NCI National Clinical Trials Network
a National Cancer Institute program

Clinical Trials Monitoring Branch (CTMB) Audit Guidelines

Introduction To Auditor Training and the NCI CTMB Audit Program

Transcript:

Welcome to the Auditor Training Modules sponsored by the Clinical Trials Monitoring Branch (CTMB) at the National Cancer Institute (NCI). These modules apply to auditors and audits conducted for the NCI National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP).

Purpose of the Auditor Training

To provide:

- An overview of the *NCI Guidelines for Auditing Clinical Trials for the NCI National Clinical Trials Network (NCTN) Program Including NCI Community Oncology Research Program (NCORP) and NCORP Research Bases* (hereafter referred to as the Audit Guidelines), including the latest updates;
- A standardized approach to auditor training; and
- Information on the technology used for audit preparation, conduct, and reporting.

Transcript:

Purpose of the Auditor Training: These modules are not meant to be a remedial course; rather they are meant to: provide an overview on the CTMB Audit Guidelines (the full title of which is *NCI Guidelines for Auditing Clinical Trials for the NCI National Clinical Trials Network (NCTN) Program Including NCI Community Oncology Research Program (NCORP) and NCORP Research Bases*) to ensure all auditors follow them as written; share the latest updates to the Audit Guidelines; and deliver training on the technology used for audit preparation, conduct, and reporting.

Training Information

All auditors must complete this training to be assigned to an audit!

This includes:

- "Staff" auditors and
- "Volunteer" or "ad hoc" auditors.

The training consists of a series of five short modules, and you can complete them all at once or individually over time.

Transcript:

Training Information: All auditors must complete this training. This includes "staff" auditors who are employed by an NCTN Group or other entity performing audits of NCI-sponsored clinical trials, as well as those who are "volunteer" or "ad hoc" auditors. You must complete this training before you can be assigned to an audit.

The training has been broken down into a series of five short modules, so that you have the choice of doing it all at once or over time.

Transcript:

Training Modules: As stated previously, this training currently comprises five separate modules.

This module serves as an introduction to the training and the CTMB audit program. The next three modules cover the three components of an audit, i.e., regulatory documentation review; pharmacy review; and patient case review. Please note that the material shared in these first four modules comes from the Audit Guidelines. Your organization may have more stringent policies or procedures than what is included in the Audit Guidelines, but what is presented here is what is mandated by CTMB. Do follow your organization's procedures.

The fifth module covers the Site Audit Portal (SAP) as well as the process of documenting Targeted Source Data Verification, or TSDV, in the Rave clinical data management application, a part of patient case review. You may not be assigned this fifth module, depending upon which organization you audit for. The primary sources for the content in the TSDV module are two sets of Help Topics content on the CTSU website. The next screen will show the locations for these resource documents.

It is possible that with time, additional modules will be added to this training program. If so, you will be notified by CTMB and/or your organization.

Primary Resources

- *NCI Guidelines for Auditing Clinical Trials for the NCI National Clinical Trials Network (NCTN) Program Including NCI Community Oncology Research Program (NCORP) and NCORP Research Bases*
  - View the CTMB Audit Guidelines
- CTSU Help Topics
  - *Instructions for Navigating the Site Audit Portal*
  - *Using Targeted Source Data Verification (TSDV) in Rave*
  - Both are accessible within the Site Audit Portal screens of the CTSU members website

Transcript:

Primary Resources: As noted previously, the primary sources for the content of this auditor training are the CTMB Audit Guidelines and the Help Topics on the CTSU website.

The CTMB Guidelines are publicly available and can be directly accessed by clicking on the link on the screen.

The audit-related Help Topics are accessible within the Site Audit Portal screens on the CTSU members website.

References to these and other resource documents will be included as appropriate in the upcoming modules.

Now, let's get started.

What is an Audit?

- An audit is a systematic and independent examination of trial-related activities and documents.
- It determines whether the evaluated activities were accurately conducted, recorded, analyzed, and reported according to the protocol, the sponsor's standard operating procedures, Good Clinical Practice (GCP), and the applicable regulatory requirements.
- It ensures compliance with requirements for Sponsor oversight of a clinical trial.

Transcript:

What is an audit? It is a systematic and independent examination of trial-related activities and documents to determine whether the evaluated activities were accurately conducted, recorded, analyzed, and reported according to the protocol, the sponsor's standard operating procedures, Good Clinical Practice (GCP), and the applicable regulatory requirements. Audits ensure that study sponsors such as NCI are compliant with requirements regarding their oversight of clinical trials.

Audits – Main Objective

- Verify study data that could affect the interpretation of the primary study endpoints. (Audit Guidelines, Section 1.3)
- There is no mandate from CTMB to verify 100% of data points for each audited patient case.
  - This is the impetus for TSDV.

Transcript:

As stated in Section 1.3 of the Audit Guidelines, the main objective of auditing is to verify study data that could affect the interpretation of the primary study endpoints. Do notice the wording of "primary study endpoints." Your organization may audit differently, but there is no mandate from CTMB to verify 100% of data points for each audited patient case. This is the impetus for TSDV, wherein only the critical data points are verified.

Audits – Other Purposes

Audits provide opportunity to:

- Detect problems;
- Plan and take corrective action on any problems found; and
- Provide feedback, education, and training.

Transcript:

Audits serve an important purpose beyond what was covered in the previous screen. They provide an opportunity to detect any problems and plan and then take any necessary corrective actions. Furthermore, audits provide an opportunity for the audit team to share feedback and best practices concerning data quality, protocol compliance, and other aspects of quality assurance with the site's research staff.

Audit Location

- Audits may be held on-site, off-site/remote, or via a hybrid approach (combination of on-site and off-site review); this is at the discretion of the auditing organization.
- For on-site and off-site visits, the institution may require auditors to provide/display a government-issued ID.
  - Personally identifiable information (PII) should not be requested of auditors (e.g., birth date, social security number).

Transcript:

Audits may be held on-site, off-site (meaning remotely), or via a hybrid approach, that is, using some combination of on-site and off-site review. Which approach is used is at the discretion of the auditing organization.

For both on-site and off-site visits, the institution being audited may require auditors to provide/display a government-issued ID. That being said, personally identifiable information such as birth date or social security number should not be requested of auditors.

Approaches to Obtaining Remote Access

- Fully or partially remote audits require that there be methods for auditors to access documents at sites, including source documentation related to patient cases.
- If possible, auditors should receive remote access to Electronic Medical Records (EMR) systems at the audited sites.
- This approach is limited to source documentation maintained in their EMR system, so additional methods may be required.

Transcript:

Approaches to obtaining remote access: Fully or partially remote audits require that there be methods for auditors to access documentation at the site, including source documentation related to patient cases. If possible, auditors should receive remote access to Electronic Medical Records (EMR) systems at the audited sites. This approach is limited to source documentation maintained in the EMR system, so additional methods may need to be utilized. The following screen covers one possible method.

More Approaches to Obtaining Remote Access

- Organizations can conduct remote audits using the CTSU Source Document Portal (SDP).
  - Sites upload source documentation to the SDP for auditor review.
  - Currently limited to source documentation related to review of patient cases.
  - Auditors must complete a separate mandatory training prior to accessing uploaded source documentation in the CTSU SDP.
  - The CTSU website contains instructions on how to conduct the patient case portion of a remote audit via the SDP for auditors as well as for site staff.
- The cited approaches are considered secure methods. However, there are other methods that auditing organizations may utilize for review, and which may be used in combination with the methods mentioned above.

Transcript:

More Approaches to Obtaining Remote Access: Organizations have the option to conduct remote audits using the CTSU Source Document Portal (SDP), wherein staff from the audited site upload source documentation into the SDP for auditor review. The use of the SDP is currently limited to source documentation related to review of patient cases. Auditors who will be using the SDP for remote audits must complete a separate mandatory training before being able to access the source documents. Note that the CTSU website contains instructions on how to conduct the patient case portion of a remote audit via the SDP for auditors as well as for site staff.

The cited approaches are considered secure methods. However, there are other methods that auditing organizations may utilize for review, and which may be used in combination with the methods mentioned above.

Timing of Audits

All institutions are required to be audited at least once every 36 months, although audits can take place more frequently.

- The initial audit for a new Network Group Main Member (Tier 1) is due within 18 months of the first enrolled patient at that site.

If a re-audit is required due to an Unacceptable rating, it should be conducted within one year or when sufficient patients have been accrued.

Transcript:

All institutions are required to be audited at least once every 36 months, although audits can take place more frequently.

The initial audit for a new Network Group Main Member (Tier 1) is due within 18 months of the first enrolled patient at that site.

If a re-audit is required due to an Unacceptable rating, it should be conducted within one year or when sufficient patients have been accrued.

Types of Audits

- Routine
- Re-audit: Conducted in response to an Unacceptable rating
- Off-cycle
  - For cause audit
  - Response audit
  - Special protocol audit

Transcript:

Types of Audits: Routine audits are the ones conducted at least every 36 months, to determine the quality of the research at a site.

Re-audits are conducted in response to an Unacceptable rating at a routine audit.

Off-cycle audits are those that do not fit the above definitions, and include for cause audits, response audits, and special protocol audits. These are defined on the next screen.

Off-Cycle Audits

- **For cause audits** may be conducted due to concerns or irregularities found through quality control procedures or when allegations of possible scientific misconduct are made.
- **Response audits** are requested if promising preliminary findings from a particular trial warrant verification of the findings.
- Special protocol audits apply to certain trials that require **more frequent audits** (e.g., registration trials); these are typically conducted by the Lead Protocol Organization (LPO), regardless of which organization was credited for enrollments.

Transcript:

As noted on the previous screen, there are several types of off-cycle audits. For cause audits are those conducted due to concerns or irregularities at a site found through quality control procedures or when allegations of possible scientific misconduct are made.

Response audits are requested if promising preliminary findings from a study trial warrant verification of the findings.

Special protocol audits apply to certain trials that require more frequent audits (e.g., registration trials); these are typically conducted by the Lead Protocol Organization, or LPO, regardless of which organization was credited for enrollments.

In general, all audits, whether routine, for cause, or a different type of off-cycle audit, should be conducted in the same manner.

Composition of the Audit Team

- Audits are typically conducted by a team of auditors representing the credited organization. Most teams will have a Lead Auditor.
- All auditors must have completed this training as well as training in GCP, and must be knowledgeable about clinical trial methodology, NCI policies, and Federal regulations.
- The audit team should be selected based on knowledge of the protocols to be reviewed and knowledge of the organization's audit guidelines and procedures.
- The team must include a physician or other qualified individual to provide medical assessments, evaluate protocol compliance, and conduct an effective exit interview with the responsible Clinical Investigator (CI) and institution staff.
- Audits may also be attended by CTMB staff.

Transcript:

Composition of the Audit Team: Audits are typically conducted by a team of auditors representing the auditing organization, although a small audit could be conducted by a single auditor. Most auditing organizations assign an individual to serve as the Lead Auditor on a given audit. The role of lead auditor can differ by organization, and you should check with yours about what the role entails and how you can expect to interact with that individual (or what it means if you are the lead auditor). All auditors must have completed this training as well as training in GCP. Auditors must also be knowledgeable about clinical trial methodology, NCI policies, and Federal regulations.

The audit team should be selected based on knowledge of the protocols to be reviewed and knowledge of the organization's audit guidelines and procedures. The team must include a physician or other qualified individual to provide medical assessments, evaluate protocol compliance, and conduct an effective exit interview with the Clinical Investigator (CI) and institution staff.

CTMB staff, or an NCI designee, may be present during an audit and must be given full access to all documents and materials present for the audit.

Audit Components

- Review of regulatory documentation
- Review of accountability of investigational agents and pharmacy operations
- Review of patient case records

Transcript:

An audit consists of three main components:

- A regulatory documentation review, in which you assess documentation and conformance to IRB and informed consent content requirements, as well as delegation of tasks logs (DTLs);
- A pharmacy review, in which you assess pharmacy operations, procedures, and documentation on NCI-approved drug logs; and
- Patient case review, in which you assess compliance with the protocol and accuracy of the data submitted.

These will be addressed more thoroughly in the individual modules.

Conducting the Audit

- The CTMB Audit Guidelines mandate reviewing a minimum of **four protocols** at a site, when applicable. Priority review: registration trials, IND trials, multi-modality trials, advanced imaging trials, and preventive/cancer control trials, as well as high accruing trials.
- EMR use: You may be provided with hardcopies from the EMR or given EMR access. If EMR access is provided, a site staff member **must** be present to assist with navigating the system.
- Certain documents related to pharmacy and regulatory review may be reviewed prior to the audit date.
  - Must be included in the preliminary report, the exit interview, and the final audit report.

Transcript:

Conducting the Audit: The CTMB Audit Guidelines mandate reviewing a minimum of four protocols at a site, when applicable. Priority should be given to the following types of trials: registration, IND, multi-modality, advanced imaging, and preventive or cancer control, as well as high-accruing trials.

If an EMR system is used by the site, they may print out hardcopies of source documentation for your review, or they may provide you with EMR access. If EMR access is provided, a site staff member must be present to assist with navigating the system.

Certain documents related to the pharmacy and regulatory components may, at the discretion of the auditing organization, be reviewed prior to the audit date. These may include drug accountability forms, informed consent documents, and Investigational Review Board (IRB) approval documentation, among others. These reviews must be included in the preliminary report, the exit interview, and the final audit report.

Audit Results: Component Ratings

Each of the three components of the audit will independently be rated:

- Acceptable;
- Acceptable Needs Follow-Up; or
- Unacceptable.

The ratings are to be based on deficiencies and non-compliances found *at the time of the audit*.

Transcript:

Audit Results: Component Ratings.

Each component of an audit will be reviewed independently during the visit, and each will receive a rating. These ratings are derived from the number and types of deficiencies found during the audit visit, although the pharmacy component is a bit different, and is based on the number of non-compliant items, not deficiencies per se. Deficiencies are described a bit further on the next screen, and examples of deficiencies and non-compliant items are provided as appropriate in each of the individual component training modules.

During an audit, you and your audit team will assign each of the three components (Regulatory, Pharmacy, and Patient Case Review) a rating of Acceptable, Acceptable needs Follow-Up, or Unacceptable (although do note that the pharmacy review has a couple of additional rating options, those will be covered in the pharmacy review module). These ratings are to be based on findings at the time of the audit, and the definitions of these ratings are explained further in each component's training module.

Audit Results: Major and Lesser Deficiencies

- **Major Deficiency**: a variance from a protocol-specified procedure that makes the resulting data questionable.
- **Lesser Deficiency**: a finding that is judged to not have a significant impact on the outcome or interpretation of the study and is not described above as a major deficiency.

Transcript:

Audit Results: Major and Lesser Deficiencies: As just stated, for two of the three audit components, the audit rating stems from the number and type of deficiencies discovered during the visit.

Most audit findings will fall into the category of major deficiencies or lesser deficiencies. Critical deficiencies are described on the next screen.

A major deficiency is defined as any variance from protocol-specified procedures that makes the resulting data questionable, while a lesser deficiency is any variance that is judged to not have a significant impact on the outcome or interpretation of the study data. Do note that an unacceptable frequency or quantity of lesser deficiencies should be assigned as a major deficiency in determining the final assessment of a component or category.

Again, some examples of these different types of deficiencies will be provided in later modules.

Audit Results: Critical Deficiencies

- **Critical Deficiency**: any condition, practice, process or pattern that adversely affects the rights, safety, or well-being of the patient/study participant and/or the quality and integrity of the data; includes serious violation of safeguards in place to ensure safety of a patient/study participant and/or manipulation and intentional misrepresentation of data.
  - View more information on deficiencies from the European Medicines Agency

Transcript:

Audit Results: Critical Deficiencies: Critical Deficiencies refer to any condition, practice, process, or pattern that adversely affect the rights, safety, or well-being of the patient/study participant and/or the quality and integrity of the data. This category includes, but is not limited to, serious violation of safeguards in place to ensure safety of a patient/study participant and/or manipulation and intentional misrepresentation of data. For more information about critical deficiencies, please use the hyperlink on the screen to view a document from the European Medicines Agency.

A particular type of critical finding is described on the next screen.

Allegations of Research Misconduct

- One type of critical deficiency involves research misconduct, which is defined in 42 CFR 93 as "fabrication, falsification, or plagiarism in proposing, performing, or reviewing research or in reporting results."
- CTMB has created a Guidance for Allegations of Research Misconduct, which describes the process for reporting research misconduct allegations within the NCI extramural program and identifies the policies and procedures to be followed when reporting research misconduct allegations.
  - The guidance document is included in the Audit Guidelines as Appendix 1.
  - View the Guidance for Allegations of Research Misconduct.
- Any findings suggestive of research misconduct should be reported to CTMB immediately at 240-276-6545 or CTMBResearchMisconductConcerns@mail.nih.gov.

Transcript:

One type of critical finding involves research misconduct, which is defined in 42 CFR 93 as "fabrication, falsification, or plagiarism in proposing, performing, or reviewing research or in reporting results."

CTMB has created a document called the Guidance for Allegations of Research Misconduct, which describes the process for reporting research misconduct allegations within the NCI extramural program and identifies the policies and procedures to be followed when reporting research misconduct allegations. This document is available as Appendix 1 to the CTMB Audit Guidelines and can also be accessed directly using the link on the screen.

Any findings suggestive of research misconduct should be reported to CTMB immediately, either by phone at 240-276-6545 or at the email address included on the screen.

Audit Follow-up

- Acceptable Needs Follow-Up or Unacceptable ratings require the site to submit a satisfactory written response and/or Corrective and Preventative Action Plan (CAPA).
- A re-audit will be mandatory if an audit component was Unacceptable (within one year of the audit, or when sufficient patients have been accrued).
- In some circumstances, a re-audit may be designated for a component(s) rated Acceptable Needs Follow-Up.

Transcript:

Audit Follow-Up: If a component is deemed Acceptable Needs Follow-Up or Unacceptable, the site must submit a written response and/or Corrective and Preventative Action Plan (CAPA) to the auditing organization, which along with CTMB will determine if the response or plan is satisfactory.

A re-audit will be mandatory if an audit component was Unacceptable, and it is to be conducted within one year from that audit, or when sufficient patients have been accrued (assuming the site continues to participate in Group or Research Base research).

In some circumstances, a re-audit may be designated for a component or components rated Acceptable Needs Follow-Up.

Conducting the Exit Interview

- An exit interview takes place regardless of whether the audit was conducted on-site or off-site/remotely.
- The responsible CI and their research staff are expected to be present.
- Review preliminary findings, items reviewed offsite, and recommendations.
- Discuss any action items (e.g., CAPAs) and timelines.
- Utilize this opportunity for education, immediate dialogue, feedback, and clarification.

Transcript:

Conducting the Exit Interview: At the end of the audit, your team must conduct an exit interview. The responsible CI and their designated research staff are expected to be present at this meeting.

Your audit team is to review preliminary findings, discuss the items reviewed offsite, and present recommendations. Do discuss any CAPAs needed, and the timeframe for submission, if applicable. Keep in mind that this meeting is an opportunity to educate the staff, have immediate dialogue about the findings, provide feedback, and give and receive clarification about potential findings.

Preliminary Report of Audit Findings

- Due within one business day of audit completion.
- Should include critical and major deficiencies.
- CTMB should be contacted immediately if there are suspicions of intentional misrepresentation of data and/or disregard for regulatory safeguards.
- A revised preliminary report may be submitted within 10 business days of Day 1 of the audit.
- A separate report is required for each audited institution, unless the audit was conducted "as a whole" (i.e., a parent plus their non-auditable child institutions).

Transcript:

Preliminary Report of Audit Findings: Ensure that you report all critical and major findings to your audit team lead in a timely manner, as the preliminary report of audit findings is due to CTMB within one business day of audit completion. Remember that CTMB should be contacted immediately for any suspicions of intentional misrepresentation of data and/or disregard for regulatory safeguards.

A revised preliminary report may be submitted within 10 business days of the audit, if, for instance, a site is able to provide documentation that leads to the deletion of a major deficiency. Note that all deficiencies documented in the initial preliminary report must be included in the final audit report, and any revisions of that initial report would need to be explained in the final report.

A separate report is required for each audited institution, unless the audit was conducted "as a whole," meaning a parent site plus their non-auditable child institutions.

Final Report Submission

- Must be submitted within 70 calendar days of Day 1 of the audit.
- Summarize the items audited, the audit process, the findings from each of the three components of the audit, plus the discussions from the exit interview.
- A separate report is required for each audited institution, unless the audit was conducted "as a whole."

Transcript:

Final Report Submission: The final audit report must be submitted in the CTMB's Audit Information System (AIS) within 70 calendar days of Day 1 of the audit. This institution-specific report should summarize: the items audited, the audit process – for instance, what was reviewed on-site and what was reviewed off-site - the findings at the time of the audit for each of the three components of the audit, plus the discussions at the exit interview. Recommendations from the auditing organization should be noted in the general comments or exit interview sections of the final audit report.

As with the preliminary report, a separate final audit report is required for each audited institution. However, if the audit was conducted 'as a whole' (i.e., a parent and their non-auditable child institutions), just a single final audit report is required.

Module Complete

- You have completed the Introductory module.
- Please exit and return to the course screen in CLASS.
- The module should now show as *Complete*.
- You can revisit completed modules in your My Courses screen.

This and the other training modules in this series were developed for the Clinical Trials Monitoring Branch of the Cancer Therapy Evaluation Program, Division of Cancer Treatment & Diagnosis, National Cancer Institute.
https://ctep.cancer.gov/branches/ctmb

This version produced: March 2023

Transcript:

Module Complete: You have completed the Introductory module. Please exit the module using the X in the upper right corner of this window, and return to the course screen in CLASS, where the module should now show as complete. You can always revisit this and other completed modules in your My Courses screen.

Note, this and the other training modules in this series were developed for the Clinical Trials Monitoring Branch of the Cancer Therapy Evaluation Program, Division of Cancer Treatment & Diagnosis, National Cancer Institute. For more information on the CTMB, visit the URL shown on the screen. This version of this individual module was produced in March 2023.