TrialNet Clinical Research Network

Audit Guidelines

October 16, 2008
Revised March 13, 2009
Revised March 27, 2009
Revised April 1, 2014
Administrative Update March 23, 2015

INTRODUCTION

The TrialNet Data and Technology Coordinating Center (TNCC) audit site visit guidelines are in accordance with the NIH NCI-CTMB Guidelines for monitoring of clinical trials for cooperative groups. The current guidelines are available at online.

COMPONENTS OF AN AUDIT SITE VISIT

- Subject case records
- Pharmacy operations and IND accountability, if applicable
- Regulatory compliance – IRB documentation and informed consent content

Electronic Regulatory Binder

In November of 2013, TrialNet implemented an electronic regulatory binder which allows for centralized organization of all regulatory documents including: essential documents, ethics board approvals, and site certifications. Ongoing audit of regulatory files may be conducted remotely.

SELECTION OF INSTITUTIONS/INVESTIGATORS

Observational Studies:

Observational studies are not routinely audited; special audits may be scheduled as needed.

Intervention Studies:

All TrialNet intervention studies will be audited. An initial audit will be conducted within 12 months of the first, and prior to the 5th, subject randomized to each intervention protocol. Routine audits will recur each calendar year. Audit frequency may be adjusted based on enrollment and study activity at each site.

If audit findings require follow-up to assess resolution of problems identified at a previous audit, a re-audit may be conducted (usually at 3-6 months after a routine audit or sufficient subject accrual). If the re-audit findings are acceptable, the next full audit will be scheduled according to the annual schedule.

AUDIT TEAMS

The auditor(s) will be selected by the TNCC and will be suitably qualified for the types of studies being audited. They will be knowledgeable about clinical trials methodology, NIH policies, and Federal regulations.

Local IRB representatives may observe the audit.

An NIH representative or other members appointed by the TrialNet Executive Committee may elect to be present at an audit to monitor the audit process.

ARRANGING THE AUDIT

An audit date mutually convenient to the audit team and the site will be selected. Clinical Centers will be notified at the confirmation of applicable Affiliate site audits.

A list of announced cases will be sent to the site approximately 14 days in advance of the audit to allow time for record preparation.

The Principal Investigator and a research coordinator at the institution being audited- who is familiar with the selected cases- must be available on the date(s) selected.

The length of an audit depends on the number of cases being reviewed and which areas will be audited (i.e. pharmacy, regulatory compliance, IRB). Audits will usually last between a minimum of 4 hours and a maximum of 2 days.

The site is responsible for ensuring that all relevant materials are available for review at the time of the audit.

SELECTION OF CASES

The TNCC will select all cases for all audits.
Approximately 10% of the total cases accrued at the site on TrialNet intervention studies – with a minimum of 5 and a maximum at auditor discretion - will be audited; if less than 5 subjects have been accrued at the site, then all cases will be audited.

Following the initial audit, routine audits will include a minimum of one unannounced case (as applicable at sites with greater than 5 subjects enrolled). Additional unannounced cases may be selected at the time of the audit visit. Unannounced cases may have a limited audit consisting at a minimum of informed consent and eligibility. If the unannounced cases only receive a limited review, then these cases do not count towards the minimum of 10%.

If selected cases have been previously audited, then follow-up to previous audit findings and data collected since the previous case audit will be reviewed. Selected cases are typically those accrued since previous audit; however, any case is subject to audit.

PREPARATION BY THE INSTITUTION BEING AUDITED

The site is required to provide adequate and accurate documentation of study conduct. Source documents should be labeled to correspond with subject identifiers and date of collection. A member of the research team should be available to answer questions from the audit team for the duration of the audit site visit.

Items that should be provided at the audit include:

- Orientation by the site staff to the organization of the site files
- Suitable location for auditors to conduct their review
- Original source documents for each subject being audited
- All subject consent forms
- Documentation of IRB approval for all protocols being audited
  Including: original protocol approval, all amendment approvals, and annual re-approval
- Most current copy of each protocol with all addenda
- A visit to the pharmacy should be scheduled for audits of studies utilizing drug(s) dispensed by a pharmacy at the site; drug logs should be available for review
- If the drug(s) is not dispensed by a pharmacy at the site but by the study team, the drug ordering, handling and storage procedures must be shown to the audit team.

REQUIRED DOCUMENTS

The TrialNet site is expected to have study regulatory documentation with the following information:

Essential documents	• Principal Investigator and sub-investigators' Curriculum vitae • Principal Investigator 1572, if applicable • Proof of Human Subject Protection education training for PI and all research staff handling subject data • Site Delegation Log • Letters of initial and continuing IRB approval • IRB committee composition (roster) • Required regulatory authority's(ies') authorization/approval

	• Normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) that are locally obtained • Certification/accreditation for medical/laboratory/technical procedures/tests at start of the study and updates during the conduct of the study for local labs. • Important sponsor and/or TNCC correspondence including: letters, meeting notes, notes of telephone calls • Subject identification list – list of all subjects entered on the study with their sequence number • Subject screening / identification logs, as applicable
Original IRB submission	• Current Protocol • Advertisement(s) to recruit subjects • Informed consent • Any other written information provided to subjects • Study agent Investigator's Brochure or package insert (if request by IRB for submission) • Case report forms (if request by IRB for submission)
Protocol amendment submission	• Amended protocol • Amended informed consent • Any other amended written information provided to subjects • Amended advertisement(s) • Amended case report forms (if request by IRB for submission)
All IRB correspondence	• Annual renewal/continuing reviews • Updates to Investigator's Brochure • Adverse event reporting • Acknowledgement of DSMB reports
Study agent documentation	• Receipts sent with shipment of study agent • Study agent accountability logs that reflect log in of study agent shipments • Study agent accountability logs that reflect each time study agent is dispensed • Study agent accountability logs that reflect return or destruction of unused study agent • Sample of label(s) attached to investigational product container(s) (what the subject sees) • Procedures for unbinding trial, if applicable • Master randomization list, if applicable

The TrialNet site is expected to have source documents to support data points on CRFs:

Acceptable source documentation may include, but is not limited to:	• Laboratory results • Participant Questionnaires • Progress notes • Medication records • Medical records • Notes to file • TrialNet Assessment Tools Subject diaries and/or calendars • Demographic forms

Good standard of practice for source documentation includes:

- Subject identifier information legible on all documents
- All entries are legible and signed by staff
- All entries are made in ink or are typewritten

- Data corrections as follows:
    - Do not ablate incorrect information. Use a strike through so that original information is still legible
    - Write the date that the document is changed
    - Include initials of the person making the change
    - If corrected information cannot be inserted so it is legible, insert an addendum page with the correction
    - Reports officially issued by a department such as radiology or pathology may only be changed by that department. Changes must be reflected in an officially issued amended report
    - Documentation with erasures or use of correction tape/fluid is not acceptable

RECORD RETENTION

IRB records (45 CFR 46.115(b) and 21 CFR 56.115)

The records required by this policy shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research. All records shall be accessible for inspection and copying by authorized representatives of the department or agency at reasonable times and in a reasonable manner.

Study agent records (21 CFR 312.57(c), 312.62(c))

A sponsor shall retain the records and reports required by this part for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigation use is discontinued and FDA has been so notified.

DATA RECONCILIATION

Auditors will review source documentation and compare it to data submitted on case report forms. Auditors will identify any discrepancies found between source documentation and case report forms to the TrialNet study site.

DATA DELINQUENCY

The TNCC will monitor data delinquency on an ongoing basis. Investigators will be queried for missing data forms that are not received within 30 days of the due date. The rate of data delinquency will be reviewed at the time of audit. Persistent data delinquency may be considered a deficiency.

AUDIT FINDINGS

A summary of audit findings will be discussed during an exit interview conducted by the audit team leader with the TrialNet site Principal Investigator and TrialNet site staff at the conclusion of the audit.

A minor deficiency is deviation that does not affect the outcome and interpretation of the study or jeopardize participant safety or welfare.

A major deficiency is a protocol variance that makes the resulting data questionable or impacts participant safety or welfare. An unacceptable frequency of lesser deficiencies will be treated as a major deficiency in determining the final assessment of a component.

Major deficiencies may include, but are not limited to, the following examples:

IRB Documentation / Study Conduct

Study Approval	• Protocol never approved by IRB • Initial IRB approval documentation missing • Inappropriate initial approval by expedited review [45 CFR 46.110 non-compliance] • Registration and/or treatment of subject prior to full IRB approval (initiation of study related procedures prior to IRB approval) • Registration of subject on protocol during a period of delayed re-approval • Reportable adverse events not reported to IRB • Lack of IRB approval of a protocol amendment

Informed Consent

Omissions of one or more of the elements required by federal regulations 21 CFR 50.25 / 45 CFR 46.116:	• Statement that the study involves research • Explanation of the purposes of the research • Expected duration of the subject's participation • Description of the procedures to be followed • Identification of any procedures which are experimental • Description of any reasonably foreseeable risks or discomforts to the subject • Description of any benefits to the subject or to others which may reasonably be expected from the research • Disclosure of appropriate alternative procedures or courses of treatment (if any) that may be advantageous to the subject • A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records • For research involving more than minimal risk, an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained • An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject • A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled
Additional consent content issues:	• Omissions of multiple risks / side effects as listed in the model informed consent document and/or in subsequent serious adverse event reports • Multiple/cumulative effect of minor problems for a given informed consent

Additional consent process issues:	• Consent form missing • Consent form not signed & dated by subject • No documentation that consent was given and the form was signed by the subject prior to protocol-related studies or procedures • Consent form is missing signatures • Consent form not current IRB-approved version at time of subject enrollment • Consent form not protocol-specific • Consent form doesn't include updates or information as required by IRB • Consent obtained in wrong language

Subject Case Records

Eligibility:	• Protocol specific eligibility requirements not met • Missing source documentation of eligibility requirements
Treatment administration:	• Incorrect study agent/treatment used • Additional agent used which is not permitted by that protocol • Dose calculated incorrectly • Dose modifications not justified • Treatment doses incorrectly administered, calculated or documented
Toxicity:	• Failure to assess toxicities and adverse events according to protocol • Grades, types or dates/duration of serious toxicities inaccurately recorded • Toxicities cannot be substantiated • Follow up procedures necessary to assess toxicities not performed • Failure to report toxicity and adverse events
Data quality:	• Recurrent missing source documentation to support data points on CRFs • Protocol specific procedures not documented • Frequent and recurrent data inaccuracies • Frequent and recurrent errors in submitted data

Pharmacy Operations

Accountability and storage of Study Agent:	• Study agent not stored separately by protocol • Study agents not stored under proper conditions • Study agent stored in insecure dispensing area • Inability to track receipt, use and disposition of study agent per protocol • Study agent used for non-registered subjects • Multiple drug accountability records incomplete and/or not kept up on timely basis • Drug accountability records routinely filled out incorrectly (e.g. Incorrect agent, dose, route of administration, or dates documented)

AUDIT REPORTS

During the audit, forms to document those present at the audit and details of the studies and cases reviewed will be completed and retained in the TrialNet site's file. Any problems or concerns regarding compliance or data validity, accuracy or completeness will be noted. Any suspicion of scientific misconduct will be reported immediately to the NIH.

First Preliminary Report of Audit Findings

This form documents major deficiencies in regulatory, pharmacy or subject cases. It will be e-mailed to Site PI, the NIH, the Clinical Monitoring Subcommittee Chair, the TNCC Principal Investigator and the Site Study Coordinator within 48 hours of the completion of the audit.

Second Report of Audit Findings

A narrative summary letter outlining the findings of the audit will summarize overall findings and determination of the audit. Deficiencies found during the audit will be noted and description of any corrective action requested will be described. The exit interview will be summarized. The audit team's overall assessment of the audit and recommendations to the site will be included with the notation that it is pending NIH and Clinical Monitoring Subcommittee review. This report is due within 10 working days of the audit to the TrialNet site Principal Investigator. This report will also be sent to the NIH, the Clinical Monitoring Subcommittee, the TNCC Principal Investigator, the Site Study Coordinator, and the Clinical Center (as applicable for Affiliate sites). The second report will serve as the final report when no response is required or received.

Final Report of Audit Findings

As necessary, a third and final report will incorporate findings noted in the second report with responses received from the site, the NIH, and the Clinical Monitoring Subcommittee. This will be completed and sent to the TrialNet site Principal Investigator following review by the Clinical Monitoring Subcommittee and resolution to all items requiring follow-up. A copy of the final report will also be sent to the site study coordinator, the NIH, the Clinical Monitoring Subcommittee, the TNCC Principal Investigator, and the Clinical Center (as applicable for Affiliate sites).

FINAL AUDIT DETERMINATION

The following determinations will be assigned to each protocol and component reviewed.

Acceptable	• No deficiencies identified • Few lesser deficiencies identified • Major deficiencies identified that were addressed and/or corrected prior to the audit completion
Acceptable, Needs Follow-Up	• Multiple lesser deficiencies identified • Major deficiencies identified during the audit not corrected and/or addressed prior to audit completion
Unacceptable	• Multiple major deficiencies identified • Single flagrant major deficiency identified • Multiple lesser deficiencies of a recurring nature found in a majority of the subject cases reviewed

Acceptable assessments do not require a response from the investigator. Voluntary responses received within 4 weeks of the date of the second report will be included in the final audit report.

Acceptable, Needs Follow-Up assessments require a written response from the TrialNet site Principal Investigator within 4 weeks of the date of the second report of audit findings. Required time for site response and corrective action may be adjusted as deemed necessary to protect subject safety. The response must address corrective action requested in the audit report. The response must include a corrective plan that details communication, education, staffing changes or other internal measures taken to ensure that deficiencies do not recur. The audit response and corrective action plan will be reviewed by the Clinical Monitoring Subcommittee. A follow-up re-audit may be required.

Unacceptable assessments require a written response from the TrialNet site Principal Investigator within 4 weeks of the receipt of the second preliminary report of audit findings. Required time for site response and corrective action may be adjusted as deemed necessary to protect subject safety. The response must address each specific problem found during the audit and any general problems that were noted. The response must include a corrective plan that details the communication, education, staffing changes or other internal measures taken to ensure that deficiencies do not occur. A copy of the written response and corrective action plan will be forwarded to the TNCC

Principal Investigator, Clinical Monitoring Subcommittee and the NIH in the Final Report. Re-audit is mandatory for all unacceptable assessments.

SPECIAL AUDITS

Special audits may be warranted when there are significant irregularities found through quality control procedures or when allegations of scientific misconduct are made. It is the responsibility of the TNCC to immediately notify the NIH if they learn of any significant irregularities or allegations related to scientific misconduct by a staff member or institution participating in their research program. Selection of auditors to conduct special on-site audits will be made jointly by the NIH, and the TNCC, and a joint course of action will be planned. Other Federal agencies or offices may be invited to participate in a special audit at the discretion of the NIH.

References:

NIH NCI-CTMB Guidelines for monitoring of clinical trials for cooperative groups, as posted online

Required Study Documentation: E6 GCP ICH 8.2

IRB records: 45 CFR 46.115(b) and 21 CFR 56.115

Study agent records: 21 CFR 312.57(c)and21 CFR 312.62(c)

Requirements for Expedited IRB approval: 45 CFR 46.110

Subject recruitment and advertising documentation: 21 CFR 50.20, 50.25, 56.111(a)(3),812.20(b)(11)

Informed Consent Requirements: 21 CFR 50.25 and 45 CFR 46.116