



Department of Radiology and Radiological Science

Clinical Trials Audit Manual

This manual documents policies for conductance of audits for clinical trials within the Department of Radiology .

This document serves as a starting point for beginning a formal audit system within our department. We plan to audit all existing clinical trials following this document within the next several months. Ultimately, an audit schedule that best suits the types of clinical trials conducted in the department of radiology will be devised. The development of an audit program is one mission of the Department of Radiology's Research Office. The purpose of the clinical trials audit program described in this manual is to ensure patient safety, verify accuracy of data collected, identify problem areas, and take corrective action when necessary.

Protocol Selection

The clinical research auditor will select protocols based on the study type (investigator initiated, industry sponsored, and federally funded cooperative group), the number of subjects accrued, principal investigator previous clinical trials experience, and the clinical division in which the clinical trial is operating.

- Investigator initiated and federally funded trials: will be audited at least once over the duration of the study. Studies that are deemed high-risk will take priority. A protocol becomes eligible for audit after three subjects are accrued.
- Industry and Cooperative Group Trials: If specified in the protocol that trial monitoring and/or audits will be conducted by external entity, the results of these external reviews will be required to be submitted to the clinical trials review committee within one month of receipt. Once a year at least one industry and cooperative group trial will be audited by a clinical research auditor in the department.
- For cause audits of protocols requested by the clinical trials committee, IRB, or a data safety monitoring board.
- Rapidly accruing studies as indicated by the clinical trials review committee that are expected to finish in less than a year or if the accrual rate is 1.5 times faster than expected.
- Protocols led by new PIs or clinical research investigators.

Subject Selection:

10% of all subjects accrued to the study will be selected by the clinical research auditor from the selected protocol. However, the number of subjects may vary depending on the complexity of the protocol and the number of subjects enrolled. The subjects will be selected randomly.

Scheduling Audits:

The clinical research auditor will contact the PI and study coordinator by email three to four weeks in advance of the audit. The email will function as the official audit notification and will contain a list of subjects to be audited, the procedures of the audit, and audit preparation tips. The clinical research auditor will compare the information recorded on the clinical report forms to the clinical source documents and make sure that the protocol was followed and the data documented in the CRFs is accurate. It is expected that the PI and study team will be available during the audit period to assist the clinical research auditor as needed.

An exit interview to take place within 72 hours of the audit completion will be scheduled by the clinical research auditor with the PI and the rest of the study team.

Audit Preparation

Clinical Research Auditor

Prior to audit, the clinical research auditor is responsible for the following:

- The clinical research auditor will obtain patient registration confirmation from shared radiology research server.
- Review the regulatory file of the protocol within the MUSC eIRB system and verify the completion of:
 - Initial IRB Approval
 - IRB approval of Amendments
 - IRB approval of Renewals
 - Current version of protocol and informed consent document
 - Reported adverse events
- If necessary, contacting pharmacy to set up time to review all records regarding the dispensing of investigational drugs.
- Contact members of the study team a few days prior to the audit to confirm date, time, and place.

Principal Investigator and Study Team

Prior to audit, the principal investigator and study team is responsible for the following:

- Gathering all clinical records for the selected subjects
- Gathering completed case report forms (CRFs) and research files for the selected subjects
- Gathering original eligibility checklists, consents, and off-study forms for the selected subjects (if not in clinical charts or files)
- Flagging or organizing the required elements of the protocol in the selected subject charts
 - i.e. Eligibility, Enrollment, Imaging Exams/Procedures, etc.. Source documentation should exist and be flagged for all required items.

- Create a “note-to-file” when there is a discrepancy that requires clarification in the record. Sign and date any note-to-file and include how the information was obtained. (Note: note-to-files do not replace the need for deviation or violation submissions, when applicable).
- Ensure the regulatory binder is complete and up-to-date

Audit Visit

For each subject selected, the clinical research auditor will complete an audit review form. The specific elements to be reviewed in each subject’s source documentation and documented on the audit review form are:

- Informed consent
- Eligibility
- Imaging Exam(s)/Interventional Procedure
- Adverse Events
- Lab Tests/Study Procedures
- Data Management Assessment
- Other

See Appendix A for Template of Audit Review Form

Exit Interview

The exit interview will ideally take place within 72 working hours of the completion of the audit. The PI is required to attend. The study staff is also strongly encouraged to attend.

At this interview, the clinical research auditor will present the findings of the audit and answer any questions raised by the PI and study team. Any questionable issues should be discussed and the opportunity to clarify issues raised will be provided. Any missing, incomplete, or incorrect data should be resolved and given to the clinical research auditor within one week of the exit interview.

The clinical research auditor will describe the audit reporting and follow-up process at the end of the exit interview. The final audit rating will not be determined until after the exit interview.

Audit Report and CTRC Review

The clinical research auditor will complete the final report within two weeks of the exit interview. The specifics of the audit will be listed and will include the dates of the audit, institutional sites, study team members, regulatory review findings, pharmacy review findings (if applicable), a detailed list of major and minor violations (See Appendix B), and final audit rating.

The clinical research auditor will send a signed hardcopy and an electronic email attachment of the completed final report to the PI and study team within two weeks of the exit interview. The PI and study team should review the final audit report and discuss a corrective action plan if needed.

Audit Ratings

One of four ratings will be assigned to each audit:

- Exceptional –
 - Evidence of superior source documentation, data quality, protocol compliance, and regulatory compliance. No formal PI response is required.

- Satisfactory -
 - Few minor violations noted. No formal PI response required.

- Acceptable, needs follow-up-
 - Audit with any major violations, which does not fit into the “unacceptable” definition. Formal PI written response is required.

- Unacceptable –
 - Number of audit-wide major violations per subject is greater than or equal to 0.6. Formal PI written response is required.

OR

 - A single life-threatening major violation for a subject. Formal PI written response is required.

OR

 - Concern for misconduct or fraud. Formal PI written response is required.

Clinical Trials Review Committee Policy for Reviewing Audit Ratings

“Exceptional”, “Satisfactory”, or “Acceptable, needs follow-up” Ratings

For audits deemed “Exceptional” or “Satisfactory”, the clinical trials review committee will simply review the final audit report at the next scheduled meeting.

For audits deemed “Acceptable, needs follow-up”, the clinical trials review committee will review the final audit report and the PI’s written response at the next scheduled meeting. The clinical trials review committee will make a decision of whether to accept or conditionally accept. If the committee specifies conditional acceptance, the conditions of the acceptance would be required to be implemented:

Examples of conditions might include:

- Implementation of new procedures regarding the individual protocol or possibly system wide changes within the department.
- Re-audit of protocol in question
- Auditing of related protocol if the previously audited protocol is closed
- Suspension of the protocol to accrual
- Recommendation of permanent closure of the protocol to the IRB

The clinical research auditor, will contact the PI of the audited protocol in writing within one week of the committee meeting to relay the results of the clinical trials review committee's evaluation.

Unacceptable Rating

For audits deemed "Unacceptable", the clinical research auditor must notify the Vice Chair of Research for Radiology, the Chair of Radiology, and three physician members of the clinical trials review committee. The notified individuals must review the major violations within 48 hours of the exit interview. The notified members must review the major violations and inform the Clinical Research Auditor if they agree with the "Unacceptable" evaluation within 24 hours. If the majority agrees with the Unacceptable rating, a formal standardized letter from the Radiology Chair to the PI will accompany the final audit report. This formal letter will be sent within 24 hours of the majority vote and will alert the PI of the department leadership's agreement with the audit rating and will instruct the PI to prepare a written response to the major violations outlined in the final audit report within five working days.

Protocol violations involving patient safety will require that MUSC Risk Management and patient safety officers be notified.

The radiology department can take immediate action for unacceptable rating based on findings that could include suspension of the trial, and/or recommendation of closure to the IRB if deemed necessary. Immediate action would be warranted if there are suspected patient safety risks, research fraud, or an extremely deficient audit.

Appendix A. Audit Review Form

The Clinical Research Auditor uses the audit review form as a checklist during the audit. One audit review form is completed for each audited subject.

Protocol # Subject MRN Date of Review Audit Mgr

Please √ responses appropriately		Source			Data Forms			If no, please comment
		YES	NO	N/A	YES	NO	N/A	
Informed Consent	Is there a consent form for the subject enrolled?							
	Was the consent the correct IRB approved version?							
	Did all the required individuals sign and date the consent?							
	Is the research staff member who signed the consent approved by the DF/HCC policy?							
	Did the subject sign the consent prior to enrollment (and prior to starting study specific tests/procedures)?							
	If subject had to be re-consented, is the informed consent form available for review?							
	Was the consent process properly documented for initial consent and any re-consents?							

	Is there documentation that a copy of the consent was given to the subject?						
	Was the subject registered correctly?						
	Other (Specify)						
Eligibility	Did the subject meet all inclusion/exclusion criteria?						
	Were all pre-enrollment activities completed per protocol?						
	Other (Specify)						
Treatment	Did the subject discontinue any protocol-prohibited medication according to protocol?						
	Was the correct treatment regimen given?						
	Was study drug dispensed per protocol?						
	Was only protocol therapy given?						
	Was the subject dosed properly per protocol?						
	Was the correct treatment schedule followed?						
	Was there adequate documentation of treatment, including pre-meds or others?						
	Other (Specify)						

Adverse Events	Were dose adjustments done per protocol and were the reasons for dose adjustments provided?							
	Were type, grade, dates/duration, and attribution of adverse events adequately reported?							
	Were SAE's reported correctly and within the required time frame per protocol?							
	Other (Specify)							
Response	Was response accurately assessed, documented and recorded per protocol requirements?							
	Other (Specify)							
Lab Tests/ Study Procedures	Were tests/procedures implemented as approved by the IRB?							
	Were the labs/procedures for this subject documented in the study records?							
	If a procedure was missed, was the reason properly documented?							
	Was there documentation of lab specimen collection and storage?							
	Other (Specify)							
Data Management Assessment	Is follow-up being done per protocol for this subject?							
	Is the data quality complete and acceptable?							

	Are the research file and clinic chart organized?						
	Was data completed in a timely manner?						
	Was the data accurately recorded on the case report forms?						
	Was the audit preparation completed according to QACT guidelines for this subject?						
	Other (Specify)						
Other	Were deviations or violations properly documented for this subject?						
	Other (Specify)						

Appendix B: Examples of Major and Minor Violations

Major and Minor Violations:

A major violation is generally defined as 1) An infringement, which significantly alters the clinical effectiveness of a device/treatment or the evaluation of its toxicity, 2) An infringement which violates Federal or MUSC requirements or policies or 3) Cumulative minor violations of the same nature.

Minor violations are problems that occur when the protocol is not followed exactly, but the data are usable and valid or small deviations from Federal or MUSC policies.

The following list is not all inclusive but is intended to give guidance to types of issues that result in major violation flag and a minor violation flag.

MAJOR VIOLATIONS

A. Informed Consent

- Failure to document properly obtained subject consent or IRB or Sponsor mandated re-consent
- Consent dated after registration/treatment of subject
- Consent not obtained in a language fully understood by the subject
- Outdated consent used

B. Eligibility

- Does not meet eligibility criteria
- Many eligibility criteria not documented in the medical record

C. Registration/Randomization/Stratification

- Subject not registered prior to treatment
- Information given at registration is inconsistent with actual data in medical records chart (wrong stage, diagnosis, cell type, etc.)

D. Forms/Data Submission/Special Requirements

- Submission of data outside of protocol guidelines
- Incorrect data (substantial amounts of data are

MINOR VIOLATIONS

A. Informed Consent

- Consents do not have date/appropriate signature
- Consents do not have unique subject identifiers on each page

B. Eligibility

- Small variations of criteria with reasonable explanation/approval (Phase II and III only)
- One or more criteria not documented in medical record

C. Registration/Randomization/Stratification

- Date of birth, date of diagnosis, lab values or dates inconsistent

D. Forms/Data Submission/Special Req.

- Incorrect data (sporadic pieces of data are incomplete or inaccurate)

incomplete or inaccurate for 1 or more forms)
 -Substantial number of forms not submitted to Sponsor

-Few forms not submitted to Sponsor

E. Contrast Agent Administration

-Inappropriate administration of non-protocol contrast agent
 -Failure to document drug administration
 -Repetitive or systemic errors in dosing

E. Contrast Agent Administration

-Wrong amount of contrast agent administered

F. On-Study Procedures

-Unacceptable frequency of required evaluation violations

F. On-Study Procedures

-Missing a small number of minor required evaluations or tests

G. Response/Follow-Up

-Failure to assess disease status according to the required protocol guidelines either pre-intervention or in response to intervention

G. Response/Follow-Up

-Missing minor measurements
 -Missing one of several minor measurements used to assess response and scans

H. Data Quality

-Unacceptable level of missing documentation
 -Missing charts
 -Repetitive failure to obtain protocol specified laboratory tests or diagnostic studies
 -Frequent inaccuracies or errors in submitted data

H. Data Quality

- Acceptable level of missing documentation with explanation
 - Minor and sporadic missing tests
 - Few errors in submitted data

I. Regulatory Requirements

-Unacceptable level of missing documentation in Regulatory Binder
 - Failure to comply with Institutional Review Board (IRB) approval and reapproval guidelines, including lapsed or expired annual continuing reviews, inappropriate use of less than full-board review and approval and improper review of appropriate amendments or revisions (i.e. subject entered prior to IRB approval.)

I. Regulatory Requirements

- Few missing documents in Regulatory Binder

