

Version Number: 1	Research & Development Policy 151-23	Supersedes Document Dated: N/A
Effective Date: 02/01/2011	INVESTIGATOR NOTIFICATION OF SAFETY ALERT DISTRIBUTION RELATED TO HUMAN SUBJECTS RESEARCH	Expiration Date: 01/31/2015

PURPOSE

This procedure outlines the process by which drug-related or device related communications from the Food and Drug Administration (FDA) and other credible sources are disseminated information to providers and when appropriate to patients according to VHA Directive 2008-072.

The Pharmacy Benefits Management (PBM) Services alerts and MedWatch Alerts broadcast drug-related and device-related safety information from a variety of sources (e.g., FDA, manufacturers, wholesalers). Examples of the safety information communicated are drug recalls, shortages, labeling changes, or new information relevant to providers and patients. The safety alerts also contain standard information about the drug or device sectioned according to issue(s), background, recommendation(s), and reference(s) and may include provider notification as well as actions for the provider to perform. When warranted, recommended actions include patient notification in person, by phone, and/or letter and confirmation that actions have been completed.

For the purpose of this SOP, investigator means principal investigator (consistent with FDA interpretation). For the purpose of this SOP, references to the IRB Chair will mean the chair or designee.

RESPONSIBILITIES

1. **Facility Director.** The facility Director is responsible for:
 - a. Disseminating all Drug Safety Alert documents within the facility.
 - b. Confirming document dissemination and follow-up action to the VISN Director when required.
 - c. 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.
 - d. 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.
 - e. Ensuring participation of research staff with appropriate departments or groups involved in the ADE process for the coordination of ADE reporting and risk assessments.

2. **The Chief of Staff (COS) is responsible for:**
 - a. Disseminating all Drug Safety Alerts and related materials to the Associate Chief of Staff (ACOS) for Research and Development (R&D);

- b. Verifying all required actions, including mailing patient letters, and appropriate documentation of all actions are complete.
- c. Reporting to the facility Director that all research subjects have been notified when required.

3. The ACOS R&D is responsible for:

- a. Disseminating all Drug Safety Alerts and related materials to investigators and to the Institutional Review Board (IRB) through the IRB Chair and/or HRPP Administrator;
- b. Communicating to the facility COS that all required actions were completed within the designated time frame.
 - (1) When there is a Drug Safety Alert the ACOS R&D must assure that all required actions have been completed and must notify the COS of the completion within 10 days of the date of the alert.
 - (2) When there is an Emergent Drug Safety Alert the ACOS R&D must assure that all required actions have been completed and must notify the COS of the completion within 5 days of the date of the alert.
- c. If not a physician, consulting with the COS or designee regarding any determination that are made for the safety alerts.

4. The ACOS R&D and the Administrative Officer (AO) R&D are responsible for (from 2008-072):

- a. Maintaining a current list of all investigational drugs, comparator drugs, or study-related drugs being used in the facility's VA approved human subjects research. The list must be computerized, and must contain the name of the investigator and the study name. It must be provided electronically to the Pharmacy Service.
- b. Reviewing all National PBM Bulletins or National PBM Communications or MedWatch Alerts as soon as they are received.
- c. Determining whether or not the specific pharmaceuticals addressed in National PBM Bulletins or National PBM Communications or MedWatch Alerts are on the current list of drugs (investigational drug, comparator drug, study-related drug) or devices being used in any of the facility's human research protocols.
- d. If the drug/device is being used in a protocol:
 - (1) Contacting the investigator (verbally and in writing) as soon as possible and always within 5 working days and forwarding a copy of the National PBM Bulletin or National PBM Communication or MedWatch Alerts to the IRB with the name of the study involved.
 - (2) Ensuring that records are maintained of all notifications and the resulting actions and communications.
 - (3) Determining 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.*

e. Notifying the COS that all research subjects have been notified if notification was required, and that the notification of the research subjects was appropriately documented. If all research subjects were not notified, the COS must be informed in writing that they have not and why they were not notified.

5. The facility investigator is responsible for (from 2008-072):

- a. Confirming that the alert does or does not pertain to their research by contacting the ACOS R&D, IRB Chair, and/or HRPP Administrator.
- b. Determining in consultation with the ACOS R&D, the Chief, Pharmacy Service, or other qualified individuals, whether the information in the National PBM Bulletin or National PBM Communication or MedWatch Alerts represents apparent immediate harm or potential increased risk to research subjects.
- c. The following is enacted if it is determined that there is increased risk or possible harm to research subjects:
 - (1) A list of research subjects who may be at risk must be compiled.
 - (2) If there is **apparent immediate harm to subjects**, the following actions must be taken:
 - (a) Immediate action is to be implemented (if necessary without IRB approval) to eliminate apparent immediate harm to subjects and to protect the safety of subjects.
 - (b) The IRB Chair is to be notified as soon as possible but within 3 working days of becoming aware of the apparent immediate harm.
 - (c) The protocol and informed consent must be appropriately amended immediately.
 - Modifications in the amendment may be instituted prior to IRB approval to protect the safety of subjects.
 - (d) If modifications 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: Notification letter will be sent to the investigators, IRB, and Data Monitoring Committee (DMC). The DMC will convene within 5 day if practicable, and will submit a summary of their findings to the IRB within 24 hours of the meeting.*
 - (3) Notifying the IRB Chair of the possible increased risk to the subject within 5 working days of the investigator becoming aware of the risk.
 - (a) The notification should 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.

- (b) The proposed plan may include amendments to the protocol and the informed consent.
 - i) Modifications approved or required by the IRB are to be initiated in a timeframe required by the IRB.
 - ii) Implementation of modifications is to be documented in research record and as appropriate, in the subject's medical record.
 - iii) Changes may include, but are not 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.
 - *NOTE: If the 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.*
 - *NOTE: It may be necessary to develop a timeline for implementation depending on the number, the complexity, and the urgency of the modifications. In addition, the documentation may need to include such issues as: when attempts at contact were made, and the content of the material provided to the subject; notation of the date and content of subject's response; dates of all successful or unsuccessful attempts to contact the subject; date when subject signed the amendment to the informed consent; and the date and content of any oral discussion of the issue with the subject (in person or by phone).*
 - d. 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 will be notified to stop taking the drug, noting how the drug should be stopped, and if any additional follow-up is required.
 - e. Documenting adverse drug events of research subjects into CPRS and VA Adverse Drug Event Reporting System as required by VHA Directive 2008-059. All other requirements in that directive must also be followed.
6. **The IRB responsibilities include but are not limited to (from 2008-072):**
- f. Determining and documenting what steps are required to protect human subjects from harm upon receiving information on a National PBM Bulletin or Communication or MedWatch Alert from the investigator, ACOS R&D, or the facility's COS that there is an apparent immediate harm to subjects.
 - *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.*
 - b. Upon determining that specific immediate actions have not been but must be implemented, communicating these determinations to the investigator in a timeframe

consistent with the potential for apparent immediate harm to the subject. This must also be communicated to the full IRB as required by the IRB Role and Function SOP.

- *NOTE: If the research subjects and/or the investigators are blinded and do not know if individual research subjects are on the medication addressed in the National PBM Bulletin or National PBM Communication or MedWatch Alert because it may be either the investigational drug or comparator drug, the required notifications, re-consenting or other steps should be sent to all subjects as determined by the IRB.*

c. Upon making its determinations, notifying the investigator, the R&D Committee Chair, the ACOS R&D, the COS, and the Facility Director the steps that will be taken based on the apparent immediate harm to the subjects.

- *NOTE: The investigator must be directed to initiate the required steps and the timeframe in which they must be implemented.*

d. If there is a possible increased risk to subjects, reviewing and taking action on the information submitted by the investigator as required by the facility's SOPs. The information may include an amendment to the protocol or the informed consent form. During its review the IRB must determine:

(1) If the new information provided in the notification represents increased risk to the research subjects. What, if any, communication must be sent to the research subjects (current and/or former research subjects) and in what time frame.

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

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

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

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

e. Conveying the determination in writing to the investigator in a time frame that is appropriate to the possible increased risk posed by the drug/device.

(1) The notification must include a timeframe for all actions.

(2) Copies of the written communication must be filed in the IRB's records.

f. Recording all IRB deliberations and requirements in the IRB records.

7. The R&D Committee is responsible for (from 2008-072):

a. Reviewing the findings of the IRB and making any other appropriate recommendations.

b. Communicating these recommendations to the investigator and the IRB.

NOTE: If the recommendations require an amendment to the protocol or the informed consent, these amendments must be approved by the IRB.

c. Documenting all recommendations and communications with the investigator and the IRB.

- d. Ensuring that the facility's Research Compliance Officer or other designated individual audits all aspects of the requirements of this directive to ensure compliance in the appropriate timeframe.
- e. Ensuring that the R&D Committee minutes appropriately document all discussions and actions taken.

SUMMARY OF PROCEDURE

Step 1

1. The ACOS R&D maintains a database of all study drugs and devices along with other drugs names in the consent forms as part of research studies.
 - a. The research data base includes PI's name, study name, MIRB number, date of approval, drugs, and devices.
2. The ACOS R&D delegates maintenance of the research drug database to the HRPP Administrative Staff

Step 2

- ACOS R&D receives e-mail message with safety alert from a VA source.

Step 3

- ACOS R&D forwards the e-mail message with safety alert to all investigators, the IRB Chair, HRPP Administrator, and the Research Pharmacist.

Step 4

Investigator examines the alert, determines if it is applicable, and contacts the ACOS R&D and IRB if it is applicable to coordinate the action.

Step 5

The HRPP Administrator checks the alert against the drug/device database and notifies the IRB Chair if the alert involves any of the IRB/R&D approved drug/device human subject protocols. The IRB Chair then determines if there is an immediate risk to subjects.

- a. If there is an immediate patient safety risk:
 - (1) The IRB Chair may suspend or terminate approval of research and consider and/or recommend actions to take according to the IRB Role and Function SOP.
 - (2) It is referred to the IRB for review.
 - (3) The IRB Chair communicates with the investigator.
 - (4) The IRB Chair communicates with the ACOS R&D, COS, the R&DC Chair and the Facility Director.
- b. If there is no immediate patient safety risk, it is referred to the IRB for review for the IRB Chair to present at a convened IRB meeting. This with the Board's determination is included in the minutes.

Step 6

The HRPP Administrator places the safety alerts and related materials on the IRB meeting agenda(s). In addition to the electronic records of the drug/device database, copies of the safety alerts and related materials are maintained in the IRB Office.

Step 7

The investigator communicates with the IRB about the completion of the required action.

Step 8

The IRB Chair or HRPP Administrator communicates with the R&DC and the ACOS R&D about the completion of the required action.

Step 9

The ACOS R&D communicates completion of the required action to the COS.

Step 10

The COS communicates completion of the required action to the Director, who communicates with the VISN Director when required.

REFERENCES

2008-078 National PBM Drug Safety Alert Distribution, 119 - Pharmacy Service

2008-072 Research Personnel Notification of Pharmacy Benefits Management Drug Safety Alerts and Adverse Drug Events Related to Interventional Human Subjects Research Studies, 12 - Research and Development Service

2008-059 Adverse Drug Event Reporting and Monitoring, 119 - Pharmacy Service

RESPONSIBILITY Syracuse VAMC Research and Development Service will be responsible for the content, update, and recertification of this SOP.

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RESCISSION: None - new

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