

Wayne State University Human Investigation Committee	
SUBJECT	Identifying, Defining, and Managing Non-compliance in Human Research
Section	
Form Date	06/08
Approvals	Office of General Counsel 2/12/07, Steering Committee 03/12/07, Administrative Approval 03/26/07, General Counsel 02/29/08

Background

Investigators, research team members, the Institutional Review Board (IRB) members and/or Wayne State University (WSU) administrative staff are required to conduct research ethically and in accordance with federal regulations and WSU and/or IRB policies. Non-compliance occurs when research involving human participants is conducted in a manner that disregards or violates federal regulations, ethical standards, and WSU and/or IRB policies and procedures governing research and human research protection. Non-compliance with respect to human research participant protection requirements violates WSU's Federal Wide Assurance (FWA 00002460). Regardless of intent, any unapproved and non-compliant research activity may place a research participant at unnecessary risk. (See [38 CFR 16.103(b)(5)(i); 38 CFR 16.116(b)(5); 45 CFR 46.103(b)(5)(i); 21 CFR 50.25(b)(5).25(b)(5); 21 CFR 56.108(b)(2); VHA Handbook 1200.5 7]).

Non-compliance applies to investigators, research team members, the IRB members, and/or WSU HIC administrative staff.

Authority

WSU has granted the IRB the authority to approve, require modifications (to secure approval), disapprove, and suspend or terminate approval of research activities not being conducted in accordance with IRB requirements; and to observe or have a third party observe the informed consent process and the conduct of the research. The Vice President for Research has delegated the authority for research compliance activities to the Associate Vice President for Research.

Definitions

Allegation - An assertion of non-compliance made by a party that must be supported with evidence.

Confirmed non-compliance – Non-compliance that has been verified as a result of a for-cause audit or investigation.

| *Continuing non-compliance* – a repeated pattern of non-compliance with all federal regulations, including Veterans regulations and guidance, by an individual investigator or research staff member either on a single protocol or multiple protocols. Examples of noncompliant activities include:

- Conducting research without IRB approval (i.e., either before IRB approval is obtained, or after an approved research protocol expires);
- Non-use or misuse of consent forms (i.e., consent/assent not obtained, wrong consent document used, missing signatures, failure to document consent process);
- Failure to follow approved protocol;
- Modifying or changing protocol without prior IRB approval;
- Failure to report unexpected problems, unanticipated events or adverse reactions or not reporting in a timely fashion;
- Failure to maintain adequate records;
- Inadequate training of investigators or research staff;
- Other failure to follow University policies and federal regulations;
- Failure to comply with an IRB request.

Non-compliance- the failure to comply with all federal regulations, including Veterans Administration regulations and guidance, state and local requirements, WSU Policy and determinations of the IRB.

Serious non-compliance – the failure to comply with all federal regulations, including Veterans 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;
- Exposing research participants to a significant risk of substantive harm;
- Compromising the privacy and confidentiality of research participants;
- Damage caused to scientific integrity of the research data that has been collected;
- Willful or knowing non-compliance on the part of the investigator;
- Adversely impacting ethical principles.

Human Investigation Committee (HIC) Policy

Reporting Allegations to the IRB

Non-compliance may be reported to the IRB by an investigator or his/her designee. It is then routed to the Process Improvement/Compliance Coordinator; in their absence it may be reported to the Education Coordinator.

Non compliance or potential non-compliance may also be discovered by the IRB through audits or other routine review or quality control activities. Allegations of potential non-compliance may also be reported to the IRB by non-investigators.

Allegations of non-compliance may be reported to the HIC Process Improvement/Compliance Coordinator (313-577-2901) or the Associate Vice President for Research (AVPR) (313-577-9064).

Investigators must report the following circumstances to the HIC Office **within 10 days** of the investigator's knowledge of the circumstance unless it is a serious adverse reaction or unexpected event (AR/UE) which must be reported **within 5 days** of the investigator becoming aware. (See HIC Policy/Procedure: "Unexpected Problems").

- Information that indicates a potentially detrimental change to the risks or potential benefits of the research. For example: (a) an interim analysis indicates that participants have a lower rate of response to treatment than initially expected; (b) safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected; (c) a paper is published from another study that shows that an arm of the research study is of no therapeutic value
- A breach of confidentiality
- Change in FDA labeling or withdrawal from marketing of a drug, device or biologic used in a research protocol
- Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research participant
- Incarceration of a participant in a protocol not approved to enroll prisoners
- Event that requires prompt reporting to the sponsor
- Complaint of a participant when the complaint indicates unexpected risks or cannot be resolved by the research team
- Protocol deviation or violation (meaning an accidental or unintentional change to the IRB approved protocol if it presents potential or actual harm to the participant or the data)
- Sponsor imposed suspension for risk

For VA research:

1. Any adverse event (i.e., an untoward physical, psychological, social, or economic occurrence) in a human subject, or an imminent threat of an adverse event, that results in a substantive action by the Institutional Review Board (IRB) under VHA Handbook 1058.1 on *Reporting Adverse Events in Research* (attached).
2. Any unexpected death of a human subject under VHA Handbook 1058.1 NOTE: Such deaths must be reported within 24 hours of the IRB's determination that the death was unexpected or within 10 working days if the IRB has not yet made a determination about whether the death was unexpected.
3. Any unanticipated problem involving risks to subjects or others that result in the taking of substantive action by the IRB.
4. Any for-cause suspension or termination of VA human subject research by the IRB, the VA facility, or a VA affiliate institution. This does NOT include suspensions or terminations resulting solely from the expiration of the IRB approval period.
5. Any serious or continuing noncompliance with federal regulations or VHA policies for the protection of human subjects (including 38 CFR Part 16; 45 CFR Part 46; 21 CFR Parts 50, 56, 312 or 812; and VHA Handbook 1200.5).
6. Any serious or continuing noncompliance with IRB requirements or determinations.

7. Any findings of noncompliance in human research protections from the VHA Office of Research and Development (ORD) or other VA office. NOTE: The report to ORO should include a copy of the official findings. The facility should promptly provide ORO with copies of all subsequent correspondence between the office and the facility until the issue is resolved.
8. Any findings of noncompliance in human subject protections from external oversight agencies such as the Office for Human Research Protections (OHRP), the Food and Drug Administration (FDA), etc. NOTE: The report to ORO should include a copy of the official findings (e.g., FDA Form 483, *Inspectional Observations*). The facility should promptly provide ORO with copies of all subsequent correspondence between the agency and the facility until the issue is resolved.
9. Any change in the research facility's accreditation status from a VA-recognized accreditation organization for human research protections, or in the accreditation status of an affiliate institution or other VA facility upon which the facility relies.
10. Any change in the research facility's Federal-wide Assurance (FWA) or designated IRB(s) as filed with OHRP. NOTE: Report such changes directly to ORO Central Office and simultaneously copy the ORO Regional Office.
11. Any significant change in the facility's Memorandum of Understanding (MOU) with an affiliate institution or other VA facility regarding the designation of IRB(s) or other human research protection function. NOTE: Report such changes directly to ORO Central Office and simultaneously copy the ORO Regional Office

HIC Procedures

The Human Investigation Committee (HIC) receives reports of possible non-compliance with federal, state, local regulations, VA regulations or University or HIC policies related to protections of human research subjects through various means of communication. Individuals making such reports are referred to the HIC Chair or the HIC education/compliance coordinators for initial review. If after a review of all relevant materials (e.g. IRB file, communications with PI, research materials, past audits) the IRB Chair or education/compliance coordinator determines that the report may meet the criteria for serious or continuing non-compliance and has a basis in fact, they consult with the AVPR. If the AVPR concurs with this initial determination, further processing of the report proceeds as described below and according to the HIC policy.

When reports of noncompliance are determined by the IRB Chair or HIC education/compliance coordinator not to meet the definition of serious or continuing by a review of the materials listed above, and the remedial actions, if any, are determined to be appropriate for the reported incident(s), this must be documented on the report form and included in the research file.

If the HIC Chair or the HIC education/compliance coordinators or the AVPR determine that immediate actions are required to protect the safety and well-being of research participants (see the Determination of Non-compliance check-list), the IRB Chair is notified. Depending on the initial availability of information and the immediacy of the reported event, the AVPR or IRB Chair may place an administrative hold or suspension on the protocol or specific research activities or initiate other corrective steps such as requesting an interview with the investigator, an audit, a focused review, educational remediation,

notification of currently enrolled participants, etc. The HIC Policy and Procedure "Suspension and Termination of Research Protocols" outlines the steps to take for those actions.

If the HIC Chair or HIC education/compliance coordinators or AVPR determine that the problem does not require immediate action, an internal review of the protocol, a focused review with phone or in-person interviews with the research staff and /or PI, or a for-cause audit is conducted to gather more information on the problem. The initial report and the supporting data will be presented at the next convened meeting of the appropriate IRB. Depending on the initial availability of information, the AVPR or IRB Chair may place an administrative hold or suspension on the protocol or specific research activities. The HIC Policy and Procedure "Suspension and Termination of Research Protocols" outlines the steps to take for those actions.

For reports determined to have a basis in fact and that meet the definition of serious or continuing noncompliance, the convened IRB will make the final determination of whether the report meets the definition of serious or continuing non-compliance. (See Non-Compliance Checklist). If the reported activity or non-activity is determined to be serious or continuing, the Committee will consider the following possible actions: suspension or termination of the research; notification and/or re-consenting of current participants if such information could affect the participants' willingness to continue in the research; modifications of the protocol or consent document; provision of information to past participants; early continuation review; re-auditing to monitor the research at a specified interval, and required educational sessions for the PI and research team members. For distribution of the findings, see "Reporting of Unanticipated Problems, Terminations, Suspensions, and Serious & Continuing Non-Compliance".

The IRB Committee can request additional guidance on actions to take for the reported event from the HIC Steering Committee. If so requested, then the Steering Committee will review the report of the findings and make recommendations to the IRB Committee. If the IRB Committee asks the HIC Steering Committee to adjudicate the findings of a report and to make final decisions on the protocol, the Steering Committee will act as a duly constituted IRB, with appropriate representation to review the particular protocol (eg. VA member present for all VA protocols) the discussion and decision will be documented in the meeting minutes and a copy will be distributed to all members of the IRB of record.

If a decision is made to terminate a protocol then the PI may appeal either in person or in writing to the IRB Committee of record. The Committee of record will review the appeal at the next convened meeting, and inform the PI of their decision, in writing, within 30 days.

Reporting of Non-compliance:

The final non-compliance report is written by the HIC Process Improvement/Compliance Coordinator or his/her designee and approved by the AVPR and/or the convened IRB Committee.(See HIC Policy/Procedure: Reporting of Unanticipated Problems, Terminations, Suspensions, and Serious and Continuing Non-compliance.)

The final report is distributed to the following:

- IRB of Record
- AVPR/ HIC Chair

- Appropriate institutional officials (Chairs, Deans, Directors)
- OHRP, VA, FDA as appropriate and/ or other regulatory officials
- Privacy Officer at all involved institutions
- Sponsor, if appropriate

For VA Research

- Reports should be provided to the Office of Research Oversight, and the VAMC Research and Development Office within 10 days after the issue has come before the IRB. If the IRB has not made a final determination as to disposition of the issue within this 10 day period, the IRB chair should provide ORO with a preliminary report and with follow-up reports as needed until the issue is resolved.

Roles and Responsibilities

Vice President for Research (VPR)

The Vice President for Research is the Institution (WSU) Official responsible for ensuring that human participant research is conducted in compliance with all state and local laws, federal regulations and University policies. Allegations of non-compliance may be reported to the VPR, especially if the issues concern misconduct on the part of the IRB. The VPR will then determine the appropriate venue for an investigation of allegations of misconduct.

Associate Vice President for Research (AVPR)

The AVPR, as the official charged with oversight of the research compliance program, is responsible for reviewing serious and continuing allegations of non-compliance. If the alleged non-compliance is determined to pose an immediate risk to the well-being of participants, then the AVPR, in conjunction with the HIC Chair or designee and, possibly the HIC Steering Committee, will take immediate action to protect participants. Possible actions include but are not limited to suspension and termination of the research. If it is determined that the possibility of serious or continuing non-compliance exists, the AVPR will request an audit be conducted by the Process Improvement/Compliance Coordinator. The AVPR will also review the final non-compliance report and ensure that all reporting responsibilities have been satisfied. The AVPR will also keep track of non-compliance cases to determine if there is a pattern that may require process improvement or more education and training of the research community.

HIC Chair

The HIC Chair will review allegations of non-compliance and determine whether they meet the criteria of serious or continuing non-compliance. If it is determined that there is an immediate risk to the well-being of participants, the HIC Chair or designee, in conjunction with the AVPR, will take immediate action to protect participants. Possible actions include but are not limited to: suspension and termination of the research.

IRB Committee

Any of the IRB committees may initiate or review allegations of non-compliance. The IRB of Record makes the final determination on whether the evidence supports a finding of serious or continuing non-compliance and prescribes any corrective action plan(s) that may be required.

Process Improvement/Compliance Coordinator

It is the responsibility of the Process Improvement /Compliance Coordinator to accept allegations/reports of non-compliance make a determination on the validity of the claim; and if serious or continuing non-compliance is suspected, transfer the allegation/report to either the HIC Chair or AVPR. The Process Improvement/Compliance Coordinator also conducts for-cause audits and in conjunction with the AVPR drafts the fact finding report or corrective action plan.

Education Coordinator

The Education Coordinator also accepts allegations/reports of non-compliance, and refers them to the Process Improvement/Compliance Coordinator. The Education Coordinator works with the Process Improvement/Compliance Coordinator to develop and administer required or optional educational programs as specified in the correction action plan.

Contact Numbers:

Allegations/reports of non-compliance may be reported to:

- Process Improvement and Compliance Coordinator- (313-577-2901)
- Education Coordinator-(313-577-9534)
- Associate Vice President for Research Compliance-(313-577-9064)
- Vice President for Research- (313-577-9600)