NCI/DCTD/CTEP/CTMB

Summary of Changes to the CTMB Audit Guidelines

Revised: August 2017

[Effective: 6 September 2017]

Information related to the Summary of Changes table:

- Italicized text in the enclosed table, under the 'New/Current Text' (Added/Revised) column, represents an explanation of the addition or revision; it is not a representation of the actual text in the audit guidelines.
- Editorial revisions throughout the document that did not change the meaning are not outlined in the enclosed table.

Summary of Changes to the CTMB Audit Guidelines (6 September 2017)

Item #	Section	Previous Text	New/Current Text (Added/Revised)
1	Document Name	[Title] NCI Guidelines for Auditing Clinical Trials for the NCI National Clinical Trials Network (NCTN) Program, Community Clinical Oncology Program (CCOP)/NCI Community Oncology Research Program (NCORP) and Research Bases	**[Revised]** [Revised Title] 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
2	List of Appendices	[List of Appendices] Appendix 1 - Roster and Auditing Activity Appendix 2 - Audit Tool/Checklist – Listing of Audit Deficiencies Appendix 3 - Preliminary Report - Templates Appendix 4 - Final Audit Report - Templates	**[Revised]** [Revised List of Appendices] Appendix 1 – Audit Tool for Regulatory Documentation Review Appendix 2 – Audit Tool for Pharmacy Review Appendix 3 – Audit Tool for Patient Case Review
3	Section 1.2	[Section 1.2 Background] [Background - end of 5th paragraph including bullets] The CTSU's role with auditing was also modified with the implementation of the NCI NCTN. Its auditing activities are primarily limited to: • Provision of qualified auditors for non-endorsed accrual for legacy trials that may have transitioned from the former Cooperative Group program to the new NCTN (until approximately 2016). • Provision of IT system integrations to support roster and limited audit activities. • Assisting with teleconferences or meetings between NCI and Network Group staff to discuss new policies and procedures to improve auditing activities.	**[Revised]** [Revised Text] The CTSU's role in CTEP's Quality Assurance program is constantly evolving, currently their activities primarily include: • Establishing the ability to electronically capture Source Data Verification (SDV) activity as part of the auditing of patient cases • Provision of IT system integrations to support roster and limited audit activities • Coordinating activities of multi-Group audits for the Single Site Audit initiative • Posting of regulatory documentation in RSS (Regulatory Support System) • Assisting with teleconferences or meetings between NCI and Network Group staff to discuss new policies and procedures
4	Section 1.3	[Section 1.3 Purpose and Objectives] [Purpose and Objectives – last paragraph] In order for NCI to review the Group's compliance with this requirement, each Network Group must conduct a comprehensive review of all its current membership. This includes all main members, affiliates, sub affiliates, CCOP/NCORPs, CCOP/NCORP components, NCORP sub components, LAPS main members, LAPS IC, LAPS A, LAPS AA, LAPS SA, and LAPS ASA; and their audit activity. A listing of all	**[Revised]** [Revised Text] The major objective of the audit program used by the Network Groups is to verify study data that could affect the interpretation of primary study endpoints. This is done through independent verification of study data with source documents. 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' require all institutions to be audited at least once every 36

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		institutions, regardless of membership type and their CTEP site code must be provided in tabular format by each Network Group in the competing or non-competing continuation application. A separate table must be provided for each Membership Study Type (eg, Treatment, Prevention). This table must include: (1) start date of affiliation or withdrawn date with the Group; (2) membership role, (3) parent CTEP site code of each institution, (4) auditable flag, (5) status of institution, (6) date of the institution's last audit date, (7) the projected accrual for the upcoming year; (8) accrual for the immediate preceding 48 months (4 years) broken down by year; and (9) the projected date (month/year) of the next proposed audit. This requirement is part of the NCI National Clinical Trials Network Group Program guidelines. A template of the 'Roster and Auditing Activity' can be found under Appendix 1.	months. To ensure the Group's compliance with this requirement, CTMB annually reviews all current membership institutions for each Group. This includes review of all main members, affiliates, sub affiliates, LAPS main members, LAPS affiliates, LAPS sub affiliates, LAPS integrated components, LAPS aligned affiliates, LAPS aligned sub affiliates, NCORPs, NCORP components, and NCORP sub components and audit activity for each.
5	Section 2.2.2.4	[Section 6.5 Clinical Trials Monitoring Branch – Audit Information System (CTMB-AIS)] The CTMB has designed an information system which permits the on-line submission and collection of all data related to audits and audit findings. This includes scheduling and tracking audits, transmission of final audit reports, and collection and tracking of follow-up responses to audit findings, and capturing documentation for the review of preliminary reports, final audit reports and follow-up responses. The system allows restricted access to the stored data and will keep a record of any data changes. The CTMB-AIS can be accessed after providing a username and password at: https://ctepcore.nci.nih.gov/CTMBWeb/	**[Revised]** [Revised Text] The CTMB has designed an information system which permits the on-line submission and collection of all data related to audits and audit findings. This includes scheduling and tracking audits, transmission of final audit reports, and collection and tracking of follow-up responses to audit findings, and capturing documentation for the review of preliminary reports, final audit reports and follow-up responses. The system allows restricted access to the stored data and will keep a record of any data changes. The CTMB-AIS can be accessed after providing a username and password at:https://ctepcore.nci.nih.gov/CTMBWeb/
6	2.3	[Section 2.3 Community Clinical Oncology Program (CCOP)/NCI Community Oncology Research Program (NCORP)] The CCOP/NCORP utilizes the same quality assurance programs as those used by the Network Groups. The overall purpose is to ensure that clinical trials conducted by the NCORP and NCORP components adhere to the federal regulations, GCP and the CTMB audit guidelines. A CCOP/NCORP may have a Network Group or a Cancer	**[Revised]** [Revised Header] [Section 2.3 NCI Community Oncology Research Program (NCORP)] [Revised Text] The NCORP utilizes the same quality assurance programs as those used by the Network Groups. The overall purpose is to ensure that clinical trials conducted by the NCORP and NCORP components adhere to the federal regulations, GCP and the CTMB audit guidelines. A NCORP may have a Network Group or a Cancer Center serve as its Research Base.

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		Center serve as its Research Base. A CCOP may have affiliates and components, however in this document and in the CTMB-AIS, they are referred to as CCOP components. An NCORP will have components and sub components per the Division of Cancer Prevention (DCP).	
7	2.3.1	[Section 2.3.1. - Network Groups] Network Groups follow the same monitoring procedures for CCOP/NCORPs and CCOP/NCORP components as they follow for their other members.	**[Revised]** [Revised Header] Section 2.3.1 NCORP Research Bases of the Network Groups [Revised Text] Group members including all institutions as part of the NCORPs must follow the same mechanisms and processes as the other Group member institutions (i.e., LAPS, Main Members, Affiliates, etc.). monitoring procedures. They must be audited per the CTMB audit guidelines.
8	2.4 2.4.1 2.4.2	[Section 2.4 Cancer Trials Support Unit (CTSU)] The CTSU shall provide qualified auditors for non-endorsed accrual for trials in the Endorsement Program under the former NCI Cooperative Group Clinical Trials Program. This program ended July 31, 2013. To accommodate the three year audit cycle, the CTSU provides qualified auditors to assist with auditing non-endorsed cases in legacy trials transitioned to the new NCTN program which is expected to last through 2016.	**[Revised] [Added]** [Revised Text] The CTSU provides an array of support including roster management, regulatory support, patient enrollment, data collection, and posting on CTSU website. Services specifically tailored to auditing activities are: [Added Header] Section 2.4.1 Auditing Patient Cases for Studies in Medidata RAVE [Added Text] A system is utilized by auditors reviewing patient records to electronically record Source Data Verification (SDV) activity directly in Medidata Rave (Rave) for those studies using Rave to manage patient clinical data. A process has also been developed to provide a unified framework, to create a consistent workflow to facilitate pre- and post-SDV activities, and to provide transparency for the site auditing process to meet regulatory requirements. A comprehensive auditor's guide detailing this process for auditors can be found at: https://www.ctsu.org/readfile.aspx?fname=Public/CTSU-SAR-Auditors-UserGuide.pdf. In addition, the CTSU Members' Website Site Audit Portal will provide a gateway into the process for Network Groups/NCORPs and auditors, see link below: https://www.ctsu.org/RAVE/SiteAudit.aspx [Added Header] 2.4.2 Single-Site Audit Initiative (Multi-Group Audits) [Added Text] As part of an initiative between the CTMB and the CTSU, certain sites/ organizations are subject to audit by more than one Network Group at the same time, i.e., on the same date(s).

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			These multi-Group audits are intended to promote more efficient auditing practices, and are conducted in the manner described within these audit guidelines. Sites selected for a multi-Group audit can be Main Member sites, Lead Academic Participating Sites (LAPS), or NCI Community Oncology Research Program (NCORPs) sites, to include affiliates or components as appropriate. The CTSU, CTMB, and the Network Groups/NCORP Research Bases select these sites based on parameters related to accrual, Network Group audit schedules, expected audit duration, and other attributes of the site(s) or organization being audited. The CTSU facilitator for this initiative is responsible for orchestrating the logistics for a multi-group audit before, during and/or after the audit. A CTSU auditor may also assist a Group(s) with the audit or may take on the role of auditor in place of a Group auditor, per the Group's request. See link below for more information related to Multi-Group Audits: https://www.ctsu.org/readfile.aspx? fname= Public/Multi-Group-Audit-Overview.pdf
9	3.1.4.5	[Section 3.1.5 – Other Membership Types] Section 3.1.5.1 NCTN Pediatric Network Group Members Section 3.1.5.2 Sub affiliates/Sub components Section 3.1.6 Non-Member Collaborators	**[Deleted] [Rearranged]** [Deleted Header] Section 3.1.5 Other Membership Types [Rearranged & Renumbered Headers] Section 3.1.4.5 Sub affiliates/Sub components Section 3.1.4.6 NCTN Pediatric Network Group Members Section 3.1.4.7 Non-Member Collaborators *NOTE: The above 'section headers' were rearranged and renumbered, and a few editorial changes were made to the associated text under each section.*
10	3.2	[Section 3.3 Crediting of Accrual] [Crediting of Accrual – 2nd and 3rd paragraphs] Accrual must be credited to the individual institution regardless of their membership type/role that identified a patient/study participant to be consented and registered/ enrolled. Accrual credit for that identified patient/study participant may not be "rolled up" or credited to another institution that is registering this patient/study participant through a central registration or by a LAPS main member, Network Group Main Member, CCOP/NCORP, or any affiliate or CCOP/NCORP component registering for other institutions. Only sub affiliates and sub components may roll their accrual up to their 'linked-parent'. For sub affiliate and sub	**[Revised]** [Revised Text & Section #] [Section 3.2 Crediting of Accrual] Enrollment/accrual is a patient/study participant that has been consented, registered/ enrolled to a study and assigned a patient ID number. Accrual must be credited to the individual institution regardless of their membership type/role that identified a patient/study participant to be consented and registered/ enrolled. The general policy for crediting by institutions in the NCTN is governed by the NCTN guidelines. Institutions should follow the guidelines regarding general policy for accrual crediting. The CTSU will also post the general policy and any CTEP-specific changes for accrual crediting for the NCTN in conjunction with the OPEN system. The audit responsibility for an institution falls to the

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		components, registration/enrollment and the institution credited for the accrual must be captured. The general policy for crediting by institutions in the NCTN is governed by the NCTN guidelines. Institutions should follow the guidelines regarding general policy for accrual crediting. The CTSU will also post the general policy and any CTEP-specific changes for accrual crediting for the NCTN in conjunction with the OPEN system. The audit responsibility for an institution falls to the Network Group or CCOP/NCORP Research Bases that was credited with the registration/enrollment.	Network Group or NCORP Research Bases that was credited with the registration/enrollment.
11	3.3	[Section 3.9 – Non-Auditable Institutions] Non-auditable institutions may include CCOP/NCORP components, LAPS IC(s), sub affiliates, and sub components. An audit conducted for a parent and their non-auditable institutions is considered an audit 'as a whole' (combined). For these types of audits, when there are separate IRBs or pharmacies (ie, receives drug directly from PMB or other sponsors), each IRB or pharmacy must be audited. The CTEP site code, IRB name, and pharmacy location(s) must be captured on the final audit report. Protocols and patient cases must be selected for review from the parent and each non-auditable institution being audited. A single preliminary and single final audit report is required for audits conducted 'as a whole'.	**[Deleted] [Added]** [Deleted Text] Section 3.9 [Revised Header & Header #] [Section 3.3 Auditable and Non-Auditable Institutions] [Added Text] An 'Auditable' institution refers to an institution when an audit is scheduled and conducted as a single institution audit and the audit report will consist of findings only for that specific institution being audited (one final audit report by CTEP Site Code). A Preliminary Report of Audit Findings form is uploaded in the CTMB-AIS by the Group/NCORP Research Base for each audited site(s). <u>Characteristics of an Auditable Institution</u>: • The audit flag for the institution (by Group) is 'yes' • Usually these types of audits are conducted 'on-site'. On occasion, an audit can be conducted 'off-site' if for instance the Network Group/NCORP Research Base is conducting a reaudit of only the regulatory documentation. In this scenario, the audited institution will be required to send the appropriate documentation to the Group/NCORP Research Base location for review. • Auditable institutions may include NCORPs, Main Members, Affiliates, LAPS Main Member and LAPS affiliates. A 'Non-Auditable' institution refers to an institution when an audit is comprised of more than one institution and a single final audit report consists of findings for all the institutions audited (one final audit report for multiple CTEP Site Codes). One Preliminary Report of Audit Findings form is submitted for the institutions audited 'as a whole' (combined).

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			Characteristics of a Non-Auditable Institution: • The audit flag for the institution (by Group) is 'No' • Usually these types of audits are scheduled and conducted at the parent site (see Figure 1 on page 10) and corresponding Tier 2 (and Tier 3) sites being conducted 'off-site'. The scheduling and auditing of multiple sites at a single visit is considered an audit 'as a whole' (or combined). • The final audit report is generated for the parent site, and all audited sites audited are listed CTEP site codes and institution name. Other items related to the Audit Flag: • The Network Group/NCORP Research Base is responsible for designating and/or changing the audit flag for Tier 1 and Tier 2 sites, where applicable. • The audit flag for a Tier 1 and Tier 2 institution within the same NCORP cannot be both set to 'No' for an audit to be scheduled correctly. This rule applies to NCORPs and NCORP components. • The audit flag for Tier 3 institutions must be set to 'no'. The CTMB (in consultation with the Group/NCORP Research Base) may request an on-site audit (and separate final audit report) of a Tier 3 site if there are reasons for concerns. In this scenario, the audit flag would need to temporarily change from 'no' to 'yes' for the audit to be scheduled appropriately. • For audits that include non-auditable institutions, when there are separate IRBs or pharmacies (i.e., receives drug directly from PMB or other sponsors), each IRB and pharmacy must be identified in the final audit report by CTEP site code, IRB name, and pharmacy location(s). Protocols and patient cases must be selected for review from the parent and each non-auditable institution being audited. Note: Section 3.3 does not apply to Special Protocol designations, Pediatric Oncology Group institutions, and other instances when approved by CTEP.
12	3.5	[Section 3.4 - Network Group Main Member Institutions] [Network Group Main Member Institutions – 2nd paragraph] If a main member institution moves to a new location which requires a new CTEP site code and/or a decision is made	**[Revised]** [Revised Header #] Section 3.5 Network Group Main Member Institutions

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		by the NCI's Site Code Committee to change the CTEP site code to a new CTEP site code, the 18 month rule does not apply as long as the institution has been previously audited by the same Group or legacy Group	[Revised Text] The 18 month rule does not apply to an institution that has been previously audited by the same Group or legacy Group. This rule also applies if a main member institution moves to a new location which requires a new CTEP site code and/or a decision is made by CTEP to change to a new site code.
13	3.7	[Section 3.6 – CCOP/NCORP and CCOP/NCORP Components] CCOP/NCORP institutions will be audited within 18 months after entry of the first patient/study participant. If the CCOP/NCORP accrues rapidly, the initial on-site audit should be done sooner than 18 months. Following the initial audit, CCOP/NCORP institutions must be audited at least once every 36 months. For high accruing CCOP/NCORPs and NCORP components, it may be appropriate for the Network Group to audit these institutions on a more frequent interval given the high number of cases for review. A Network Group may utilize one of three audit methods to conduct an audit of its CCOPs/NCORPs, CCOP/NCORP components, and NCORP Sub components: • A separate audit may be conducted for each CCOP/NCORP and CCOP/NCORP component (including NCORP sub components). Separate preliminary and final audit reports must be submitted for the CCOP/NCORP and each CCOP/NCORP component. • One audit may be conducted for the CCOP/NCORP as a whole. Protocols and patient cases must be selected for review from the CCOP/NCORP and each component that has accrual. If the CCOP/NCORP is audited as one entity, only one preliminary and final audit report is required. • A combination of the two above audit methods may be utilized. For combined audits in instances when there are separate IRBs or pharmacies (ie, receives drug directly from PMB or other sponsors), each IRB or pharmacy must be audited and identified (by CTEP site code, IRB name, and pharmacy location) in the final audit report. The final audit report must also identify the patient cases by institution by	**[Revised]** [Revised Header] Section 3.7 NCORP and NCORP Components [Revised Text] NCORP institutions will be audited within 18 months after entry of the first patient/study participant. If the NCORP accrues rapidly, the initial on-site audit should be done sooner than 18 months. Following the initial audit, NCORP institutions must be audited at least once every 36 months. For high accruing NCORPs and NCORP components, it may be appropriate for the Network Group to audit these institutions on a more frequent interval given the high number of cases for review. A Network Group/NCORP Research Base may utilize one of three audit methods to conduct an audit of its NCORPs, NCORP components, and NCORP Sub components (see Section 3.3): Method 1: A separate audit may be conducted for each NCORP and NCORP component (including NCORP sub components). Separate Preliminary of Audit Findings form and a final audit report generated for each institution audited as part of the NCORP. Method 2: One audit may be conducted for the NCORP 'as a whole'. All NCORP component institutions (including their sub components) that have accrued patients since the previous audit may be selected and scheduled to be audited under the NCORP. One Preliminary of Audit Findings form and one final audit report include findings from all audited institutions within the NCORP. Method 3: A combination of the two above audit methods may be utilized. For example, one or more NCORP components that are considered high accruing institutions can be audited separately (Method 1) and the remaining NCORP components audited 'as a whole' (Method 2).

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		entering the applicable CTEP site code for any non-auditable institution (ie, CCOP/NCORP component, NCORP sub component). An "audit" (yes) or "no-audit" (no) flag is included in the CTMB-AIS roster to determine the method chosen by the Network Group or CCOP/NCORP Research Base. The default for this auditable flag is 'yes' (ie, each institution audited separately). The Network Group is responsible for changes to the audit flag for the CCOP/NCORP and CCOP/NCORP components.	
14	3.10		**[Added]** [Added Section Header] 3.10 Special Protocols [Added Text] The auditing policy generally requires that the Network Group credited with the enrollment is responsible for conducting the audit. An exception to this may occur for registration studies, where the Lead Network Group has pre-determined to audit a protocol more frequently, a higher percentage of cases are selected for audit, and access across all institutions without regards to which Network Group is credited. In these circumstances, a special protocol status can be designated within the CTMB-AIS to allow the Lead Network Group access to all patients regardless of which Group is credited with the enrollment. If special circumstances exist to warrant this type of approach, the Network Group may submit a request to CTMB for review and approval.
15	3.12	[Section 3.11 – Special Audits/For Cause Audits] Special audits may be conducted when there are promising preliminary findings that warrant verification of findings. CTEP, a Network Group or a sponsor may request a special audit (Response Audit) and CTEP determines if a special audit is warranted. 'For cause' audits may be warranted when there are concerns or irregularities found through quality control procedures or when allegations of possible scientific misconduct are made. It is the responsibility of the Network Group or CCOP/NCORP Research Base to immediately notify CTMB upon learning of any significant irregularities or allegations related to scientific misconduct by a staff member or institution participating in their	**[Revised]** [Revised Header & Header #] Section 3.12 Off-cycle Audit [Revised Text] Audits may be entered as an 'off-cycle' audit in the CTMB-AIS for the following scenarios: • A Response Audit may be conducted when there are promising preliminary findings that warrant verification of findings. CTEP, a Network Group or a sponsor may request this review type. • A For-Cause Audit may be warranted when there are concerns or irregularities found through quality control procedures or when allegations of possible scientific misconduct are made. • More frequent auditing may also be scheduled, if requested by CTEP/CTMB due to the nature of the study (e.g., Special Protocols, registration trials, etc.).

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		research program. CTMB may coordinate or request that the Group or CCOP/NCORP Research Base coordinate the special audits/'for cause' audits. Selection of auditors to conduct special/'for cause' on-site audits will be made jointly by the NCI, Group, or CCOP/NCORP Research Base, and a joint course of action will be planned. Other federal agencies or offices may be invited to participate in an audit at the discretion of the NCI.	
16	4.1		**[Added]** [Added Section Header] Section 4.1 - CTMB-AIS Generated Notifications/Email [Added Text] The Group/NCORP Research Base Audit Coordinator/designee assigned in the CTMB-AIS receives AIS generated emails related to audits that have not been scheduled per the audit guidelines. The Group/NCORP Research Base Audit Coordinator/designee must provide a response/explanation in writing within 5 business days of receiving the notification. The Group/NCORP Research Base response should be directed to the appropriate CTMB liaison. *NOTE: In prior version, the section for 'Arranging the Audit' was Section 4.1, it has been renumbered as Section 4.2.*
17	4.3	[Section 4.2 Selection of Protocols and Patient Cases] [Selection of Protocols and Patient Cases – 1st paragraph] The statistical, operations, or data management office for the Network Group or CCOP/NCORP Research Base selects the protocols for review. A minimum of three protocols representing studies conducted at the institution must be selected when applicable. Emphasis should be given to the following types of studies: IND, multi-modality, advanced imaging studies, prevention/cancer control trials and potential licensing trials, as well as those with high accrual.	**[Revised] [Added]** [Revised Text] These audit guidelines predominantly focus on intervention trials involving more than minimal risk. The statistical, operations, or data management office for the Network Group/ NCORP Research Base selects the protocols for review. A minimum of <u>four</u> protocols representing studies conducted at the institution must be selected, when applicable. Emphasis should be given to the following types of studies: registration trials, IND, multi-modality, advanced imaging studies, and prevention/cancer control trials, as well as those with high accrual. *NOTE: The above text was revised as a direct result of adding language requiring that the Network Group/Research Base to select a least one patient case to audit for each registration trial (see 'Added Text' below).* [Added Text] In addition to the above criteria, a patient case from every registration trial must be selected for audit. This includes patients enrolled onto a registration trial for every site being

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			audited. Depending on the volume of patients enrolled onto a registration trial, auditing additional patient cases may be required. A listing of clinical trials designated as registration trials can be found at: www.ctsu.org/RAVE/SiteAudit.aspx?nodeKey=11385 [Added Text] In the event of a patient case transfer to another institution (another CTEP site code), it is the 'date of transfer' that the responsibility shifts to the new Clinical Investigator/institution where the patient case resides.
18	4.4	[Section 4.3 Selection of On-site Audit Team] Selection of the on-site audit team should receive special consideration. Auditors should be chosen based on their knowledge of the protocol(s) to be reviewed and of Network Group and CCOP/NCORP Research Base audit guidelines and procedures.	**[Revised] [Added]** [Revised Text] Selection of the on-site audit team should receive special consideration. Auditors should be selected based on auditing experience, knowledge of the federal regulations, GCPs, NCI guidelines and other procedural documents. It is expected that each auditor also be cognizant of the audit guidelines and procedures of the Network Group/Research Base they are affiliated with. All auditors must be registered minimally as an Associate Plus (AP) level in the Registration and Credential Repository (RCR). [Added Text] It is the responsibility of the Network Group/NCORP Research Base scheduling an audit to ensure there is no 'Conflict of Interest (COI)', or potential COI, between the auditor(s) and the institution(s) being audited. Documentation such as an "Auditor Confidentiality Agreement' must be maintained by the Group and readily accessible, if requested.
19	5.0	Section 5.0 – Conducting the Audit [Section 5.0 Conducting the Audit – last paragraph] At the discretion of the Network Group or CCOP/NCORP Research Base, certain documents such as DARFs, informed consent forms and IRB documentation may be reviewed prior to the conduct of the on-site audit. Findings from 'off-site' reviews must be included in the Preliminary Report, discussed at the Exit Interview, and explained in the Final Audit Report which items were reviewed 'off site'. An audit tool/checklist for each of the components can be found under Appendix 2.	**[Revised] [Added]** [Revised Text] At the discretion of the Network Group or NCORP Research Base, certain documents such as regulatory documentation, DARFs, and informed consent forms may be reviewed prior to the conduct of the on-site audit. These documents must be made available to the Group/NCORP Research Base auditors, if requested. [Added Text] Findings from 'off-site' reviews must be included in the Preliminary Report, discussed at the Exit Interview, and detailed in the Final Audit Report which items were reviewed 'off site'. An audit tool for each of the components can be found under Appendix 1, 2 and 3.
20	5.1	Section 5.1 – Assessing Audit Findings [Assessing Audit Findings – 1st paragraph] An audit consists of reviewing and evaluating: (1) documentation	**[Revised] [Added]** [Revised Text] An audit consists of reviewing and evaluating: (1) regulatory documentation including conformance to IRB, informed

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		and conformance to IRB and informed consent requirements, (2) pharmacy operations and use of NCI DARFs, or NCI approved drug logs, and (3) individual patient cases. During the audit, each of these three components will independently be assigned an assessment of either Acceptable; Acceptable Needs Follow-up, or Unacceptable; based on findings at the time of the audit. An inclusive and precise definition of what constitutes an unacceptable finding is difficult to construct. Rather than developing an inclusive quantitative definition, all Network Groups, and CCOP/NCORP Research Bases will use a common set of terms or examples of MAJOR and LESSER deficiencies, a common system for assessing each component of an audit, and a standard audit report format using the Clinical Trials Monitoring Branch - Audit Information System (CTMB-AIS).	consent requirements, and maintenance of a delegation log (if applicable) (2) pharmacy operations and use of NCI DARFs, or NCI approved drug accountability logs, and (3) individual patient cases. During the audit, each of these three components will independently be assigned an assessment of either Acceptable; Acceptable Needs Follow-up, or Unacceptable; based on findings at the time of the audit. An inclusive and precise definition of what constitutes an unacceptable finding is difficult to construct. Rather than developing an inclusive quantitative definition, all Network Groups and NCORP Research Bases will use a common set of terms or examples of Critical, Major and Lesser deficiencies. A common system is utilized for assessing each component of an audit, resulting in a standard format for final audit reports generated in the Clinical Trials Monitoring Branch - Audit Information System (CTMB-AIS). See definitions below: [Added] 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; includes serious violation of safeguards in place to ensure safety of a patient/study participant and/or manipulation and intentional misrepresentation of data (see http://www.ema.europa.eu/ docs/ en_GB/document_library/Other/2014/12/WC500178525.pdf). [Revised Text] Major Deficiency - A variance from protocol-specified procedures or practices that makes the resulting data questionable. *NOTE: The above text was previously under Section 5.4.1*. [Revised Text] Lesser Deficiency - Finding does not have significant impact on the outcome or interpretation of the study and is not described above as a major deficiency. An unacceptable frequency/quantity of lesser deficiencies should be treated as a major deficiency when determining the final assessment of a component. *NOTE: The above text was previously under Section 5.4.2*.
21	5.2 5.4 6.2.1 6.2.2 6.3.2 6.9		[Added] *NOTE: Throughout the many Sections, the term 'Critical' was incorporated into this document. The definition, description as a deficiency type, and reference to critical as it describes actions to be taken were added, where appropriate.* Critical Deficiency is 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; includes

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			serious violation of safeguards in place to ensure safety of a patient/study participant and/or manipulation and intentional misrepresentation of data (see http://www.ema.europa.eu/ docs/ en_GB/document_library/Other/2014/12/WC500178525.pdf)
22	5.2	Section 5.2 Review of IRB Documentation and Informed Consent Content [Section 5.2.1 – IRB Documentation] [Section 5.2.2 – Informed Consent Content] [Section 5.2.3 – Assessing the IRB and Informed Consent]	**[Revised] [Added]** [Revised Header] Section 5.2 Review of the Regulatory Documentation [Revised/Added] *The following section headers were created and appropriate language incorporated under each section.* [Section 5.2.1 Review of the NCI CIRB – IRB of Record] [Section 5.2.2 Review of the Local IRB – IRB of Record] [Section 5.2.3 Listing of IRB Deficiency Types] [Section 5.2.3.1 CIRB – IRB of Record] [Section 5.2.3.2 Local IRB – IRB of Record] [Section 5.2.4 Review of the Informed Consent Content] [Section 5.2.5 Review of the Delegation of Task Log (if applicable] [Section 5.2.6 Assessment of the Regulatory Documentation Review] *NOTE: Sections were separated/created to make the distinction between the use of the NCI CIRB versus a local IRB. Language related to review of Delegation of Task Logs (DTLs) during an audit was also added.*
23	5.2.6 5.4.2	Section 5.2.3 Assessing the IRB and Informed Consent Content Findings Section 5.4.3 Assessing the Findings from the Patient Case Review [Sections 5.2.3 & 5.4.3] The following categories should be used in assigning a final assessment to this component of the audit: <u>Acceptable</u> • No deficiencies identified • Few lesser deficiencies identified • Any major deficiency identified during the audit that was addressed and/or corrected prior to the audit for	**[Revised]** [Revised Header & Section #] Section 5.2.6 Assessment of the Regulatory Documentation Review [Revised Header & Section #] Section 5.4.2 Assessing the Findings from the Patient Case Review] [Revised Text for 5.2.6 & 5.4.2] One of the following designations must be used when assigning a final assessment to this component of the audit: <u>Acceptable</u> • No deficiencies identified and no follow-up being requested • Few lesser deficiencies identified • Any major deficiency identified during the audit that was addressed and/or corrected prior to being notified of the audit for

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		which a written and dated Corrective and Preventative Action (CAPA) plan exists and no further action is required by the Network Group or CCOP/NCORP Research Base, the institution, or the principal investigator because no similar deficiency has occurred since the CAPA plan was implemented. However, this approach may not be applicable if a deficiency is associated with a safety concern and determined that further action is necessary (to be discussed with CTMB liaison). In either case, CTMB must receive a copy of the CAPA plan at the time the final audit report is submitted or by the date follow-up is due. <u>Acceptable Needs Follow-up</u> • Any major deficiency identified during the audit but not corrected and/or addressed **prior to** the audit • Multiple lesser deficiencies identified <u>Unacceptable</u> • Multiple major deficiencies identified • A single major flagrant deficiency found • Excessive number of lesser deficiencies identified	which a written and dated Corrective and Preventative Action (CAPA) plan exists and no further action is required by the Network Group, NCORP Research Base, the institution, or the clinical investigator because no similar deficiency has occurred since the CAPA plan was implemented. However, this approach may not be applicable if a deficiency is associated with a safety concern and determined that further action is necessary (to be discussed with CTMB liaison). In either case, CTMB must receive a copy of the CAPA plan at the time the final audit report is uploaded into the CTMB-AIS or by the date follow-up is due. <u>Acceptable Needs Follow-up</u> • Any major deficiency identified during the audit not corrected and/or addressed prior to the audit • Multiple lesser deficiencies identified <u>Unacceptable</u> • A single critical deficiency • Multiple major deficiencies identified • Multiple lesser deficiencies of a recurring nature found in most of the protocols or informed consent documents reviewed
24	5.3	Section 5.3 Review of Accountability of Investigational Agents and Pharmacy Operations Agent accountability and storage procedures described in this section are required under federal regulations and NCI policy for NCI-supplied study agents (by PMB/CTEP or designated company/Group for DCP and imaging agents). See NCI/CTEP policies under: http://ctep.cancer.gov/protocolDevelopment/agents_drugs.htm An Oral NCI Investigational Agent (Drug) Accountability Record Form (Oral DARF) has been created and all transactions with oral agents must be recorded on this DARF. Agent transactions for formulations other than oral must be recorded on the NCI Investigational Agent (Drug) Accountability Record Form (DARF). The auditing of DARFs is by protocol and study agent. When capturing the number of DARFs pages entered on the final audit report, it is the number of study agents (including different 'strengths') reviewed, not the number of	**[Deleted] [Revised]** [Deleted & Revised Text] Agent accountability and storage procedures described in this section are required under federal regulations and NCI policy for study-supplied agents). See NCI/CTEP/PMB policies under: http://ctep.cancer.gov/protocolDevelopment/agents_drugs.htm The NCI does not endorse any electronic DARF (eDARF) pharmacy software package. Institutions that choose to use an electronic accountability system must ensure the database can produce a paper printout that is identical to the NCI DARF. Electronic accountability system database limitations are not valid reasons for improper accountability documentation per NCI policy.

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		DARF pages. A waiver statement allowing use of electronic DARFs (eDARFs) has not been issued by the NCI and the NCI does not endorse any eDARF pharmacy package. Institutions that choose to use an electronic accountability system must ensure the database is capable of producing a paper printout that is identical to the NCI DARF. Electronic accountability system database limitations are not valid reasons for improper accountability documentation according to NCI policy.	
25	5.3.1	Section 5.3.1 Control Dispensing Area/Pharmacy The Control Dispensing Area for each investigator is identified by the shipping address provided on the Supplemental Investigator Data Form (IDF) or on the institution's Primary Shipping Designee Worksheet. The IDF is submitted with the annual CTEP Investigator Registration packet. The location is responsible for: • Direct receipt of NCI-supplied agent from the NCI • Appropriate storage and security of agent • Dispensing agent to patients/study participants as prescribed by CTEP registered investigators and dictated by the protocol • Overall inventory control (including provision of agent to satellite dispensing areas, as applicable, oversight of satellite dispensing areas, and dissemination of agent stock recovery information) • Final disposition of NCI-supplied agents (returns, transfers and authorized local destructions)	**[Revised]** [Revised Text] The Control Dispensing Area for each investigator is identified as the shipping address receiving the study-supplied agent from the supplier. • The Control Dispensing Area is responsible for: • Direct receipt of study-supplied agent from the supplier • Appropriate storage, accountability and security of study-supplied agent • Dispensing study-supplied agent to patients/study participants as prescribed by authorized, study-eligible physician investigators with an active investigator registration status with CTEP and as dictated by the protocol • Overall agent accountability and inventory control (including provision of agent to authorized, eligible physician for a study with an active investigator registration status at satellite dispensing areas, as applicable, oversight of satellite dispensing areas, and dissemination of agent stock recovery information) • Timely final disposition of non-dispensed study-supplied agents (e.g., returns, authorized transfers or authorized local destructions) • Physical destruction of patient returned study-supplied agents per applicable regulations and institutional policies and procedures
26	5.3.2	Section 5.3.2 Satellite Dispensing Area/Pharmacy The Satellite Dispensing Area receives NCI-supplied agent from a Control Dispensing Area. The Satellite Dispensing Area must store and secure agent appropriately. Agents are to be administered for research-related treatment to	**[Revised]** [Revised Text] The Satellite Dispensing Area receives study-supplied agent from a Control Dispensing Area. The Satellite Dispensing Area is under the direct responsibility and oversight of the Control Dispensing Area.

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		eligible patients/study participants as prescribed by CTEP registered investigators and dictated by the protocol. The Satellite Dispensing Area is under the direct responsibility of the Control Dispensing Area. The Satellite Dispensing Area is responsible for: • Receiving agent from the Control Dispensing Area • Dispensing agent to a patient/study participant • Returning agent to the Control Dispensing Area for further disposition (eg, continued clinical use, transfers, authorized local destruction, return to NCI)	The Satellite Dispensing Area is responsible for: • Receiving study-supplied agent from Control Dispensing Area • Appropriate storage, accountability and security of study-supplied agent • Dispensing study-supplied agent to patients/study participants as prescribed by authorized, study-eligible physician investigators with an active investigator registration status and as dictated by the protocol • Timely returning non-dispensed study-supplied agent to the Control Dispensing Area for further or final disposition • Physical destruction of patient returned study-supplied agents per applicable regulations and institutional policies and procedures
27	5.3.4	[Section 5.3.4 Guidelines for Conducting the Pharmacy Review] There are challenges with categorizing major and lesser deficiencies for the pharmacy component of the audit. As a result, the auditors/Network Group determines the rating based on identified non-compliance items. The auditor will review: drug accountability, proper use of NCI DARFs, required procedures being followed, and appropriate storage and security measures are adhered to for NCI-sponsored trials using NCI-supplied study agents, including cancer control/ prevention and imaging agents. Cancer control/prevention and imaging agents may be supplied by other vendors. The following is a detailed listing of compliance and non-compliance descriptions:	**[Revised] [Added]** [Revised] The listing of Compliance and Non-Compliance items (pages 33-36), reference to 'NCI-supplied study agent' was replaced with 'study-supplied agent', where appropriate. Also, if item is specific to NCI-supplied agent, the item (listing of Compliance and Non-compliance) is prefaced with 'For NCI-sponsored Study'. [Added] Findings such as 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; includes serious violation of safeguards in place to ensure safety of a patient/study participant and/or manipulation and intentional misrepresentation of data should be cited as a Critical-Non-Compliance. The following pages outline the various types of descriptions to assess overall Compliance and Non-Compliance:
28	5.3.5	Section 5.3.5 Assessing the Accountability of Investigational Agents and Pharmacy Operations The following categories should be used in assigning a final assessment to this component of the on-site audit: <u>Acceptable</u> • Compliant in all categories • Any non-compliant item identified during the audit that was addressed and/or corrected prior to audit for which a written and dated Corrective and Preventative Action (CAPA) plan exists and no further action is required by the Network Group, CCOP/NCORP Research Base, the	**[Revised]** [Revised Text] Items audited under the pharmacy component must be assessed as one of the following: • Critical-Non-Compliant* • Non-Compliant • Compliant • Not Reviewed * Any finding identified before or during an audit that is suspected to be fraudulent activity should be cited as Critical-Non-Compliant (see definition for critical under Section 5.1)

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		institution, or the principal investigator because no similar non-compliance issue has occurred since the CAPA plan was implemented. However, this approach may not be applicable if the non-compliance is associated with a safety concern and determined that further action is necessary (to be discussed with CTMB liaison). In either case, CTMB must receive a copy of the CAPA plan at the time the final audit report is submitted or by the date follow-up is due.
		<u>Acceptable Needs Follow-up</u>
		• Category found non-compliant during the audit which was not corrected and/or addressed **prior to** the conduct of the audit
		<u>Unacceptable</u>
		• Inability to track the disposition of NCI-supplied study drugs
		• Multiple non-compliant categories
		<u>No Assessment Required</u>
		• No IND or NCI-supplied study drug is in stock or in use during the audit period and the pharmacy is not inspected
			If an item that was planned to be reviewed as part of the audit was not reviewed for any reason, it must be explained in the pharmacy narrative of the final audit report. One of the following designations must be used when assigning a final assessment to this component of the audit:
			<u>Acceptable</u>
			• Compliance in all categories and no follow-up being requested
			• Any Non-Compliance item identified during the audit that was addressed and/or corrected prior to being notified of the audit for which a written and dated Corrective and Preventative Action (CAPA) plan exists and no further action is required by the Network Group, NCORP Research Base, the institution, or clinical investigator because no similar Not Compliant issue has occurred since the CAPA plan was implemented. However, this approach may not be applicable if a Not Compliant item is associated with a safety concern and determined that further action is necessary (to be discussed with CTMB liaison). In either case, CTMB must receive a copy of the CAPA plan at the time the final audit report is uploaded into the CTMB-AIS or by the date follow-up is due.
			<u>Acceptable Needs Follow-up</u>
			• Any non-compliance identified during the audit that requires follow-up
			<u>Unacceptable</u>
			• A single Critical-Non-Compliance
			• Multiple Non-Compliance items
			• Inability to track the 'chain-of-custody' of a study-supplied agent(s)
			<u>No Assessment Required</u> *(applies to 'on-site' pharmacy audits only)*
			• No study-supplied agent in stock or in-use for the timeframe being reviewed/audited
			• This designation applies under the following two conditions:
			  ○ The review of the pharmacy consists of only security, storage and review of pharmacy procedures to ensure investigator has an active PMB registration.
			  ○ Review of security, storage and pharmacy procedures (described above) were found to be 'compliant'.

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			Limited Review Needs Follow-up *(applies to 'on-site' pharmacy audits only)* • Non-compliance identified under Pharmacy and audit was limited to review of storage, security and/or pharmacy procedures; and CAPA plan or follow-up response is requested.
29	5.3.5	Section 5.3 Assessing the Accountability of Investigational Agents and Pharmacy Operations For institution audits that are performed 'off-site', it is strongly recommended that an 'on-site' visit be conducted every six years (every other routine audit or full reaudit). The audit may be conducted within 6 months prior to or on the day of the audit. An on-site pharmacy inspection can be done by the Network Group. The Network Group may designate this responsibility to the Main Member institution or the CCOP/NCORP. The pharmacy audit findings must be included in the final audit report of the affiliate or the CCOP/NCORP. This would assure that pharmacy inspections and inventory controls are adequately reviewed on-site.	**[Deleted] [Added]** [Deleted Text] See text under 'Previous Text' column [Added Text] For other routine pharmacy audits, the Groups/NCORP Research Base can use their own discretion to determine if/when an on-site audit of the pharmacy should be conducted.
30	5.4.1	Section 5.4.1 Examples of Major Deficiencies [Examples of Major Deficiencies – 1st paragraph] A major deficiency is defined as a variance from protocol-specified procedures that makes the resulting data questionable. The following are examples of major deficiencies. This does not represent an all-inclusive list of major deficiencies that may be found during the audit. The term 'intervention' is intended to include non-treatment studies such as cancer control, prevention, advanced imaging, etc.	**[Revised]** [Revised Header Name] Deficiency Type by Category [Revised Text] The following examples of deficiencies do not represent an all-inclusive list of possible deficiencies that may be found during the audit. The term 'intervention' is intended to include non-treatment studies such as cancer control, prevention, advanced imaging, etc. *NOTE: Previous text related to describing a major deficiency was moved under Section 5.1.*
31	5.4.1	Section 5.4.1 Examples of Major Deficiencies Informed Consent Failure to document properly obtained informed consent such as: • Consent form document missing • Consent form document not signed and dated by the patient/study participant • Translated consent or short form not signed and dated by a non-English speaking patient/study participant	**[Revised]** [Revised Text] Informed Consent – Critical Deficiencies • Any finding identified before or during an audit that is suspected to be fraudulent activity (see definition for Critical under Section 5.1) • Consent form document not signed and dated by the patient/study participant (or parent/legally authorized representative, if applicable) • Patient/study participant signature cannot be corroborated

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		• Consent form not signed by patient prior to study registration/enrollment • Consent form does not contain all required signatures • Consent form used was not the current IRB-approved version at the time of patient registration • Consent form not protocol specific • Consent form does not include updates or information required by IRB • Re-consent not obtained as required • Consent of ancillary/advanced imaging studies not executed properly	• Consent form not protocol specific Informed Consent – Major Deficiencies • Failure to document the informed consent process with the study participant • Patient/study participant signs consent form document containing changes not approved by the CIRB/IRB • Consent form document missing • Translated consent, short form or other form of translation not available or signed/dated by a non-English speaking patient/study participant • Consent form not signed by patient prior to study registration/enrollment • Consent form does not contain all required signatures • Consent form used was not the most current IRB-approved version at the time of patient registration • Consent form does not include updates or information required by IRB • Re-consent not obtained as required • Consent of ancillary/advanced imaging studies not executed properly • Other (explain)
32	5.4.1	Section 5.4.1 Examples of Major Deficiencies Eligibility • Review of documentation available at the time of the audit confirms patient/study participant did not meet all eligibility criteria and/or eligibility requirements were not obtained within the timeframe as specified by the protocol • Documentation missing; unable to confirm eligibility Exception: Patients deemed ineligible based on laboratory/pathology reports following registration and changes based on central review of material.	**[Revised]** [Revised Text] Eligibility – Critical Deficiency • Any finding identified before or during an audit that is suspected to be fraudulent activity (see definition for Critical under Section 5.1) Eligibility – Major Deficiencies • Review of documentation available at the time of the audit confirms patient/study participant did not meet all eligibility criteria and/or eligibility requirements were not obtained within the timeframe as specified by the protocol • Documentation missing; unable to confirm eligibility [Exception: Patients deemed ineligible based on laboratory/pathology reports following registration and changes based on central review of material.] • Other (explain)

Item #	Section	Previous Text	New/Current Text (Added/Revised)
33	5.4.1	Section 5.4.1 Examples of Major Deficiencies Treatment • Incorrect agent/treatment/intervention used • Additional agent/treatment/intervention used which is not permitted by protocol • Dose deviations, modifications, or incorrect calculations (error greater than +/- 10%) • Dose modifications/treatment interventions not per protocol • Treatment/intervention incorrect or not administered correctly, incorrectly calculated, or not adequately documented • Timing and sequencing of treatment/intervention not per protocol • Unjustified delays in treatment/intervention	**[Revised]** [Revised Text] Treatment – Critical Deficiencies • Any finding identified before or during an audit that is suspected to be fraudulent activity (see definition for Critical under Section 5.1) • Incorrect agent/treatment/intervention used Treatment – Major Deficiencies • Additional agent/treatment/intervention used which is not permitted by protocol • Dose deviations or incorrect calculations (error greater than +/- 10%) • Dose modification/treatment/intervention not per protocol; incorrectly calculated • Treatment/intervention incorrect, not administered correctly, or not adequately documented • Timing and sequencing of treatment/intervention not per protocol • Unjustified delays in treatment/intervention • Other (explain)
34	5.4.1	Section 5.4.1 Examples of Major Deficiencies Disease Outcome/Response Failure to evaluate response according to the protocol, for example: • Inaccurate documentation of initial sites of involvement • Tumor measurements/evaluation of status or disease not performed or not documented according to protocol • Protocol-directed response criteria not followed • Claimed response (PR, CR, etc.) cannot be verified or auditor could not verify the reported response • Failure to detect cancer (as in a prevention study) or failure to identify cancer progression	**[Revised]** [Revised Text] Disease Outcome/Response – Critical Deficiency • Any finding identified before or during an audit that is suspected to be fraudulent activity (see definition for Critical under Section 5.1) Disease Outcome/Response – Major Deficiencies • Inaccurate documentation of initial sites of involvement • Tumor measurements/evaluation of status or disease not performed, not reported, or not documented per protocol • Protocol-directed response criteria not followed • Claimed response (i.e., partial response, complete response, stable) cannot be verified or auditor could not verify the reported response • Failure to detect cancer (as in a prevention study) or failure to identify cancer progression • Other (explain)
35	5.4.1	Section 5.4.1 Examples of Major Deficiencies Adverse Events Failure to assess and report adverse events according to	**[Revised]** [Revised Text] Adverse Events – Critical Deficiency • Any finding identified before or during an audit that is suspected

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		protocol, for example: • Grades, types, or dates/duration of serious adverse events inaccurately recorded • Adverse events cannot be substantiated • Follow-up studies necessary to assess adverse events not performed • Failure to report or delayed reporting of an adverse event that would require filing an expedited Adverse Event (AE) report or reporting to the Group • Recurrent under- or over-reporting of adverse events	to be fraudulent activity (see definition for Critical under Section 5.1) Adverse Events – Major Deficiencies • Failure to report or delayed reporting of an adverse event that would require filing an expedited Adverse Event (AE) report or reporting to the Group • Adverse events not assessed by the investigator in a timely manner (per protocol) • Grades, types, or dates/duration of serious adverse events inaccurately recorded • Adverse events cannot be substantiated • Follow-up studies necessary to assess adverse events not performed • Recurrent under- or over-reporting of adverse events • Other (explain)
36	5.4.1	Section 5.4.1 Examples of Major Deficiencies General Data Management Quality • Recurrent missing documentation in the patient/study participant records • Protocol-specified laboratory tests not reported or not documented • Protocol-specified diagnostic studies including baseline assessments not done, not reported or not documented • Protocol-specified research/advanced imaging studies not done or submitted appropriately • Frequent data inaccuracies • Errors in submitted data • Delinquent data submission (> 6 month delinquency is considered a major deficiency; a 3-6 month delinquency is considered a lesser deficiency)	**[Revised]** [Revised Text] General Data Management Quality – Critical Deficiency • Any finding identified before or during an audit that is suspected to be fraudulent activity (see definition for Critical under Section 5.1) General Data Management Quality – Major Deficiencies • Recurrent missing documentation in the patient/study participant records • Protocol-specified laboratory tests not done, not reported or not documented • Protocol-specified diagnostic studies including baseline assessments not done, not reported or not documented • Protocol-specified research/advanced imaging studies not done or submitted appropriately • Frequent data inaccuracies • Errors in submitted data • Delinquent data submission (> 6 months delinquent is considered a major deficiency; a 3-6 month delinquency is considered a lesser deficiency) • Other (explain)

Summary of Changes to the CTMB Audit Guidelines (6 September 2017)

Item #	Section	Previous Text	New/Current Text (Added/Revised)
37	5.4.1	Section 5.4.2 Lesser Deficiency A lesser deficiency is a deficiency 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/quantity of lesser deficiencies should be treated as a major deficiency in determining the final assessment of a component.	**[Revised]** [Revised Text] Assigning Lesser Deficiencies As defined under Section 5.1, a lesser deficiency may be assigned under each of the above categories if it 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/quantity of lesser deficiencies should be treated as a major deficiency in determining the final assessment of a component.
38	5.6	Section 5.6 Exit Interview It is expected that the Principal/Responsible Investigator and designated staff will be present at the exit interview. During the exit interview the audit team will review with the institution, the preliminary findings, items reviewed 'off-site', and discuss any recommendations from the audit team. This interview provides opportunity for education, immediate dialogue, feedback, and clarification.	**[Revised]** [Revised Text] It is expected that the responsible Clinical Investigator and designated staff be present at the exit interview. During the exit interview the audit team will review with the institution, the preliminary findings, items reviewed 'off-site', and discuss any recommendations from the audit team. If applicable, the auditors should mention the expectation of providing a response/CAPA plan to the audit findings and clarify approximate timeframe of when the institution will need to submit their response(s). The exit interview should be an opportunity for education, immediate dialogue, feedback, and clarification for both the institution staff and the auditors.
39	6.1	6.1 Preliminary Report of Audit Findings	**[Added]** [Added Section Header] CTMB-AIS Generated Notifications/Emails] [Added Paragraph] The Group/Research Base Audit Coordinator/designee assigned in the CTMB-AIS receives AIS generated emails related to overdue follow-up/CAPA plans per the audit guidelines. The Group/Research Base Audit Coordinator/designee must provide a response/explanation in writing within 5 business days of receiving the notification. The response should include when the follow-up/CAPA plan is expected to be submitted and/or what actions have been taken so that the follow-up/CAPA plan is uploaded in the CTMB-AIS as soon as possible. The Group/NCORP Research Base response should be directed to the appropriate CTMB liaison. *NOTE: Section 6.1 Preliminary Report of Audit Findings was moved and renumbered as Section 6.2*.

Summary of Changes to the CTMB Audit Guidelines (6 September 2017)

Item #	Section	Previous Text	New/Current Text (Added/Revised)
40	6.2.1	Section 6.1.1 Submission [1st paragraph] The Preliminary Report of Audit Findings form (see Appendix 3) must be faxed to CTMB (240) 276-7891 or sent by email to: NCICTMBPrelimForms@mail.nih.gov within one business day of completing the audit. Any data irregularities identified through quality control procedures or through the audit program that raise any suspicion of intentional misrepresentation of data must be immediately reported to CTMB, CTEP, NCI. The CTMB must be notified immediately by telephone (240) 276-6545 of any findings suspicious and/or suggestive of intentional mis-representation of data and/or disregard for regulatory safeguards for any of the three components (regulatory, pharmacy and patient cases) of an audit. Similarly, any data irregularities identified through other quality control procedures suspicious and/ or suggestive of intentional misrepresentation of data must be immediately reported to CTMB. It is the responsibility of the Network Group or CCOP/NCORP Research Base to immediately notify CTMB when they learn of any significant irregularities or allegations related to scientific misconduct by a staff member or institution participating in their research program. It should be emphasized that the irregularity/misrepresentation of data does not need to be proven, a reasonable level of suspicion suffices for CTEP notification. It is also essential that involved individual(s) and/or institutions follow their own institutional misconduct procedures in these matters. [Last paragraph] Deficiencies identified and briefly described in the Preliminary Report must be included in the Final Audit Report. A revised Preliminary Report may be submitted if it is within ten business days of the audit. Any revision to the Preliminary Report must be explained in the Final Audit Report.	**[Revised] [Added]** [Revised Text] The Preliminary Report of Audit Findings Form must be uploaded into the CTMB-AIS within one business day of completing the audit. Any data irregularities identified through quality control procedures or through the audit program that raise any suspicion of intentional misrepresentation of data must be immediately reported to CTMB. The CTMB must be notified immediately by telephone (240) 276-6545 of any findings suspicious and/or suggestive of intentional mis-representation of data and/or disregard for regulatory safeguards for any component (regulatory documentation, pharmacy, and patient case review) of an audit. Similarly, any data irregularities identified through other quality control procedures suspicious and/or suggestive of intentional misrepresentation of data must be immediately reported to CTMB. It is the responsibility of the Network Group or NCORP Research Base to immediately notify CTMB when they learn of any significant irregularities or allegations related to scientific misconduct by a staff member or institution participating in their research program. It should be emphasized that the irregularity/misrepresentation of data does not need to be proven, a reasonable level of suspicion suffices for CTMB notification. It is also essential that involved individual(s) and/or institutions follow their own institutional scientific misconduct procedures in these matters. [Added Text] Regulatory Documentation Section – Briefly describe all deficiencies identified; and label as critical or major. Pharmacy Section - Briefly describe all non-compliance items identified; label as critical-non-compliance or non-compliance. If pharmacy was a limited review (i.e., review of storage, security and/or pharmacy procedures to ensure investigator has an active CTEP registration, state 'limited review', and describe the non-compliance, if any. If the pharmacy is not reviewed, the pharmacy section should state 'No NCI-supplied drug in use during this audit period', if this applies. Or state, 'Not Reviewed' and mention why it was not reviewed in this section. In the latter two scenarios, the 'yes' or 'no' designation should not be circled on the form. Patient Case Section - Briefly describe all deficiencies identified, and appropriately label each deficiency as critical or major. If not an unannounced case, explain if any patient case was not reviewed in full.

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			[Revised Text] A revised preliminary report may be uploaded into the CTMB-AIS if it is within ten business days of the audit. Deficiencies identified and briefly described in the Preliminary Report must be included in the Final Audit Report. Any revisions to the Preliminary Form must also be explained before uploading into the CTMB-AIS.
41	6.3.1		**[Added]** [Added Text] Final Audit Reports that are returned to the Group/Research Base/CTMS for a correction or clarification must be returned (uploaded in the CTMB-AIS) within two weeks. Also, all corrections or clarifications made should be explained in the General Comments section of the report.
42	6.3.2.1	6.2.2.1 General Information • Provide information specific to the institution such as number of cases audited, average annual accrual, and institutional staff present at the audit • Identify members of the audit team; indicating title and affiliation • Identify co-site visitor(s) and affiliation	**[Revised]** [Revised Text] • Front page of the final audit report, include information specific to the institution such as number of cases audited, average annual accrual, and institutional staff present at the audit • List the members of the audit team; indicating title and affiliation • List Co-site visitor(s) and affiliation, if applicable
43	6.3.2.2	6.2.2.1 IRB and Informed Consent • Provide the title of each protocol audited and list the number of patients/study participants audited, the IND drugs, treatment modalities used and the disease(s) studied in each protocol • For each protocol, indicate whether OK, major, or lesser deficiencies were found and describe each major and lesser deficiency • Indicate Yes or No that informed consents were reviewed • If reviewed, identify any deficiencies • Indicate if the informed consent content was reviewed 'off site' • Provide an overall assessment for this component and indicate if a re-audit is required and the time frame	**[Revised]** [Revised Header & Header #] 6.3.2.2 Regulatory Documentation [Revised Text] • The CTMB-AIS will populate each protocol title for protocols audited and list the number patient cases selected for audit, the IND drugs, treatment modalities used and the disease(s) studied in each protocol (if drug is NCI-supplied study agent) • For each protocol, indicate if each protocol selected for audit is utilizing the NCI CIRB or a local IRB • Designate whether critical, major, or lesser deficiencies were identified under CIRB/IRB and ICC and describe each critical, major or lesser deficiency; otherwise indicate OK • Designate whether major or lesser deficiencies were identified for review of the Delegation of Tasks – Log, if so, describe; otherwise indicate OK • Indicate if any portion of the Regulatory Documentation review was audited 'off-site'

Item #	Section	Previous Text	New/Current Text (Added/Revised)
			• Provide an overall assessment for this component and indicate if a re-audit is required, including timeframe
44	6.3.2.3	6.2.2.1 Accountability of Investigational Agents and Pharmacy Operations • Indicate Yes or No if INDs or NCI supplied agents were used at this institution during the period covered by this audit • Indicate the number of DARFs reviewed (ie, number of study agents reviewed) • For off-site audits, indicate 'Not Reviewed' for return of drug (unless verified by returned receipt from PMB/sponsor), storage, and security • Indicate Compliant, Non-compliant, or Not Reviewed for maintaining accurate records, including primary transaction and satellite records, and specific regulations related to protocol and drugs, storage and security; for each item identified as non-compliant, select the appropriate non-compliant item or items • The pharmacy narrative must provide an overall assessment for this component and can include guidance provided to the institution • Examples of information that may be included under the pharmacy narrative are: descriptions of non-compliance issues not outlined in the audit guidelines; review of temperature logs and excursions; rationale of why IND or NCI-supplied study agents were not selected for review, etc.	**[Revised]** [Revised Text] • Indicate the number of DARFs reviewed (i.e., number of study agents reviewed), and the number of patients cross-checked against the DARF, if applicable • For each item identified as Critical-Non-Compliance and/or Non-Compliance, select the appropriate Not Compliant description or descriptions; otherwise indicate OK or Not Reviewed • Summarize in the pharmacy narrative any items that require a response, any items not reviewed and explain why they were not reviewed (see Section 5.3.5); also, include guidance or recommendations provided to the institution. [Other examples of information that may be included under the pharmacy narrative may include descriptions of non-compliance issues not outlined in the audit guidelines; review of temperature logs and excursions; rationale of why IND or study-supplied agents were not selected for review, etc.] • For a full review of the pharmacy component provide an overall assessment (Acceptable, Acceptable needs F/U, or Unacceptable), and indicate if a re-audit is required, including timeframe • For a limited review of the pharmacy, indicate which items were reviewed (i.e., storage, security, and/or pharmacy procedures). If follow-up is required when conducting a limited review, describe the non-compliance finding(s). The overall assessment for a 'limited review' of the pharmacy should be: 'No Assessment Required' or 'Limited Review Needs Follow-up' (see page 38)
45	6.3.2.4	Section 6.2.2.1 Patient Cases For each category, indicate if major or lesser deficiencies were found and describe, otherwise indicate OK or Not Reviewed The CTMB Audit Information System (CTMB-AIS) pre-populates and summarizes the deficiencies for each patient/study participant and category in a table; this table identifies the total number of major and lesser deficiencies for the total patient cases reviewed	**[Revised]** [Revised Text] For each category, indicate if critical, major or lesser deficiencies were found and describe; otherwise indicate OK or Not Reviewed (explain if not reviewed) The CTMB Audit Information System (CTMB-AIS) pre-populates and summarizes the deficiencies for each patient/study participant and category in a table; this table identifies the total number of critical, major and lesser deficiencies for the total patient cases reviewed

Summary of Changes to the CTMB Audit Guidelines (6 September 2017)

Item #	Section	Previous Text	New/Current Text (Added/Revised)
		Provide an overall assessment for this component and indicate if a re-audit is required and the time frame All patient cases including those registered/enrolled under each sub affiliate/sub component must be identified by institution	All patient cases including those registered/enrolled under each sub affiliate/sub component are identified by institution (CTEP site code) Provide an overall assessment for this component and indicate if a re-audit is required, including timeframe
46	6.4	6.3 Follow-up/Corrective and Preventative Action (CAPA) Plan If a component is rated as Acceptable Needs Follow-up or Unacceptable, each audited institution will be required to submit a written response and/or CAPA plan to the Network Group or CCOP/NCORP Research Base. This written response must address the specific audit findings and be signed by the appropriate investigator at each audited institution. A copy of the written response/CAPA plan, along with an assessment of adequacy by the Network Group or CCOP/NCORP Research Base of the response/CAPA plan, must be forwarded to CTMB by the Network Group within 45 calendar days of the date the final audit report is submitted in the CTMB-AIS. Network Group or CCOP/NCORP Research Base policies and procedures may recommend and/or require additional actions or sanctions. A re-audit is mandatory, if an institution continues to participate in the Group or CCOP/NCORP Research Base for any component rated as Unacceptable. A reaudit should be done no later than one year after an Unacceptable audit or when sufficient patients/study participants have been accrued.	**[Revised]** [Revised Text] If a component is rated as Limited Review with Follow-up, Acceptable Needs Follow-up or Unacceptable, each audited institution will be required to submit a written CAPA plan/ response to the Network Group/NCORP Research Base. The CAPA plan/response must be uploaded into the CTMB-AIS by the appropriate Network Group/NCORP Research Base within 45 days from the date the final audit report was also uploaded into the CTMB-AIS. In addition to the CAPA plan, the Group/NCORP Research Base may also upload any pertinent correspondence/ emails related to the audit. All documentation uploaded to the Document Management tab in the CTMB-AIS must be by Group/NCORP Research Base and applicable audit date.
47	6.6		**[Added]** [Added Section Header] Section 6.6 For Cause (Off-cycle) Audits [Added Text] A ‘for cause’ audit may be warranted when there are concerns or irregularities found through quality control procedures or when allegations of possible scientific misconduct are made. It is the responsibility of the Network Group/NCORP Research Base to immediately notify CTMB upon learning of any significant irregularities or allegations related to scientific misconduct by a staff member or institution participating in their research program. CTMB may coordinate or request that the Group or NCORP Research Base coordinate the ‘for cause’ audit. Selection of auditors to

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			conduct 'for cause' on-site audit will be made jointly by the NCI, Network Group, or NCORP Research Base, and a joint course of action will be planned. Other federal agencies or offices may be invited to participate in an audit at the discretion of the NCI.
48	6.7		**[Added]** [Added Section Header] Section 6.7 Probation of a Clinical Investigator [Added Text] If there are concerns that appear to be investigator specific identified before, during or after an audit, mentoring and retraining will be the primary focus, if appropriate. After further evaluation by CTMB in collaboration with the NCTN Program Director the investigator may be taken off probation if documentation exists that support the specific actions were taken. Repeated and deliberate failure to comply with the federal regulations, GCP and/or these audit guidelines may result in one or more of the following actions: • Replace Clinical Investigator • Re-analyze or retract published results • Request a formal investigation by the Office of Research Integrity • Revoke the Investigator's FDA Form 1572 • Privileges in participating on any NCI sponsored clinical trial will be terminated