.

d. ACOS for R&D, Deputy ACOS for R&D, Research Pharmacist and R&D Office:

(1) The R&D office will maintain a computerized, searchable list of all investigational drugs, comparator drugs, or study-related drugs being used in active VA approved human subjects research protocols. The STVHCS Research Pharmacist has ready access to this database.

(2) When the ACOS, Deputy ACOS for R&D or his/her designee becomes aware of a PBM Bulletin or Communication through the Chief of Pharmacy Service, the active research protocol database will be searched to identify if the listed pharmaceuticals are being used in any VA- approved human research protocols. If active protocols are identified the PBM Bulletin or Communication will be disseminated to the appropriate Investigators.

(3) Investigators, who have an active research protocol involving the pharmaceuticals listed in the PBM Bulletin or Communication, will be forwarded a copy via email within 5 working days of receipt by the ACOS, Deputy ACOS for R&D or his/her designee. The investigator will be reminded of the requirement to promptly notify the IRB if they feel the information contained in the PBM Bulletin or Communication requires any changes to the active protocol or the associated informed consent.

(4) Investigators will be provided instruction to file the PBM Bulletin or Communication in the research record along with a Note to File should they decide that the information contained in the PBM Bulletin or Communication does not represent a new risk or a change to an already known risk, or require any changes to how they will safely conduct their research.

(5) The ACOS,Deputy ACOS for R&D or his/her designee will also promptly report the PBM Bulletin or Communication to the UTHSCSA IRB Director and the R&D

Committee Chairman for all PBM Bulletins or Communications involving pharmaceuticals being used in an active protocol along with the name and IRB number of the study involved. This will be communicated by a CC on the email correspondence to the Principal Investigator with the attached PBM Bulletin or Communication.

(6) Reports of UPIRSOs and UADEs that result from PBM Bulletins or Communications received by the ACOS for R&D, or his/her designee, will be reported to the Medical Center Director, other STVHCS institutional officials, and external regulatory and oversight agencies as described in Research SOP for UPIRSO, UADE, and AE Reporting.

(7) If the search of active research protocols does not reveal any active protocols using the pharmaceuticals listed in the PBM Bulletin or Communication, the Chief of Pharmacy Services will be notified of this and the information in the PBM Bulletin or Communication will be presented at the R&D Committee meeting for information purposes.

(8) If the search of active research protocols does not reveal any active protocols using the pharmaceuticals listed in the PBM Bulletin or Communication, but active investigators who have listed a primary research interest in the therapeutic area related to the information are identified, the PBM Bulletin or Communication will be forwarded to these investigators via email for information purposes. This communication will be copied to the IRB Director and the R&D Committee Chairman.

(9) The R&D office will maintain a database of all PBM Bulletins and Communications received; notifications to investigators, Pharmacy Service, IRB Director, and R&D Chairman; and resulting actions and communications.

(10) Summaries of all PBM Bulletins and Communications received in the R&D Office will be presented to the R&D Committee for review, recommendations, and action if needed.

(11) If the PBM Bulletin or Communication recommends discontinuing a study-related drug and this recommendation is approved by the Office of Research and Development (ORD), the ACOS or Deputy ACOS for Research will convey ORD's decision to the UTHSCSA IRB and the investigator.

(12) In the event that notification of research subjects regarding information contained in a PBM Bulletin or Communication is required, the ACOS or Deputy ACOS for Research will ensure the Principal Investigator has notified all subjects and has appropriately documented the notification. Information regarding the notification of subjects will be forwarded to the Chief of Staff (COS). In the event that all research subjects were not notified, the COS will be informed of this in writing with the Principal Investigators reasons for not notifying the subjects.

e. Research Compliance Office

(1) The Research Compliance Officer, or designee, will audit all aspects of this SOP and the VHA Directive 2007-072 to ensure compliance in the appropriate timeframe.

4. **REFERENCES:** VHA Directive 2008-072; VHA Directive 2008-078; VHA Directive 2008-059; STVHCS Research SOP for UPIRSO, UADE, and AE Reporting; UTHSCSA UPIRSO and UADE Policy

5. **RESPONSIBILITY:** Associate Chief of Staff for Research (151)

6. **RECISSION:** None

7. **RECERTIFICATION:** November 2017

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