WAYNE STATE UNIVERSITY

HIC Policy/Procedure

Wayne State University Human Investigation Committee	
Subject:	**Unexpected Problems Involving Risk to Participants**
Section:	
Form Date:	11/2008
Approvals	Office of the General Counsel 1/08/07, Steering Committee 2/05/07, Administrative Review 02/28/07, General Counsel 03/14/08, Administrative Approval 10/29/08, Office of General Counsel 11/7/08, Administrative Approval 02/04/09

Background

An Institutional Review Board (IRB) is required to promptly report unanticipated problems involving risks to subjects and others, to the IRB, appropriate institutional officials, and departmental or agency heads.

At Wayne State University (WSU), the Institutional Official has delegated authority to the Associate Vice President of Research (AVPR) for reporting these situations to supporting agencies and appropriate regulatory authorities.

Scope

This HIC Policy and Standard Operating Procedure applies to all research conducted at WSU or any of its affiliate institutions.

Definitions

Unexpected problem: risks to participants or others- a problem that is unforeseen and indicates that participant's or others are at increased risk of harm. The following are examples of unexpected problems:

1. **Adverse Event**: Any harm experienced by a participant regardless of whether the event was internal (on-site) or external (off-site) and regardless of whether the event meets the FDA definition of "serious adverse event", which in the opinion of the principal investigator are both ***unexpected*** **and** ***related (definitely, probably, more likely than not or unable to determine)***.

    a. An adverse event is "unexpected" when its specificity and severity are not accurately reflected in the informed consent document, the protocol or the investigator's brochure.

b. An adverse event is "related to the research procedures" if in the opinion of the principal investigator it was more likely than not to be caused by the research procedures, or if it is more likely than not that the event affects the rights and welfare of current participants.

2. **Any harm experienced by a participant or others** as a result of involvement in research activities (internal or external **excluding** adverse events).

3. Information that indicates a **change to the risks or potential benefits** of the research. For example:
    a. An interim analysis or safety monitoring report indicates that frequency or magnitude of harm or benefit may be different than initially presented to the IRB.
    b. A paper is published from another study that shows the risks or potential benefits of your research may be different than initially presented to the IRB.
    c. Study put on hold by the PI, FDA, or the Sponsor for reasons that may include safety, toxicity and/or efficacy.

4. **A change in FDA labeling** or withdrawal from marketing of a drug, device, or biologic used in a research protocol.

5. **Change to the protocol** taken without prior IRB review to eliminate an apparent immediate hazard to a research participant.

6. **Research conducted without prior WSU IRB approval.**

7. **Event that requires prompt reporting to the sponsor**.

8. **Unanticipated adverse device effect**: Any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, a device if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

9. **Sponsor-imposed suspension for risk**.

10. **Complaint of a participant** when the complaint indicates unexpected risks or cannot be resolved by the research team.

11. **A breach of confidentiality.**

12. **Protocol violation/deviation** (meaning an accidental or unintentional change to the IRB-approved protocol) that harmed participants or others, that indicates participants or others may have been placed at increased risk of harm, or rights of research participant s were violated. For example:
    a. Failure to draw safety labs
    b. Request for continuation submitted late to the HIC three years in a row
    c. Wrong informed consent signed or failure to obtain informed consent

13. **Incarceration of a participant** in a protocol not approved to enroll prisoners.

14. **All** deaths within **30 days** of the last study intervention.

15. **Any death, if the PI feels that it is significant** no matter when it occurs.

HIC Policy

Principal investigators must report any of the above to the IRB as soon as possible, **but in all cases within 5 working days.**

VA Reporting Requirements:

a. Each Veterans Hospital Administration (VHA) facility must report to the appropriate Office of Research Oversight (ORO) (see subparagraph 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 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 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. 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.

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 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, or be sent when the IRB minutes become available, but in no case no later than 4 weeks after the IRB meeting.

HIC Procedure

The Process Improvement Coordinator, in consultation with the HIC Chair or Associate Vice President for Research Compliance if necessary, will review all unexpected problem reports to determine if they meet the following criteria:

- the event is unforeseen; **and**
- the event indicates that participants or others are at increased risk of harm.

The event must meet **both** criteria to meet the definition of an unexpected problem involving risks to participants or others (see above for definitions).

If the event does not meet both criteria, no further action will be taken unless it is determined that serious or continuing non-compliance has occurred (See "Identifying, Defining, and Managing Non-compliance in Human Research" in HIC Policies/Human Research Protection Program Manual).

- *Non-Compliance*- the failure to comply with federal regulations, including Veterans Administration regulations and guidance, state and local requirements, WSU Policy and determinations of the IRB. For studies performed at the Veteran's Administration Medical Center (VAMC), studies must also comply with VAMC regulations and guidance [38 CFR 16.103(b)(5); 21 CFR 56.108(b)(1)

- *Continuing Non-Compliance* – a repeated pattern of non-compliance with all federal regulations, including Veterans Administration regulations and guidance, by an individual investigator or research staff member either on a single protocol or multiple protocols.

- *Serious Non-Compliance*–the failure to comply with federal regulations, including Veteran's Administration regulations and guidance, state and local requirements, WSU Policy and determinations of the IRB that involves one or more of the following:

    - Harm to research participants;
    - Exposure of research participants to a significant risk of substantive harm;
    - Compromised privacy and confidentiality of the participants;
    - Damage caused to scientific integrity of the data that has been collected;
    - Willful or knowing non-compliance on the part of the investigator; or
    - An adverse impact on ethical principles.

Unexpected problems that meet the above criteria are referred to the convened IRB of record and then reported to regulatory agencies and appropriate institutional officials following the Policy and Procedure on "Reporting Unexpected Problems, Suspensions and Terminations, Serious & Continuing Non-Compliance and the Institutional Official's Responsibilities."

IRB Procedures

The Wayne State University IRB uses the primary/secondary reviewer system. Each committee selects a member with the necessary expertise, to review the unexpected problem reports that have been previously determined to meet the required criteria or when no preliminary determination could be made. The secondary reviewer is always the committee Chair. In case of the Behavioral Committee (B3) the committee Chair is the only initial reviewer.

The Unexpected Problem Checklist is used by all of the reviewers throughout the process.

Prior to the next convened meeting, IRB staff provide the primary reviewer, the committee Chair, and the committee members with:

1. the Unexpected Problem reporting form including any interim actions that may have been taken;

2. appropriate sponsor reports or memos (e.g., Data Safety Monitoring Board (DSMB) reports, MedWatch);
3. HIC file/research protocol (if appropriate);
4. informed consent document; and
5. any supplemental information deemed necessary by the reviewer.

The IRB (HIC Chair, committee Chair, designated IRB reviewer and/or committee members) will determine if it is necessary to take any of the following actions:

- Suspension of enrollment of new participants
- Suspension of research procedures in currently enrolled participants
- Suspension of the research
- Termination of the research
- Notification of participants when such information may relate to current participants' willingness to continue to take part in the research or there is a risk to the health or safety of the past or current participants
- Request additional information or clarification from the PI and/or data safety monitoring committee
- Require changes in the protocol, consent form or other protocol documents
- Require current participants to be re-consented to protocol with the changes in the informed consent
- Note the occurrence of the Unexpected Problem, but take no action
- Accept report as submitted pending amendment with consent form changes
- Require a change in the continuing review period
- Require additional monitoring by the IRB
- Request a for-cause audit of the protocol, if not already done, and/or a follow-up audit
- Request further inquiry into other protocols utilizing the experimental drug/device/intervention or procedure in question
- Determine if a detailed plan for safe withdrawal of participants from the research must be developed to protect their rights and welfare of participants
- Require that this plan be submitted to the IRB for review and approval
- Require that appropriate federal regulatory agencies, sponsors, and institutional officials be notified of any unexpected adverse reactions or unexpected events involving risks to participants or others according to the HIC Policy/Procedure "Reporting Unexpected Problems, Suspensions and Terminations, Serious & Continuing Non-Compliance and the Institutional Official's Responsibilities"
- No other action required
- Other action