NCI National Clinical Trials Network
a National Cancer Institute program

Clinical Trials Monitoring Branch (CTMB) Audit Guidelines

Regulatory Documentation Review

Transcript:

Clinical Trials Monitoring Branch (or CTMB) Audit Guidelines, Regulatory Documentation Review. In this module, we will examine the three main categories of regulatory review, reveal differences for sites that utilize the National Cancer Institute Central Institutional Review Board (NCI CIRB), and provide some examples of critical, major and lesser deficiencies.

Goals of the Regulatory Documentation Review

Assess these regulatory aspects at the institution (Note: protocols with no patient enrollment are not required to be selected for audit):

- Documentation and conformance to Institutional Review Board (IRB) requirements.
  - Review initial approvals, amendment approvals, re-approvals, safety updates.
- Conformance to informed consent content (ICC) requirements.
  - Do a comparison between the local informed consent document (ICD) and the model ICD, ensure that required elements are included.

Transcript:

The goal of the regulatory documentation review is to assess the institution's conformance to various regulatory requirements, and this is done by looking at three categories of documentation. Do note that protocols with no patient enrollment at the site are not required to be selected for audit.

The first category involves ensuring compliance with Institutional Review Board (IRB) requirements, which are assessed by reviewing initial approvals, amendment approvals, re-approvals, safety updates, etc.

The second category involves confirming compliance with informed consent content (ICC) requirements, which are assessed by reviewing local informed consent documents (ICDs), comparing them to the NCI model consent form, and ensuring that required elements are included.

Goals of the Regulatory Documentation Review (cont.)

- Compliance with requirements related to the Delegation of Tasks Log (DTL), when applicable.
  - Review the DTLs and ensure they correspond with clinical site staff involved in the audited studies.

Your organization may conduct much of the regulatory review off-site, prior to the audit. In that case, the site(s) will submit documents such as IRB approvals, local informed consent templates, and DTLs for review as instructed in advance of the visit.

Transcript:

Finally, the third category involves confirming compliance with requirements related to the use of delegation of tasks logs (DTLs) when required for a given study. This is done by reviewing the DTLs and ensuring they correspond with clinical site staff involved in the conduct of the study or studies in question. Each of these areas will be reviewed in more detail as we proceed through this module.

By the way, your organization may conduct much of the regulatory review off-site, prior to the audit. In that case, your organization will request, and the site or sites will submit, documents such as IRB approvals, local informed consent templates, and DTLs for review as instructed in advance of the visit.

Classification of Deficiency Types

- **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 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.

Transcript:

Classification of Deficiency Types: As you audit the regulatory component, keep these definitions of critical, major, and lesser deficiencies in mind:

Critical deficiencies refer to any condition, practice, process, or pattern that adversely affects the rights, safety, or well-being of the patient or 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 the safety of a patient or study participant and/or intentional misrepresentation of data. Critical deficiencies must be reported to CTMB immediately.

Classification of Deficiency Types (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.

Examples of findings that fit into these categories will be described as we go along.

Audit Tool for Regulatory Documentation Review

Location of the Regulatory Documentation Audit Worksheet, which lists deficiencies by category:

- On the CTEP/CTMB website, posted as Appendix 2 of the CTMB Audit Guidelines (under the link to the Guidelines themselves)
  - View the Regulatory Documentation Audit Worksheet
- From a tab in the CTMB Audit Information System (CTMB-AIS); under *Templates & Worksheets*

Transcript:

Audit Tool for Regulatory Documentation Review: The CTMB provides a listing of lesser, major, and critical deficiencies to assist you during the regulatory documentation review.

You can find the Regulatory Documentation Audit Worksheet posted as Appendix 2 of the CTMB Audit Guidelines, on the CTEP/CTMB website, along with the Audit Guidelines themselves, as well as by clicking on the direct link to the Regulatory Documentation Audit Worksheet 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 regulatory reviews.

Notes Regarding Review of IRB Approvals

- The CTMB guidelines denote the minimum requirements for review. For instance, you are not mandated to audit IRB approval of editorial- or administrative-only amendments. However, your organization may choose to do a more stringent review.
- Any findings identified before or during the regulatory review that meet the definition of a critical finding as defined in Section 5.1 of the Audit Guidelines must be reported to CTMB immediately.

Transcript:

Notes Regarding Review of IRB Approvals: As you audit, keep this in mind about the review of IRB approvals:

The CTMB guidelines denote the minimum requirements for review. For instance, you are not mandated to audit IRB approval of editorial- or administrative-only amendments. However, your organization may choose to do a more stringent review. Please note that any regulatory findings before or during the audit that meet the definition of a critical deficiency as defined in Section 5.1 of the Audit Guidelines must be reported immediately to CTMB.

Review of IRB Approvals When a Local IRB is the IRB of Record

For each protocol selected for audit, the following IRB approval items will be reviewed *at a minimum*:

- Full IRB initial approval;
- Full IRB annual re-approval;
- IRB approval for amendments *that affect more than minimal risk*;
- IRB approval or re-approval prior to patient registration;
- Appropriate use and conduct of expedited reviews; and
- Submission of internal and external safety reports.

Transcript:

Review of IRB Approvals When a Local IRB is the IRB of Record: Please note that when it comes to IRB-related documentation, there are some differences between sites using a local IRB versus those using the NCI CIRB as their IRB of record for a given study; the latter are described in a future screen.

For each protocol selected for audit, the following IRB approval items will be reviewed at a minimum: full IRB initial approval, full IRB annual re-approval, IRB approval for amendments that affect more than minimal risk, IRB approval or re-approval prior to patient registration, appropriate use and conduct of expedited reviews, and timely submission of internal and external safety reports.

Dates and Timing of IRB Approvals When a Local IRB is the IRB of Record

Make note of the IRB(s) used by each site, and the dates and timing of each approval. Examples of timing-related deficiencies include:

- Patient registered/treated on study prior to initial approval or during a period of delayed re-approval or temporary suspension (*major deficiency);*
- Delay of protocol re-approval of ≤ 30 calendar days (*lesser deficiency*);
- Delay of protocol re-approval of > 30 calendar days (*major deficiency*);
- Expiration of IRB approval, i.e., re-approval delayed > 1 year (*major deficiency*); and
- Amendments (greater than minimal risk) IRB-approved > 90 calendar days (> 120 calendar days for sites outside of the U.S.) after notification (*major deficiency*).

Transcript:

Dates and Timing of IRB Approvals, When a Local IRB is the IRB of Record: Make note of the IRBs used by each site, including affiliates. Also note the dates and timing of each approval reviewed. Determine when the first patient was registered on that study at that site, and check that the initial IRB approval occurred prior to that date. If it did not, assign a major deficiency.

If continuing review re-approval was delayed up to 30 calendar days, assign a lesser deficiency; if re-approval was delayed more than 30 calendar days or completely expired, it is a major deficiency.

IRB approval of greater-than-minimal-risk amendments more than 90 calendar days after notification (or 120 calendar days after notification for sites outside of the U.S.) would also constitute a major deficiency.

The Regulatory Documentation Review Worksheet provides a more comprehensive list of deficiencies related to the IRB approvals category.

Safety Reports/Unanticipated Problems When a Local IRB is the IRB of Record

- External:
  - Review a random sample of ≥10% of unanticipated problems, external safety reports, and/or action letters for each protocol selected for the audit.
  - If the IRB does not require submission, need documentation of that policy.
  - If reporting is required, submission to the IRB must be within 90 calendar days of notification. (Note dates.)
- Internal:
  - Review submission of local unanticipated problems.

Transcript:

Safety Reports/Unanticipated Problems When a Local IRB is the IRB of Record: While performing the IRB section of the regulatory assessment, review a random sample of at least 10% of the unanticipated external safety reports for each protocol selected for the audit. If submission is not required by the site's IRB, you need to see documentation of that policy. If reporting is required, submission to the IRB must be within 90 calendar days of notification. (Note that for sites receiving notification via the Cancer Trials Support Unit, or CTSU, the 90-day clock starts on the "effective date" noted in the relevant drug safety notification [DSN] table on the CTSU website; this date corresponds to the date of the CTSU Bi-Monthly Broadcast that included the DSN.) Note the dates of submission and ensure they are within the window.

You must also review local unanticipated problems, and it is a major deficiency if internal reportable adverse events were reported late or not reported to the IRB.

IRB Approval for Sites Using the NCI CIRB

- Look for the approval of the Study-Specific Worksheet (SSW), indicating that the CIRB has approved the site to conduct that study. (*Lesser deficiency if not found.*)
- Ensure that CIRB approval was obtained prior to any patients being registered to the study.
- Sites **do not** have to submit unanticipated external safety reports to the CIRB, as they will already have been submitted by the Lead Protocol Organization (LPO).
- Sites **do** need to report unanticipated local problems, serious non-compliance, and/or continuing non-compliance (per the Office for Human Research Protections i.e., OHRP) to the CIRB.
  - Review the OHRP guidance

Transcript:

IRB Approval for Sites Using the NCI CIRB: There are some differences in the IRB part of the regulatory review for sites that are using the NCI CIRB as their IRB of record for a particular study. These are the minimum items to look for when auditing such a site:

Look for the approval letter from the CIRB to the site clinical investigator for the site's Study-Specific Worksheet (SSW); this is the primary indicator that the CIRB has approved the site to conduct the study and that it is now the IRB of record for the study. This approval must be obtained prior to the site enrolling any patients to the study. It is a lesser deficiency if this document cannot be accessed or located.

Barring any changes to their local context considerations (as noted and approved in the SSW), a site does not need to take any direct action with the CIRB to approve protocol amendments.

With respect to safety reports, sites do not have to submit unanticipated external safety reports to the CIRB, as they will already have been submitted by the Lead Protocol Organization, or LPO. However, unanticipated local problems do need to be reported to the CIRB, as do reports of serious non-compliance and/or continuing non-compliance (as defined by the Office for Human Research Protections, or OHRP). Some examples of these types of reportable problems could include, but are not limited to, enrollment of ineligible participants, as well as incorrect dosing of participants. Per the CIRB Administrator, deficiencies related to these types of issues are common. Failure to report issues such as these, or unanticipated local problems, is a major deficiency.

Review of Informed Consent Content – All Sites

- Review the content of current, local ICDs for at least four variable-type protocols (if four or more protocols will be audited).
- Ensure that the federally-required elements are present, as listed in the Regulatory Documentation Audit Worksheet.
  - If any required elements are missing, it is a major deficiency.
- Confirm that the risks and side effects language matches the NCI-approved model informed consent.

Transcript:

Review of Informed Consent Content for All Sites: The second main area within the regulatory review component of an audit is the review of informed consent content, or ICC. This involves:

Reviewing the content of current, local ICDs for at least four variable-type protocols (if four or more protocols will be audited); ensuring that the federally-required elements are present, as listed in the Regulatory Documentation Audit Worksheet (any missing category would be considered a major deficiency); and confirming that the risks and side effects language matches the NCI model consent.

Review of Informed Consent Content – All Sites (cont.)

- Check that any revisions to the ICD per an amendment or in response to an NCI Action Letter have been made.
- Make certain that any changes made to the ICD were approved by the IRB of record.

Each auditing organization may have additional rules regarding ICD requirements and language.

The Regulatory Documentation Audit Worksheet contains the list of required elements.

Transcript:

Reviewing ICC also involves checking that any revisions to the consent per an amendment or in response to an NCI Action Letter have been made; and making certain that any changes made to the consent document were approved by the IRB of record.

Auditors should recognize that their organization may have additional rules regarding consent requirements and language; please check with them to find out about those. Also, there are some items to note with respect to ICC when auditing sites using the NCI CIRB; they are on the next screen.

Please look over the list of required elements of informed consent listed in the Regulatory Documentation Audit Worksheet.

Review of ICC For Sites Using the NCI CIRB

- Review the CIRB approval of local context information, which is part of the SSW, and ensure that the **only** changes to the site's ICD (from the CIRB-approved version) are those included on the SSW.
- Failure to have the ICD revised when needed (after CIRB amendment approval) and locally implemented within 30 calendar days of notification (i.e., posting on the CTSU website) is a lesser deficiency.

Transcript:

Review of ICC for Sites using the CIRB: As noted previously, there are a couple of items to note when it comes to auditing ICC for sites using the NCI CIRB as their IRB of record.

First, review the CIRB approval of local context information, which is part of the SSW, and ensure that the only changes to the site's ICD (from the CIRB-approved version) are those included on the SSW. According to the CIRB, changes beyond what is included in the SSW are a common finding.

Second, note when any amendment-driven changes to the ICD were implemented, and recognize that failure to have the ICD revised when needed (after CIRB amendment approval) and locally implemented within 30 calendar days of notification (i.e., posting on the CTSU website) is a lesser deficiency.

Delegation Of Tasks Log

- Utilized by a clinical investigator to delegate clinical research duties to their staff for a study, based on training, education, and experience.
- Documents the roles and responsibilities of any individual contributing efforts to a clinical trial.
- One log per site and per protocol, for studies designated by CTMB.

Transcript:

Delegation of Tasks Logs: Due to the nature and complexity of conducting clinical research, a clinical investigator may delegate activities or duties associated with the clinical trial to his or her staff. These duties should be allocated based on training, education, and experience.

To document the roles and responsibilities of any individual contributing efforts to certain clinical trials, a DTL must be maintained by site and by protocol and must be signed by the clinical investigator. CTMB and/or your organization will let you know which protocols require DTLs.

How to Access DTLs

- Can be provided by site staff.
- An organization's audit staff members who are *on the CTSU administrative roster* affiliated with their organization can access the Site DTL Browser screens in the DTL application and view/print DTLs for sites they audit.
- The CTSU recommends that auditors use the **DTL Summary Report,** available under the Action column on the Site DTL Browser (as opposed to using the *View DTL* option). This report provides the task assignments over the history of the DTL at the site (or for selected date parameters).

Transcript:

How to Access DTLs: Auditors can request that site staff access and then print out DTLs. Alternatively, an organization's audit staff members who are *on the CTSU administrative roster* affiliated with their organization can access the Site DTL Browser screens in the DTL application and view or print DTLs for sites they audit. In most cases this means that a Lead Auditor for an organization can access and provide DTLs for the audit team.

The CTSU recommends that auditors use the **DTL Summary Report** which is available under the Action column on the Site DTL Browser (as opposed to using the *View DTL* option). The summary report provides the task assignments over the history of the DTL at the site (or for selected date parameters), so is the best way to compare the DTL with the source documentation over a period of time.

Review of DTLs

The auditor will review the DTLs for the protocols being audited to ensure proper implementation and maintenance.

- The DTL should list anyone who contributes significant trial-related duties and must be kept current; it must also be signed annually.
- Review the enrollment information for the enroller, Rave for the data coordinator, and source documents for healthcare professionals working with the trial. Compare to staff listed on the DTL and ensure the tasks assignments were active at the time they were performed.
- Examples of major deficiencies include trial-related duties being performed by an individual not listed on the DTL, staff performing duties not assigned to them, or performing study-related activities without an approved DTL. (See the DTL list of deficiencies in the Regulatory Documentation Audit Worksheet for a full list.)

Transcript:

Review of Delegation of Tasks Logs, DTLs: Your role as the auditor is to review the logs to ensure appropriate implementation and maintenance.

The DTL should list anyone who contributes significant trial-related duties and must be kept current with any staff changes; it must be signed annually. To audit this category, review the enrollment information for the name of the enroller; review Rave for the data coordinator's name; and review source documentation for the names of healthcare professionals working with this trial and patient. Compare these names to the entries on the DTL and ensure that the task assignments were active at the time they were performed.

Examples of major deficiencies include a finding that trial-related duties are being performed by an individual not listed on the DTL, staff are performing duties not assigned to them, or performing study-related activities without an approved DTL. See the DTL list of deficiencies in the Regulatory Documentation Audit Worksheet for a full list.

Assessing the Regulatory Review

The auditing organization will assess the regulatory 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 and no follow-up being requested; or
  - A major deficiency that was addressed and corrected **prior to being notified of the audit** (with a written and dated Corrective and Preventative Action Plan [CAPA]) and no further action is required. (Check with CTMB if the deficiency is associated with a safety concern.)

Transcript:

Assessing the Regulatory Review: The auditing organization will assess the regulatory 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 and no follow-up being requested; or a major deficiency that was addressed and corrected prior to being notified of the audit (with a written and dated Corrective and Preventative Action Plan [CAPA]) and no further action is required. (Check with CTMB if the deficiency is associated with a safety concern.)

Assessing the Regulatory 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 protocols or ICDs 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 protocols or informed consent documents reviewed.

Module Complete

- You have completed the Regulatory 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 Regulatory Review 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 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 for the CTMB home page shown on the screen. This version of this individual module was produced in March 2023.