Office of Research Compliance, in affiliation with the North Texas Regional IRB

Post-Approval Monitoring/Compliance Audits for Human Subject Research Studies: Principles and Procedures

Overview

This document describes policy and corresponding procedures establishing a mechanism for conducting two categories of post-approval monitoring and oversight research compliance audits: periodic compliance audits (also known as "post-approval monitoring (PAM) audits") and directed (for-cause) compliance audits on research projects that involve human subject research at the University of North Texas Health Science Center (HSC), for projects under the purview of the North Texas Regional Institutional Review Board (NTR IRB).

Federal Regulatory Basis:

The Office of Research Compliance (ORC), via the NTR IRB, is responsible for oversight of approved protocols of human subject research based on regulation and policy found in Title 45 Code of Federal Regulations Part 46, Title 21 CFR Part 56, and ICH Good Clinical Practice Guidelines as adopted by the FDA, the US Federal-wide Assurance and University policy.

Policy:

In order to assess compliance with IRB approved protocol, state and federal laws, and IRB principles and procedures, periodic compliance audits and directed compliance audits of research projects involving human subjects will be conducted by the Research Compliance Officer or designee and reported to the NTR IRB.

This document applies to all human subject research conducted by or at HSC, including exempt, expedited, and full review protocols reviewed and approved by the North Texas Regional IRB.

Procedures

1. Periodic Compliance Audits

All on-going HSC human research projects with IRB approval granted by the NTR IRB are eligible to be audited by the Research Compliance Officer or designee. For the most part, these post-approval audits are considered routine and "not for cause" audits. Such audits are intended to be proactive and focused on educating investigators and research staff about their ethical and regulatory responsibilities regarding human subject research.

2. Directed Compliance Audits

Directed compliance audits will be initiated by the Office of Research Compliance/ NTR IRB as a result of a complaint, suspected non-compliance, or questions/concerns regarding the safety and welfare of research participants enrolled in a research study.

3. Selection of Protocols for Audit

The Research Compliance Officer or designee will perform periodic routine and "for cause" directed audits to ensure compliance with the approved IRB protocol, federal and state regulations, as well as NTR IRB policies associated with the protection of research participants. Protocols can be selected on a random basis from any category of review: exempt, expedited, or convened meeting ("full board"). Selection of a protocol for audit does not imply any suspected noncompliance for routine audits. A risk-based selection process may be utilized or randomly selecting approved protocols reviewed by either expedited or full board procedures (see section 4 below) or determined by the NTR IRB to be exempt category.

Investigators are informed in advance of the impending audit, informed of the process, and the type of records to make ready for review (see sections 5 & 6, below). With the cooperation of the principal investigator, it is expected that a routine audit can be conducted, in most cases, in 1 to 5 days or less.

4. Criteria for Compliance Audit Selection

The Office of Research Compliance / NTR IRB may use any one or more of the following criteria for selection of a research project for compliance audit:

- At random
- At the discretion of the IRB
- Risk based selection: high risk studies as designated by the IRB; studies that include vulnerable populations (i.e. pregnant women, children, prisoners, etc.); studies reporting on-site SAEs or protocol violations; studies reporting a high local-site proportional enrollment relative to overall study enrollment; or Investigators who have limited or no prior research experience with human subjects.
- To verify compliance: For those studies in which the Investigator(s) have a previous non-compliance history or concern, or for protocols involving Investigators who have prior FDA 483, "Inspectional Observations", and / or FDA Warning Letter(s) on file; Report of suspected non-compliance or complaint; Previous suspension of the research protocol (for any reason).
- Research placed on administrative hold or closure by the IRB due to failure by the Investigator to submit a study for continuing review or failure to respond to a request for information from the IRB.

- To verify Continuing Review reports (Progress Reports), if required.

5. Documents / Processes that may be selected for review include, but are not limited to:

- Examination of the protocol and amendments, consent documents, source documents, case report forms (CRF), adverse events, advertisements, recruitment materials, and other research study related documents and correspondences.
- Regulatory submissions and correspondences with IRB, Sponsor, Monitor, etc.
- Review of subject enrollment log and recruitment practices, as needed
- Key personnel training records and site signature / responsibility log
- Review of research data, data collection tools, and procedures
- Review of serious adverse event reporting
- Examination of consent forms to verify that they are signed and dated correctly
- Examination of proper storage, maintenance, and accountability of study related items (i.e. regulatory files, IRB files, subjects' research and medical records, clinical materials, computer files, electronic data records and storage, specimens, drugs, devices, equipment, and results of procedures and tests performed during the course of the research, etc.)
- Contacting research participants either during or after their participation in research activities to evaluate their involvement in the research study, and/or,
- Observation of the consent process
- Observation of research interactions/interventions with research participants
- Monitor conflict of interest concerns to ensure that the consent document includes appropriate language and disclosures
- Other relevant research project documents or activities as deemed appropriate by the Office of Research Compliance and/or NTR IRB
- When applicable, an appropriate "Research Recovery Plan and Safety Protocol for COVID-19" was approved and in place (this applies to any in-person research procedures that were conducted during the COVID-19 pandemic, from June 2020 to May 2021, when in-person research interactions at HSC were limited).

6. Audit Process

1. The Research Compliance Officer or designee will schedule compliance audits of previously IRB-approved research studies.

2. Prior to initiation of a compliance audit, the principal investigator (PI) will be notified by the Research Compliance Officer and/or designee at least 10 working days in advance, by email, telephone (including voice mail), or by hard copy letter, that a compliance audit will be conducted. Once the PI has had time to receive the Notice of Post Approval Monitoring (NPAM), the Research Compliance Officer or designee will finalize the date and time of the compliance audit by phone or email confirmation with the PI, or their designee.

3. If the PI fails to respond to the initial NPAM for any audit within 5 working days, a follow-up email will be sent to the PI requesting verification of date of audit and location of audit (the PI's Chair or supervisor will be copied on this follow-up email). If the PI fails to reply to the follow-up NPAM email, the Principal Investigator and applicable protocol(s) will be referred to the next convened meeting of the NTR IRB for review and consideration. The NTR IRB may request a for-cause audit to be conducted and/or suspend the Principal Investigator's protocol(s) as deemed appropriate. In addition, the IRB Chairperson may exercise his/her authority to notify applicable institutional and other agency official(s) of the PI's failure to comply with NTR IRB policies and procedures.

4. The notice of compliance audit will identify the PI and the protocol to be reviewed during the on-site compliance audit. The Research Compliance Officer or designee will make every effort to be available via email/phone if the PI has more specific questions as to the nature and/or procedures of the compliance audit.

5. For a directed compliance audit only, in the interest of subject safety, there may be no pre-notification or minimal notification of a compliance audit at the discretion of the Director, Research Compliance. However, it is the intent of the Office of Research Compliance to inform the PI whenever a directed compliance audit is being implemented.

6. The PI need not be present for the compliance audit; however, either the PI or other study personnel associated with the project being reviewed should be available on-site during the audit. If the PI will not be present for the compliance audit, a designated member of the research staff knowledgeable about the conduct of the study must be available to provide access to study records and to answer questions by the Research Compliance Officer or designee.

7. *Prior* to conducting the compliance audit, the Research Compliance Officer or designee will review the research study file maintained within the electronic IRB submission system (and review any hardcopy/paper files maintained in ORC office, if applicable, as needed) to familiarize himself/herself with the IRB application, protocol synopsis, consent forms, amendments, including (if applicable) correspondence from the sponsor, monitor, and/or other regulatory/federal agencies, etc.

8. *During* the compliance audit, the Research Compliance Officer or designee will have access to all pertinent study documents, records, processes, etc. Please refer to Section 5 above, which provides a partial list of the items that may be subject to review during

the compliance audit. The Research Compliance Officer or designee will document compliance audit findings on the *Post Approval Monitoring (PAM) Audit Checklist* form.

9. After completion of the compliance audit, the Research Compliance Officer or designee will prepare the *Post Approval Monitoring (PAM) Audit Checklist* form and written memorandum and submit it to the Director of Research Compliance for review. If the audit reveals non-compliance, then a close-out meeting will be scheduled with the PI or designee, Director of Research Compliance or designee, and IRB Chair or designee to formally review the audit findings and discuss a compliance plan to ensure compliance.

10. Following the audit close-out meeting the PI will receive the final audit memorandum via Docusign (or other appropriate signature method) for signature and written response. Following receipt of the *Post Approval Monitoring (PAM) Audit Checklist / Memo*, the PI will have 15 working days to sign and respond, in writing, to the compliance audit report findings. If comments, acknowledgements, and/or clarifications by the Principal Investigator are not submitted within 15 working days to the Office of Research Compliance, a follow-up email will the sent to the PI requesting the signed report and/or written compliance action plan.

11. If the PI fails to respond to the follow-up email requesting the signed report and/or written compliance action plan, than the applicable protocol and PI will automatically be brought before the next IRB convened meeting for consideration and follow-up action. **Note that the IRB has the authority to suspend or terminate the study in accordance with federal regulations and IRB policy until a written response is received from the Principal Investigator.** Additionally, the IRB may exercise its authority to notify applicable institutional and outside agency officials of the principal investigator's failure to comply with NTR IRB policies and procedures.

12. If there are not any documented findings during the compliance audit, a *Post Approval Monitoring (PAM) Audit Checklist* and written memorandum will still be drafted and sent via Docusign to the PI for his/her signature.

13. If preliminary findings of non-compliance by the Research Compliance Officer or designee so indicate the safety and welfare of subjects is in jeopardy, the Director of Research Compliance can immediately request the IRB Chairperson to suspend the protocol, including study enrollment and/or activities, and take appropriate action to ensure the safety and welfare of the subjects until this matter can be brought before the next IRB convened meeting for further review and determination. [See "*When the safety and welfare of subjects are in jeopardy*", below for further details].

14. If the PI responds to the *Post Approval Monitoring (PAM) Audit Checklist / Memorandum* with his/her comments and/or acknowledgments, the Research Compliance Officer or his/her designee will compile the documents for IRB review and further recommendations, if needed. IRB review/acknowledgement of the *Final Audit Report* will be documented in the Meeting Notes/Chair's Report.

15. If no further follow-up is necessary, a copy of the *Board Action Notice* will be sent to the PI. If the IRB requests further follow-up, the PI will be notified of the IRB's determinations.

Failure to provide documents or access to records:

In order for effective and timely review of research protocols involving human subjects, during compliance audits of such projects, the Research Compliance Officer or designee shall have full access to all documents and processes associated with the IRB-approved protocol. Failure to provide documents or access in a timely manner may result in immediate IRB suspension or termination of the approval status of the protocol. Additionally, applicable institutional officials, sponsor(s), and/or regulatory agency officials shall also be notified of the status change of the protocol.

When the safety and welfare of subjects are in jeopardy:

In the event that a study is suspended, the IRB Chairperson will bring appropriate documentation to the next IRB convened meeting, and the Board will determine (by a simple majority vote) whether to rescind the suspension, uphold the suspension, or terminate approval of the study. The IRB will also decide the corrective and preventive action plan for the study, if any; and if applicable, the corrective and preventive actions plans for research personnel involved in the non-compliance. The corrective and preventive action plan agreed upon by the IRB will be documented and sent to the Principal Investigator.

Principal Investigator Involvement:

Additionally, a PI may be required to appear before the convened IRB or to meet with the IRB Chairperson to address issues and discrepancies identified during the compliance audit. If during the course of the compliance audit, subjects are considered at risk due to the actions of the PI or other key research personnel, appropriate officials of the institution in which the research is occurring (and, if applicable, the sponsor and regulatory agency of the research) shall be notified, and appropriate action will be taken, such as suspension and /or notifications, to ensure the safety and welfare of the subjects.

Follow-Up:

If significant findings are uncovered during a periodic compliance audit or a directed compliance audit, the Research Compliance Officer or designee may conduct a follow-up visit within six (6) months of the initial resolution of the compliance audit findings, or as otherwise instructed by the convened IRB.

Reporting:

A copy of the final compliance audit report and correspondence (s) will be maintained in the Office of Research Compliance.

Other HSC personnel may be made aware of the audit findings as deemed appropriate by the Director of Research Compliance and IRB Chairperson.

If required by federal regulations, applicable regulatory agencies will be notified.

Note, at all times, the IRB Chairperson or designee may exercise his/her authority to notify applicable institutional officials and regulatory agencies of the principal investigator's failure to comply with NTR IRB policies and procedures.

To view a copy of the ORC *Post Approval Monitoring (PAM) Audit Checklist*, please click here.