Department of Veterans Affairs **VHA HANDBOOK 1058.1**
Veterans Health Administration **Transmittal Sheet**
Washington, DC 20420 **November 19, 2004**

REPORTING ADVERSE EVENTS IN RESEARCH TO THE OFFICE OF RESEARCH OVERSIGHT

1. PURPOSE: This Veterans Health Administration (VHA) Handbook sets forth the requirements for reporting certain adverse events in research to the Office of Research Oversight (ORO)(10R) (formerly the Office of Research Compliance and Assurance [ORCA]). ***NOTE:*** *This Handbook does not address other adverse event reporting requirements within the VA or to other Federal and state agencies.*

2. SUMMARY OF MAJOR CHANGES. This VHA Handbook replaces the previous procedures for reporting all serious and unexpected adverse events in research to ORO, VHA Central Office; it includes new procedures which require reporting to the appropriate ORO Regional Office (ORO RO) all adverse events and imminent threats of adverse events in research that result in:

a. An Institutional Review Board (IRB) taking substantive action(s) with respect to a protocol, the informed consent form or process, or investigative personnel; or

b. An unexpected death of a research subject, regardless of IRB action.

3. RELATED ISSUES. VHA Directive 1058.

4. RESPONSIBLE OFFICE. The Office of Research Oversight is responsible for the contents of this Handbook. Questions may be referred to (202) 565-4835.

5. RESCISSIONS. None.

6. RECERTIFICATION. This VHA Handbook is scheduled for recertification on or before the last working day of November 2009.

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REPORTING ADVERSE EVENTS IN RESEARCH TO THE OFFICE OF RESEARCH OVERSIGHT

1. PURPOSE

This Veterans Health Administration (VHA) Handbook sets forth the requirements for reporting certain adverse events (AEs) in research to the Office of Research Oversight (ORO) (10R) (formerly, ORCA). ***NOTE:*** *This Handbook does not preempt or otherwise alter any other applicable adverse event reporting requirements, whether within the Department of Veterans Affairs (VA) or to other Federal and state agencies or commercial sponsors.*

2. BACKGROUND

a. ORO serves as the primary VHA office for advising the Under Secretary for Health on all matters of compliance and assurance related to human subjects' protections. As part of its mission, ORO is responsible for overseeing compliance with the system-wide requirements for reporting AEs in research.

b. VA is committed to supporting high quality human research protection programs (HRPPs) in all its facilities involved in research. Reporting and management of AEs in research are important aspects of HRPPs. The Institutional Review Boards (IRBs) are integral parts of institutions' HRPPs and, as such, are responsible for reviewing and managing AEs in research (Title 38 Code of Federal Regulations [CFR] 16). Specifically, VA regulation requires prompt reporting of any unanticipated problems involving risks to subjects and others to the IRB, appropriate institutional officials, and the department or agency head (see 38 CFR 16.103(b)[5]). ***NOTE:*** *Likewise, Food and Drug Administration (FDA) regulations require investigators to report promptly to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, an investigational new drug (IND) (21 CFR 312.64(b)). Further investigators must submit to the sponsor and reviewing IRB a report of any unanticipated adverse investigational device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (see 21 CFR 812.150[a][1]).*

c. Each IRB needs to develop Standard Operation Procedures (SOPs) that provide detailed instructions on how to report and manage AEs consistent with all relevant regulations and VHA policies, including the VHA Handbook 1050.1.

d. This VHA Handbook addresses only the reporting of certain AEs in research to ORO. Since ORO serves as the primary VHA office for advising the Under Secretary for Health on all matters of compliance and assurance related to human subjects' protections, ORO is responsible for overseeing compliance with the system-wide requirements for reporting AEs in research.

e. In the past, facilities were required to report all serious and unexpected AEs in research to ORO. This Handbook replaces that reporting requirement with a more narrowly defined reporting requirement. The new procedure set forth in this Handbook allows ORO to focus on

the most serious AEs in research and better assess how such incidents are being reported and managed by investigators and IRBs.

3. SCOPE

a. This Handbook:

(1) Identifies the AEs in research that must be reported to the relevant ORO Regional Office (ORO RO);

(2) Provides the timelines for reporting such AEs; and

(3) Indicates what information must be provided in such reports.

b. In addition to following this Handbook's reporting requirements, VA facilities must continue to follow all other relevant laws, regulations, and policies related to AE reporting (see par. 7). For example, VHA facilities must continue to report "unanticipated problems" and "adverse events" to their IRBs of record and to other oversight agencies such as the Office for Human Research Protections (OHRP), the FDA, and sponsors. It is essential that principal investigators report all research-related incidents to the IRB as required in the facility's IRB SOP, or any Office of Research and Development (ORD) policies on reporting of incidents. The definitions, procedures, and timelines contained in this Handbook pertain solely to the reporting requirements of this Handbook.

4. REPORTING REQUIREMENT GOALS

These reporting requirements are designed to:

a. Facilitate ORO's oversight of AEs in VA research;

b. Specify which AEs are to be reported to ORO, the details to be reported, and the timeline for reporting; and

c. Collect information to provide better oversight, guidance, and support for protecting research subjects and to assist IRBs in taking appropriate actions.

5. DEFINITIONS

a. **Adverse Event (AE) in Research.** An AE in research is defined for purposes of this Handbook as any untoward occurrence (physical, psychological, social, or economic) in a human subject participating in research. An AE in research can be any unfavorable or unintended event including abnormal laboratory finding, symptom, disease, or death associated with the research or the use of a medical investigational test article. An AE in research may occur even in the absence of any error or protocol deviation, and does not necessarily have to be caused by any identifiable aspect of the research.

b. **Imminent Threat of an AE in Research.** Any situation in which an AE in research has not yet occurred but is likely to occur, as determined by an IRB, research, or clinical team member, without preventative measures.

c. **Substantive Action.** An action taken by an IRB that materially alters the substance and meaning of a protocol, informed consent form or process, or investigator status, including, but not limited to, restriction, suspension or termination of a study or investigator participation, and actions taken to prevent future occurrence(s) of the AE in research.

d. **Unexpected Death.** The death of a research subject in which a high risk of death is not projected, as indicated by the written protocol, informed consent form, or sponsor brochure. This definition does not include deaths associated with a terminal condition unless the research intervention clearly hastened the subject's death. A subject's death that is determined to be clearly not associated with the research is also not an "unexpected death" for purposes of the reporting requirements of this Handbook.

6. REPORTING REQUIREMENTS

a. Each VHA facility must report to the appropriate ORO RO (see sub. 6b) all AEs in research and imminent threats of AEs in research conducted on site that result in either:

(1) An IRB taking substantive action(s) as defined in subparagraph 5c. A written report of the AE in research (or an imminent threat thereof), and the IRB action(s) to be taken, must be submitted to the ORO RO within 10 working days of the IRB's determination to take such action(s).

or

(2) An unexpected death of a research subject, regardless of IRB action. Such deaths must be reported to the ORO RO within 24 hours after the IRB determines that the death was unexpected, as defined in subparagraph 5d. If the IRB is unable to determine whether a research subject's death was unexpected after 10 working days of being informed of the death, the death must then be reported to the ORO RO. When a final determination is made as to whether or not the death was unexpected, a follow-up report must be made to the ORO RO.

b. **Written Report.** The institutional official (VHA facility Director), or designee, must:

(1) Prepare a separate report, for each AE in research (or imminent threat thereof) required to be reported by this Handbook, following the format indicated in Appendix A.

(2) Initial the completed report and facilitate its submission to the Director of the ORO RO that oversees the VHA facility, using express mail (e.g., Fed Ex) and either e-mail or fax. A copy of all IRB minutes from meetings in which the AE in research and subsequent actions were discussed, ratified, or summarized needs to accompany the report to the ORO RO, or be sent when the IRB minutes become available, but in no case no later than 4 weeks after the IRB meeting.

7. REFERENCES

a. Title 38 CFR 16.

b. Title 45 CFR 46.

c. Title 21 CFR 56.

d. Title 21 CFR 312.

e. Title 21 CFR 812.

f. VHA Handbook 1200.5.

g. VHA Handbook 1050.1.

Department of Veterans Affairs

ADVERSE EVENTS (AEs) IN VA RESEARCH - REPORT FORMAT

A. REPORTING INSTITUTION

INSTITUTION:	DATE OF THIS REPORT

B. STUDY IN WHICH THE AE OR IMMINENT THREAT OF AN AE IN RESEARCH OCCURRED:

1. STUDY TITLE

1A. STUDY NUMBER	1B. SPONSOR
1C. IND NUMBER	**1D. IDE NUMBER**

2. STUDY PRINCIPAL INVESTIGATOR (PI)	2A. TELEPHONE NUMBER	2B. E-MAIL ADDRESS

3. IS THIS A MULTI-SITE TRIAL?
- ☐ YES *(NOTE: Submit report only if AE occurred at your site)*
- ☐ NO

3A. IF YES, OVERALL PRINCIPAL INVESTIGATOR	3B. TELEPHONE NUMBER

C. INFORMATION ABOUT THE AE OR IMMINENT THREAT OF AN AE IN RESEARCH

1. DESCRIBE INCIDENT

2. CHECK ALL THAT APPLY

☐ AE IN RESEARCH RESULTED IN SUBSTANTIVE CORRECTIVE ACTION BY IRB

TYPE OF AE IN RESEARCH ☐ PHYSICAL ☐ PSYCHOLOGICAL ☐ SOCIAL ☐ ECONOMIC

☐ IMMINENT THREAT OF AE IN RESEARCH RESULTED IN SUBSTANTIVE CORRECTIVE ACTION BY IRB

TYPE OF AE IN RESEARCH ☐ PHYSICAL ☐ PSYCHOLOGICAL ☐ SOCIAL ☐ ECONOMIC

☐ UNEXPECTED DEATH OF A RESEARCH PARTICIPANT

3. DATE OF INCIDENT	3A. DATE PI BECAME AWARE OF INCIDENT
3B. DATE IRB INFORMED OF INCIDENT	**3C. DATE OF IRB ACTION** *(If any)*

4. PARTICIPANT STATUS

☐ RECOVERED/RESOLVED ☐ NOT RECOVERED/NOT RESOLVED ☐ DEATH

☐ RECOVERING/RESOLVING ☐ RECOVERED WITH SEQUELAE

5. HAVE OTHER AEs IN RESEARCH BEEN REPORTED IN THIS STUDY?

☐ YES ☐ NO

D. SUBSTANTIVE ACTION(S) TAKEN

1. CHECK ALL THAT APPLY

- ☐ MAJOR CHANGE IN PROTOCOL
- ☐ MAJOR CHANGE IN CONSENT FORM
- ☐ MAJOR CHANGE IN CONSENT PROCESS
- ☐ ADDITIONAL INFORMATION PROVIDED TO ENROLLED SUBJECTS
- ☐ ADDITIONAL MONITORING OF STUDY
- ☐ RESTRICTION OF STUDY
- ☐ SUSPENSION OF STUDY
- ☐ TERMINATION OF STUDY
- ☐ RESTRICTION OF INVESTIGATOR PARTICIPATION
- ☐ SUSPENSION OF INVESTIGATOR PARTICIPATION
- ☐ TERMINATION OF INVESTIGATOR PARTICIPATION
- ☐ ACTIONS TAKEN TO PREVENT FUTURE AE
- ☐ OTHER *(Describe below)*

D. SUBSTANTIVE ACTION(S) TAKEN*(Continued)*

2. DESCRIBE ACTION(S) TAKEN *(Append IRB minutes in which the substantive actions were discussed, ratified, and /or summarized.)*

3. ARE OTHER ENROLLED SUBJECTS POTENTIALLY EXPOSED TO THIS RISK?
☐ YES ☐ NO IF YES, HAVE THEY BEEN INFORMED ABOUT THIS RISK? ☐ YES ☐ NO

4. NAME OF IRB AND IRB CHAIR

4A. TELEPHONE NUMBER	4B. E-MAIL ADDRESS

E. REPORTING INFORMATION

1. REPORTER	1A. POSITION

1B. TELEPHONE NUMBER	1C. E-MAIL ADDRESS

1D. MAILING ADDRESS

2. OTHER REPORT(S) OF THIS INCIDENT

REPORTED TO	REPORTED BY			DATE
	IRB/INSTITUTION	PI	OTHER (Name/Title)	
☐ MANUFACTURER/SPONSOR	☐	☐	☐	
☐ FOOD AND DRUG ADMINISTRATION	☐	☐	☐	
☐ OFFICE FOR HUMAN RESEARCH PROTECTIONS	☐	☐	☐	
☐ OTHER (Identify)	☐	☐	☐	

COMMENTS

APPENDIX B

OFFICE OF RESEARCH OVERSIGHT (ORO) REGIONAL OFFICES

Send report to appropriate ORO Regional Office, via express mail (e.g., Fed Ex) and fax or e-mail. For additional resources reference ORO's website: http://www.va.gov/oro/

REGION	PHONE, FAX	ADDRESS
Northeastern Region ORO VISNs 1, 2, 3	(781) 687-3850 FAX (781) 687-3858	200 Spring Road. (10R) Bldg. 7, Rm. B-08 Bedford, MA 01730
Mid-Atlantic Region ORO VISNs 4, 5, 6, 9, 10	(202) 745-8110 FAX (202) 745-8538	50 Irving St., N.W. (10R) Washington, D.C. 20422
Southern Region ORO VISNs 7, 8, 16, 17	(404) 417-2929 FAX (404) 417-2935	1670 Clairmont Rd. (10R) Decatur, GA 30033
Midwestern Region ORO VISNs11, 12,15,19, 23	(708) 202-7254 FAX (708) 202-7250	P.O. Box 5000 (10R) Bldg. 1, Rm. B-103 Hines, IL 60141
Western Region ORO VISNs 18, 20, 21, 22	(909) 801-5164 FAX (909) 801-5176	P.O. Box 7360 Moreno Valley, CA 92552-7360 **Federal Express address:** 5029 4th St. (10R) Bldg. 2641 March A.F.B. CA 92518