NCI National Clinical Trials Network
a National Cancer Institute program

Clinical Trials Monitoring Branch (CTMB) Audit Guidelines

Patient Case Review

Transcript:

Clinical Trials Monitoring Branch (CTMB) Audit Guidelines, Patient Case Review. In this module, we will examine the six categories of patient case review and delineate between the different levels of deficiencies. If applicable to your organization, the process for recording your Targeted Source Data Verification (TSDV) in Rave as part of patient case review is presented in a separate module.

Goals of the Patient Case Review

- The goals of the patient case review are to determine whether:
  - Evaluated trial-related activities were conducted according to the protocol.
  - Evaluated data were verified and accurately reported.
- Per the CTMB Audit Guidelines, the major objective of the audit program is to verify study data *that could affect the interpretation of primary study endpoints*.
  - Not necessary to review 100% of data points.
  - Follow your organization's requirements.

Transcript:

The goal of the patient case review, per the CTMB Audit Guidelines, is to determine whether the evaluated trial-related activities were conducted according to protocol and the evaluated data were verified and accurately reported.

Per the CTMB Audit Guidelines, the major objective of the audit program is to verify study data that could affect the interpretation of primary study endpoints. Thus, it is not mandatory to review 100% of the data points for each patient case selected, but instead to focus on those that are related to the primary study endpoints. Each auditing organization may, of course, have more stringent criteria, so you should check with your organization about any additional expectations.

What is Assessed During a Patient Case Review?

There are six categories to evaluate:

- Execution of patient-specific informed consent;
- Eligibility;
- Treatment;
- Disease outcome/response;
- Adverse events (AEs); and
- General data management quality.

Transcript:

What is assessed during a patient case review: While auditing patient cases, you will need to review six categories: patient-specific informed consent, eligibility, treatment, disease outcome/tumor response, adverse events (or AEs) related to treatment, and general data management quality. These will each be discussed in more detail as we proceed through this module.

Special Notes About the Patient Case Review

- Most patient cases reviewed during an audit are announced to the site four to six weeks in advance.
  - These cases should be fully reviewed for all six categories.
- Many audits also feature one or two unannounced cases, disclosed to the site shortly before or at the start of the audit.
  - These cases are often only reviewed for the informed consent and eligibility categories.

Transcript:

Special notes about the patient case review: It should be noted that the majority of patient cases selected for an audit will be announced to the site four to six weeks in advance of the visit, and auditors should review all six of these categories for those announced cases.

That being said, many audit visits also feature one or possibly two unannounced cases, which are disclosed to the site one business day prior to, or on the day of, the audit. These unannounced cases may have a more limited audit, consisting of, at a minimum, review of the informed consent and eligibility categories.

Continue to the next screen for one more special note about the patient case review.

Special Notes About the Patient Case Review (cont.)

- All patient cases, whether they undergo full or limited review, must be documented in the final audit report.
  - If a category is not reviewed for any reason, it should be found Not Reviewed and explained in the audit report.
    - Examples: Unannounced case, patient did not receive treatment, or the auditor ran out of time

Transcript:

All patient cases, whether they undergo full or limited review, must be documented in the final audit report. If a category is not reviewed for any reason, e.g., it was an unannounced case, or the patient never received treatment, or the auditor ran out of time, it should be found Not Reviewed and explained in the audit report.

Classification of Deficiencies

- **Critical Deficiency**: 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 includes manipulation and/or serious violation of safeguards in place to ensure the safety of a patient/study participant and/or intentional misrepresentation of data. Report to CTMB immediately.
- The patient case review includes some specific findings related to informed consent and treatment that are considered critical.

Transcript:

Classification of Deficiencies: Auditors will assess the patient case review category based on the number of critical, major, and lesser deficiencies identified during the audit. As you audit the patient cases, keep these definitions in mind:

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, manipulation and/or serious violation of safeguards in place to ensure safety of a patient/study participant and/or intentional misrepresentation of data. Critical deficiencies must be reported to the CTMB immediately.

In all six categories of the patient case review, any finding that meets the definition of a critical finding must be reported as a critical deficiency. However, a few categories (namely, patient-specific informed consent and treatment) have additional findings that are considered critical; they are referenced in later slides.

Classification of Deficiencies (cont.)

- **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. An unacceptable frequency or quantity of lesser deficiencies should be assigned as a major deficiency.

Transcript:

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. 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.

Possible Scientific Misconduct

Data irregularities that raise any suspicion of intentional misrepresentation of data and/or any disregard for regulatory safeguards in any component of an audit (or through any other quality control procedures), must *immediately be* reported to the CTMB by telephone at 240/276-6545 by the auditing organization.

Note that the irregularity/misrepresentation/disregard does **not** need to be proven prior to reporting it; a reasonable level of suspicion suffices. Also, follow your own organization's procedures for this situation.

Any finding of scientific misconduct is considered a critical deficiency.

Transcript:

Possible scientific misconduct: This content on possible scientific misconduct was initially presented in the introductory module but is repeated here because it comes up most often (although not always) in the patient case review portion of an audit.

Data irregularities that raise any suspicion of intentional misrepresentation of data, and/or any disregard for regulatory safeguards in any component of an audit (or through any other quality control procedures), must immediately be reported to the CTMB by telephone at 240/276-6545 by the auditing organization. Note that the irregularity, misrepresentation, or disregard does not need to be proven prior to reporting it; a reasonable level of suspicion suffices. Also, follow your own organization's procedures for this situation.

Any finding of scientific misconduct is considered a critical deficiency.

Audit Tool for Patient Case Review

Location of the Patient Case Audit Worksheet, which lists deficiencies by category:

- On the CTEP/CTMB website, posted as Appendix 4 of the CTMB Audit Guidelines (under the link to the Guidelines themselves)
  - View the Patient Case Audit Worksheet
- From a tab in the CTMB Audit Information System (CTMB-AIS); under *Templates & Worksheets*

Transcript:

Audit tool for patient case review: The CTMB provides a listing of critical and major deficiencies in each of the categories to assist you during the patient case review. You can find the Patient Case Audit Worksheet posted as Appendix 4 of the CTMB Audit Guidelines, along with the Audit Guidelines themselves, on the CTEP/CTMB website, as well as directly by clicking on the hyperlink shown on the screen.

For those with access, this audit tool is also located under the Templates and Worksheets tab in the CTMB-AIS. It is helpful to keep a copy of this audit tool nearby, either in hardcopy or electronically, for reference during your patient case reviews.

Now let's go over each of the six categories included in the patient case review, starting with informed consent on the next screen.

Informed Consent

Confirm that:

- The informed consent *process* was documented in the patient's chart, and the consent form *document* is available;
- The patient signed and dated the consent document prior to study registration/enrollment; and
- The correct version of the investigational review board (IRB)-approved consent document was used, and the consent form does not contain any changes not approved by the CIRB/IRB.

Transcript:

Informed consent: These are some of the items to confirm while reviewing a patient-specific signed informed consent. Deviations from these would be considered major deficiencies.

Ensure that the informed consent process was documented in the patient's chart, and that the consent form document is available. Check to make sure that the patient signed and dated the consent document prior to study registration/enrollment. Confirm that the correct version of the institutional review board (IRB)-approved consent document was used, and that the consent form does not contain any changes not approved by the CIRB/IRB.

Items to review for patient-specific informed consent continue on the next screen.

Informed Consent (cont.)

Also confirm that:

- When applicable, the translated consent or short form was available and signed and dated by a non-English-speaking patient;
- The consent form includes updates or information required by the IRB (e.g., initials, witness);
- All required signatures are present;
- Consent for ancillary/advanced imaging studies was executed properly; and
- Any required re-consents have been obtained and documented.

Transcript:

During your review of patient-specific informed consent, also ensure that in the case of a non-English-speaking patient, the translated consent, short form, or other form of translation was available and signed and dated by the patient. For all patients, confirm that the consent form includes updates or information required by the IRB. This may include things like requiring patient initials on every page of the consent form, or the presence/signature of a witness. Make certain that all required signatures are present, and that consents for ancillary and/or advanced imaging studies were executed properly. Finally, confirm that any required re-consents have been obtained and documented. As stated earlier, deviations from these items constitute major deficiencies.

The informed consent category also includes some specific findings that can lead to critical deficiencies; these are covered on the next screen.

Informed Consent – Critical Deficiencies

- Any finding identified before or during the review that meets the definition of a critical finding.
- Consent form document not signed and dated by the patient (or parent/legally authorized representative, if applicable).
- Patient signature cannot be corroborated.
- Consent form is not protocol-specific.

Critical deficiencies must be reported to the CTMB immediately.

Transcript:

Informed consent – Critical deficiencies: These are the critical deficiencies for patient-specific informed consent: any finding that meets the definition of a critical finding; the discovery that a consent form document was not signed and dated by the patient or their legally authorized representative; a finding that the patient's signature cannot be corroborated; or a consent form that is not protocol-specific.

Please recall that critical deficiencies must be reported to the CTMB immediately.

As a reminder, the Patient Case Audit Worksheet provides a list of deficiencies, both critical and major, related to the informed consent category.

Eligibility

Ensure that:

- Source documentation reflects that all eligibility criteria have been met and that all eligibility requirements were obtained within the timelines specified by the protocol.
  - Focus on eligibility-related tests; not all screening or baseline tests.

Transcript:

Eligibility: As you audit a patient case for eligibility, ensure the following; any inability to do so should lead to major deficiencies.

Source documentation reflects that all eligibility criteria have been met as specified by the protocol; this includes all eligibility requirements being obtained within the specified timelines. All required tests to confirm eligibility must have been performed prior to registration.

Note that the focus here is on "eligibility-related tests," not "all screening or baseline tests." For instance, if a PT/ PTT and INR are required at screening and were done out-of-window, but the results are not connected to any determination of eligibility, this would NOT be a major deficiency under the eligibility category. It would be considered a lesser deficiency under the general data management quality category, or under adverse events if applicable.

Continue to the next screen for a few more eligibility-related items to evaluate.

Eligibility (cont.)

Ensure that:

- All documentation is available and confirms eligibility.
  - An exception is a patient deemed ineligible based on laboratory/pathology reports following registration and changes based on a central review of material.
  - Missing documentation must be provided within 10 days to avoid a major deficiency.
- There is no finding meeting the definition of the critical finding.

Transcript:

All documentation must be available and is able to confirm eligibility. If any source documentation is missing, request that the site find and provide it to you within 10 business days of the audit in order to avoid a major deficiency. It is a major deficiency if eligibility criteria were not met, or if eligibility cannot be confirmed. An exception to this is a patient who is deemed ineligible based on laboratory or pathology reports following registration and changes based on central review of material.

There must be no finding meeting the definition of a critical finding.

The Patient Case Audit Worksheet provides a list of deficiencies, both critical and major, related to the eligibility category.

Treatment

Evaluate whether:

- The correct protocol treatment was given in the correct dose, correct order, with the correct timing, and is supported by documentation.
  - A dose deviation or calculation error >10% is a major deficiency; using the incorrect agent, treatment, or intervention is a **critical deficiency**.
- Cycles started on time. Were there any unjustified delays in treatment?

Transcript:

Treatment: It is worth noting that the treatment category, along with the general data management quality category, contributes the majority of deficiencies in a patient case review. Auditors should take care to ensure that the treatment requirements of a study have been met.

As you audit the treatment category of a patient case, consider the following: Evaluate whether the patient received the correct treatment, in the right dose, in the right order, and with the right timing. This must all be supported by documentation. Of note, a dose deviation or calculation error of greater than 10% would be a major deficiency, but not if less than 10%. Importantly, if a patient was given the INCORRECT agent, treatment, or intervention, you must assign a critical deficiency.

Did cycles start on time? An unjustified delay could be a major deficiency.

Continue to the next screen for a few more treatment-related items to evaluate.

Treatment (cont.)

Evaluate whether:

- Dose modifications were done in accordance with the protocol and correctly calculated;
- Any additional agents/treatments/interventions disallowed by the protocol were used; or
- There is any finding that meets the definition of a critical finding.

Transcript:

More items to evaluate as part of the treatment category: If the source documents reveal AEs that mandate a dose modification, was the dose modification applied per protocol? Or conversely, if a dose modification is noted, is there a documented rationale for that, e.g., toxicity, in the source documentation and case report forms (CRFs)? Improperly handled dose modifications constitute a major deficiency.

Use of protocol-forbidden agents/treatments/interventions also constitutes a major deficiency.

In addition to the critical deficiency noted above, note any other finding that meets the definition of a critical finding.

The Patient Case Audit Worksheet provides a list of deficiencies, both critical and major, related to the treatment category.

Note Regarding Treatment

- Review of documentation for how and when treatment is administered should focus on the study/IND agents under investigation (i.e., start/stop times) unless otherwise specified in the protocol.
- Documentation of standard of care drug(s) should include total dose and start/stop dates for prolonged IV infusions of at least 24 hours.

Transcript:

A note regarding the treatment review to keep in mind: Review of documentation for how and when treatment is administered should focus on the study/IND agents under investigation (i.e., start/stop times), unless otherwise specified in the protocol. Documentation of standard of care drug(s) should include total dose and start/stop dates for prolonged IV infusions of at least 24 hours.

Disease Outcome/Response

Ensure that:

- There is accurate documentation of initial sites of involvement;
- Re-evaluation of status of disease was performed according to protocol;
- Protocol-directed response criteria was followed; and
- Claimed response (e.g., partial response or complete response) can be verified.

Transcript:

Disease outcome/response: Disease outcome or response is a primary endpoint of phase 2 and phase 3 studies, and therefore should be reviewed carefully. As you review the disease outcome/response category, ask the following questions:

Is there accurate documentation of the initial sites of involvement? Were any areas of involvement left out without reason? Has re-evaluation of disease status been performed per protocol? Has the response been documented in the CRFs using the protocol-mandated response criteria? On this point, do not go merely by the investigator's mention of response in the clinic notes, as that may be a clinical assessment as opposed to a protocol-directed response assessment. Carefully review the claimed response (e.g., partial response or complete response). Is it correct?

Continue to the next screen for a few more items to evaluate in this category.

Disease Outcome/Response (cont.)

Ensure that:

- Cancer (in a prevention study) or cancer progression (in a treatment study) has been reported appropriately; and
- There is no finding that meets the definition of a critical finding.

Transcript:

A few more questions to ask during your review of disease outcome and response are: If the participant is on a cancer prevention study and cancer occurred, was it reported? If the participant is on a treatment study and cancer progressed, was that reported? Any issues with these examples would be major deficiencies.

Ensure that there is no finding that meets the definition of a critical finding.

The Patient Case Audit Worksheet provides a list of deficiencies related to the disease outcome/response category.

Adverse Events Related to Treatment

Confirm that:

- AEs requiring filing of an expedited AE report or reporting to the lead protocol organization were handled in a timely manner;
- AEs were assessed by the investigator in a timely manner (per protocol);
- Grades, types, or dates/duration of serious adverse events (SAEs) were accurately recorded; and
- AEs can be substantiated.

Transcript:

Adverse events related to treatment: The fifth category of patient case review is adverse events (or AEs) related to treatment. (Note the "related to treatment" aspect of this category. While AEs not related to treatment do not need to be reviewed during an audit per the Guidelines, your organization may have more stringent requirements.)

As you audit this category, confirm that there was no failure or delay in reporting AEs that require filing an expedited AE report or reporting to the lead protocol organization. It must also be confirmed that AEs were assessed by the investigator in a timely manner. Ensure that the grades, types, and dates/durations of serious adverse events (or SAEs) were accurately recorded, and that all AEs can be substantiated.

Continue to the next screen for a few more things to confirm during this part of the review.

Adverse Events Related to Treatment (cont.)

Confirm that:

- Follow-up studies necessary to assess AEs were performed;
- There was no recurrent under- or over-reporting of AEs; and
- There is no finding that meets the definition of a critical finding.

Transcript:

Confirm that any follow-up studies necessary to assess AEs were performed, and that there was no recurrent under- or over-reporting of AEs. Failures in any of these areas would be considered major deficiencies.

Ensure that there is no finding that meets the definition of a critical finding.

The Patient Case Audit Worksheet provides a list of deficiencies related to the adverse event category.

General Data Management Quality

Review cases in their entirety to ensure that:

- Documentation is complete; there should not be recurrent missing documentation.
- Protocol-specified laboratory tests and diagnostic studies (including baseline assessments) and other parameters were performed, reported, and documented.
- Protocol-specified research (e.g., QOLs, research samples) and advanced imaging studies were done and submitted properly.

Transcript:

General data management quality: As stated earlier, general data management quality issues and treatment errors account for the majority of deficiencies in patient case reviews.

During the review of general data management quality, you should review the patient case in its entirety. Ensure that documentation is complete; there should not be recurrent missing documentation. Confirm that protocol-specified laboratory tests and diagnostic studies (including baseline assessments), and other parameters were performed, reported, and documented. Likewise, check to see that protocol-specified research (such as QOLs or research samples) and advanced imaging studies were also done and submitted properly.

Continue to the next screen to see additional elements of the general data management quality review.

General Data Management Quality (cont.)

Ensure that:

- There aren't frequent data inaccuracies or errors in submitted data; data are verifiable.
- Data are redacted when appropriate.
  - Major or lesser depends on the number of instances and type of data.
- Data submission has been timely.
  - Major or lesser depends on extent of issue, type of delinquent forms, phase of the trial, status of patient on the trial, etc.
- There is no finding that meets the definition of a critical finding.

Transcript:

Check to ensure that there aren't frequent data inaccuracies or errors in submitted data, and that data are verifiable. Ensure that data has been redacted when appropriate. Note that the assignment of a major or lesser deficiency due to un-redacted data is dependent on the number of instances and type of the data that were left un-redacted. Also ensure that data submission has been timely. Determining whether lack of timeliness warrants a major or lesser deficiency depends upon the extent of the issue, the type of forms that are delinquent, the phase of the trial, whether the patient is on active treatment or follow-up, etc. Due diligence on the part of the organization's policies and decisions from the Data Quality Working Group should be taken into consideration.

Ensure that there is no finding that meets the definition of a critical finding.

The Patient Case Audit Worksheet provides a list of critical and major deficiencies related to the general data management quality category.

Assessing the Patient Case Review

The auditing organization will assess a patient case review based on the number of lesser, major, and critical deficiencies identified during the visit.

- An **Acceptable** rating may be assessed if the auditor identified:
  - No deficiencies, and no follow-up required;
  - Few lesser deficiencies, with no follow-up requested; or
  - A major deficiency that was addressed and corrected **prior to being notified of the audit** (with a written and dated CAPA), and no further action is required (check with CTMB if the deficiency is associated with a safety concern).

Transcript:

Assessing the patient case review: The auditing organization will assess a patient case review based on the number of lesser, major, and critical deficiencies identified during the visit.

An Acceptable rating may be assessed if the auditor identified: no deficiencies and no follow-up is required; few lesser deficiencies, with no follow-up requested; or a major deficiency that was addressed and corrected prior to being notified of the audit (with a written and dated CAPA) and no further action is required (check with CTMB if the deficiency is associated with a safety concern).

Assessing the Patient Case Review (cont.)

- A rating of **Acceptable Needs Follow-up** must be assessed if the auditor identified:
  - Any major deficiency that was **not** corrected and/or addressed **prior** to the audit; or
  - Multiple lesser deficiencies.
- A rating of **Unacceptable** must be assessed if the auditor identified:
  - A single critical deficiency;
  - Multiple major deficiencies; or
  - Multiple lesser deficiencies of a recurring nature found in most of the patient cases reviewed.

Transcript:

A rating of Acceptable Needs Follow-up must be assessed if the auditor identified: any major deficiency that was not corrected and/or addressed prior to the audit; or multiple lesser deficiencies.

A rating of Unacceptable must be assessed if the auditor identified: a single critical deficiency; multiple major deficiencies; or multiple lesser deficiencies of a recurring nature found in most of the patient cases reviewed.

Module Complete

- You have completed the Patient Case Review 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 Patient Case Review module. Please exit the module using the X in the upper right corner of this window and return to the course screen in the Learning Management System, where the module should now show as completed. 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.