WAYNE STATE UNIVERSITY

HIC Standard Operating Procedure

For-Cause Audits of Human Research Studies

Background

As part of the Wayne State University (WSU) Human Investigation Committee's (HIC) Human Research Protection Program, for-cause audits are conducted when there are concerns about whether or not the rights and welfare of participants enrolled in a particular research protocol are being adequately protected.

According to federal regulatory requirements, the officials of the HIC may request a for-cause audit to: 1) respond to any unanticipated problems involving risks to participants or others; 2) investigate whether or not serious or continuing noncompliance with federal and HIC policies is occurring; 3) determine if suspension or termination of the protocol is needed; and 4) to identify what required remedial actions are required by the Principal Investigator (PI) to remedy the problems identified by the audit [(45 CFR 46.113), (21 CFR 56.113) & (38 CFR 16.113)].

In addition, the for-cause audit may be used to determine if additional information is required to be submitted at the time of continuing review from an independent source to verify the ongoing safety of a protocol and to assist the Institutional Review Board (IRB) in the decision as to whether the protocol requires more than yearly review. Please refer to related HIC SOPS for definitions of terms and further information.[1]

Scope

For-cause audits may be requested for ***any*** research protocol that involves human participants that is conducted by Wayne State University and any of its affiliate institutions.

[1] "Suspension & Termination of Research Protocols", "Managing Non-Compliance in Research ", & "Reporting Unanticipated Problems, Continuing Noncompliance, & Suspensions and Terminations of Research Protocols" (in development).

Definition

For-Cause Audit- Is an in-depth examination of all components of a research study including, but not limited to all records and documents, observations of processes, and interviews with investigators, research staff members, and participants for the purpose of determining if the rights and welfare of participants are being upheld according to federal regulatory and HIC requirements.

HIC Procedures

Preparation for Audit

As soon as information becomes available to the Institutional Review Board (IRB) regarding a problem with a study, the information is provided to the Chair of HIC who determines (with input from the WSU Assistant Vice President for Research) whether or not the study should be: 1) suspended immediately due to immediate risks to participants or others, 2) placed on administrative hold, or 3) allowed to continue until the data gathered for the audit is completed. If the protocol deviations or problems that precipitate the audit do not constitute ***immediate and serious risks***, an audit may be requested prior to any immediate restrictions being placed on the protocol by the IRB. (Please refer to SOP on "Suspensions and Termination of Research Protocols" and "Determining Projects that Require Additional Verification" on the HIC website www.hic.wayne.edu under the Standard Operating Procedures link.)

A memo is sent to the Principal Investigator that outlines:

- The reason(s) for the for-cause audit,
- Any hold that has been placed on the research,
- All of the documents that are to be reviewed,
- Interviews that will be conducted,
- Planned inspections of the facilities (primarily how data is stored, drug and device storage, accountability, destruction etc.),
- When the audit will likely occur,
- Contact number for questions, and
- Whether or not the IRB has requested that the auditor observe the informed consent process with potential participants.

A member of the audit team will contact the PI or his/her designee to determine the total number of participants that have been enrolled in the study to date. From this number, a list of random numbers is generated. The number of records to be reviewed at the site will depend on the number of participants that have been enrolled to date. Usually 20 or 30% of the total number of cases will be reviewed. The selection of cases may also depend on when, since the beginning of the study, participants were enrolled. This allows the reviewer to select cases that have been enrolled at different times during the life of the study. Once a decision about the total number of cases to be reviewed and the list of random

numbers has been generated by the audit team, the PI is then requested to chronologically match the participant cases to the random numbers. These will be the cases reviewed for the audit.

The audit team members then contact the PI to arrange for the first visit to the study research office(s) or a letter may be sent, if time allows.

The audit team notifies the PI that all research records, flow charts, narrative notes, source documents, questionnaires, study binders, correspondence with the IRB and sponsor, or any other information about the study and its conduct (on-line or hard copy) must be available for review at the time of the visit.

If access to a computer database is needed, someone at the research site should be available to assist the auditors in accessing the information.

Document Review

The document review includes a thorough review of the research participant record, the source documents, all regulatory binders, and consent forms. This portion of the audit is conducted to get the most information in the most efficient way. The order of contents may vary from audit to audit and other documents may be examined as needed. The PI or designee does not need to be present during this part of the audit; however, he/she should be available to answer questions. In general, the following areas must be examined on any audit.

Regulatory Binder
Should include:

- The complete research protocols
- Informed consent documents
- Investigator CVs
- IRB documents including initial submission, amendments, continuations and adverse reactions/unexpected events that have been sent to the HIC
- IRB approval memos and other correspondence
- All sponsor communications and correspondence
- Signature lists of research staff
- Inclusion/exclusion criteria
- Serious adverse event reports
- Monitoring logs and reports
- Final study reports
- Investigator's brochure
- Other relevant documents

Consent Form

The consent forms for the research protocol will be reviewed for the following items:

- Is there a consent form for each participant?
- Who signed the consent (participant, parent, legally authorized representative)?
- When was the consent document signed in relation to when the first research activity began?
- Was the correct version (appropriate HIC Stamp Date & Version specified by sponsor and/or Protocol Version) of the consent/assent document used for the participant?
- Is the consent IRB approved/stamped?
- Did the participant place their initial and date on each page of a multiple-page consent, if required by unit and sponsor?
- Is the content in the consent document current regarding the most recently approved protocol and amendments to the protocol?
- If the consent form is different from the originally approved form, were amendments submitted for these changes?
- Where the signed consents are kept and what measures are taken to protect the confidentiality of the participant's signatures?
- Where the consent process is conducted and by whom?
- Who obtained the consent signature?
- Has the person who obtained informed consent completed the required on-line training modules (1 through 6)?

Eligibility Criteria

- Is determination of eligibility by inclusion/exclusion criteria clearly noted in record?
- Who makes the eligibility decision? How is this communicated to the PI?
- Are source documents (laboratory tests, diagnostic tests, history & physical exam results) available to verify that the eligibility criteria were met?

Adverse Reactions/Unexpected Events (AR/UE)

- Are the AR/UEs on file all reported to the HIC? (is there a match)
- Is there evidence of follow-up for the AR/UEs?
- Who reports the AR/UEs?
- Were the reports completed correctly and submitted on time to the HIC?
- Have appropriate federal regulatory agencies been notified of all serious, unexpected, and related adverse events or unexpected problems?

Questionnaires

- Are the data collection tools detailed in the protocol in each record (hard copy or on line)?
- Are they the same or different from those that were approved by the IRB?
- If different, was an amendment submitted to cover those changes? Is a change in the consent needed to cover the changes in the questionnaires?
- Are they being administered within the time frame specified by the protocol?
- If questionnaires are completed via interview, how is the privacy of participant maintained?

Protocol Adherence

- Is there evidence of a system that allows for tracking of the participant's experience throughout the protocol (e.g., flow chart)?
- Are there other documents (research worksheets) for recording tests, procedures, questions, comments, complaints, withdrawals, removals and reasons for this action in the research record?
- Is there evidence that the methods for monitoring the safety of the participants are being followed as specified by the protocol?
- Are the timelines specified by the protocol design being followed?
- Have there been any protocol deviations/violations during the course of the study?
- What actions were taken by the research team to remedy these?
- Have any of these been reported as AR/UEs, if appropriate?

Documentation

- Are there consistent procedures being followed for documenting the processes of the research study?
- Is there a system for writing narrative notes when a participant is seen for a visit/ for phone or mail contacts?
- Where are records kept? How are they kept? Who has access to the records?
- Is a Regulatory Binder/Methods/Study Binder in the Research Office?
- Where is all correspondence regarding the study kept?
- Who is responsible for training research personnel on proper documentation?
- Is the documentation accurate?
- When errors are made in documentation, how are the errors corrected?

Data Collection

- Are source documents available to verify the data collected for the study and recorded on research records?
- Is the system used to document data used consistently from case to case?

Drug/Device Oversight-Questions/ Areas of Review

Drugs:

- How are the drugs sent to the institution/PI?
- Where and how are they stored?
- Who manages the drug accountability logs?
- Who verifies the drug order, that appropriate participant consent has been obtained, and who is responsible for dispensing the drug?
- Who makes the drug available to the participant?
- What methods are used to verify that the drug was given properly?
- What are the methods of disposal or return of unused drug to the company?

Note: A visit to the investigational pharmacy may be conducted during the audit to determine if the institution's policies are being followed. The auditor will want to see the drug accountability records, storage of the drug, if and how a copy of the consent document is kept in the pharmacy, and the procedures used to handle left over drug.

Devices:

- How are the devices sent to the institution/PI?
- Where and how are they stored?
- Who manages the device accountability logs?
- Who verifies the device order?
- Who verifies the consent and actual use of the device?
- What methods are used to verify that the device was used properly?
- What are the methods of disposal or return of the unused device to the company?

Note: A visit to the locations where the investigational devices are sent and stored may be conducted during the audit of a study to determine if the institution's policies are being followed. The auditor will want to examine where how devices are stored, the accountability records for use of the device, the processes used to repair, discard, or return unused devices.

Other: If laboratory specimens are collected and kept by the research team, collection methods, specimen storage and record keeping and accountability will be evaluated.

Principal Investigator Interviews

The audit process will likely include an interview with the Principal Investigator and/or Co-Investigators for the protocol. This interview will address the following:

- Who is responsible for various protocol-related procedures?
    - Protocol submissions to IRB
    - Informed Consent
    - Subject Recruitment

        - Participant Screening
        - Data Collection
        - Protocol Interventions/Activities
        - Data Analysis
- How are prospective participants identified?
- Who is responsible for obtaining informed consent?
- How many subjects were screened?
- How many subjects were enrolled?
- Did any subjects withdraw? Why?
- Were any subjects removed from the study? Why?
- Were there any adverse reactions/unexpected events? Did any result in death? If so, were they reported?
- How do members of the research team communicate regarding ongoing management of the protocol? Are there regular team meetings? Are e-mail communications used? If so, how often are these methods used?
- When a study begins or new members join the research team, how are they trained? Who conducts the training? What methods are used to update the team and to verify that appropriate research practices are being used throughout the life of the protocol.

Key Personnel
A review of research records will be done to identify all persons that are "engaged" in research activities with research participants (interacting with research participants for research interventions or data collection that includes personally identifiable information). Once these people have been identified, verification of their status will be conducted to ensure that that they have been included as key personnel on the protocol or added via amendment, and have completed the HIC Required On-Line Training (modules 1 through 6).

Key personnel will also be interviewed regarding the items outlined above, if necessary.

Audit Report
Upon completion of the audit, the collected data will be analyzed and a report generated. The report will specifically address all findings (regulatory and HIC policy and procedure issues, and issues of Good Clinical Practice in research), and outline required and/or recommended remedial actions for the protocol.

This report is shared with the HIC Chair and the Assistant Vice President for Research prior to being sent to the PI.

The PI then has an opportunity to respond in writing to each finding in the audit, either challenging the finding, offering additional supporting evidence, submitting source documents that could not be found by the auditor, and/or carrying out the required actions specified in the audit report.

The audit report and the PI's written response is then taken to the HIC Steering Committee for further review, and additional requirements, if needed.

The PI is then notified in writing of the final decisions of the Steering Committee.

Follow-Up
The Steering Committee may request that the auditor do a follow-up review at a specified time. The PI will be notified of this additional requirement in the final notice.

Reporting
A written report is generated and sent to all required federal regulatory agencies (FDA, OHRP, ORO, DOD, etc.) after the Steering Committee's final decision. A copy of this notice is also sent to the sponsor of the study, and any appropriate institutional or departmental officials. A follow-up report may be sent to regulatory officials after a specified interval, if required. This report is generated from the office of the Assistant Vice President for Research and contains (at least) the following information:

Title of Study
Name of PI
Name of Institution
FWA Number
Name and IRB number
Sponsor
Sponsor Code
A description of the event(s) that precipitated the audit, date(s), specific remedial action requirements by the HIC, responses by the PI, and any final requirements.
A statement that follow-up reports will be forwarded, if required.

Documentation of Audit Materials
All documents generated by the audit process are filed in the Protocol Files in the HIC office. These are accessible only to appropriate members of the HIC staff, administration, the PI and his/her designees, and to appropriate regulatory (FDA, OHRP, ORO, DOD etc) personnel, if needed.

In addition, complete electronic versions of the reports are kept in a password protected database by the Process Improvement/Compliance Coordinator.