NCI National Clinical Trials Network
a National Cancer Institute program

NCI/DCTD/CTEP/CTMB

Summary of Changes to the CTMB Auditing Guidelines

Effective Date: 25 August 2025

NOTE: Throughout the document, the term ‘patient’ has been replaced with the term ‘participant’. There are also editorial revisions made to the document not reflected in the table, if it did not change the meaning.

Summary of Changes to the CTMB Audit Guidelines (15 August 2025)

Item #	Section	[Section Header Name] Previous Text	[Added, Revised, Moved or Deleted] New/Current Text
1.	1.2	**[Background]** In March 2018, FDA announced the adoption of "E6(R2) Good Clinical Practice: Integrated Addendum to E6 (R1)." The guidance was prepared under the auspices of the International Council for Harmonisation (ICH), formerly the International Conference on Harmonisation.	**[Revised]** In January 2025, FDA announced the adoption of "E6(R3) Guideline for Good Clinical Practice." The guidance was prepared under the auspices of the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use.
2.	1.3		**[Added]** This document is intended to supplement, not replace, regulatory obligations under FDA regulations and ICH Good Clinical Practice (GCP) guidelines. All participating institutions are expected to ensure compliance with these global standards.
3.	2.1		**[Added]** An audit consists of reviewing the below categories under the three components: <u>Regulatory Documentation Component</u>: • IRB of Record Documentation • Informed Consent Content (ICC) • Delegation of Tasks Log (DTL) <u>Pharmacy Component</u>: • NCI DARFs Completely and Correctly Filled Out • DARFs are Protocol and Study Agent Specific • Satellite Records of Dispensing Area • Agent Inventory and Accountability Documentation • Return of Undispensed Study Agent (NCI sponsored study) • Adequate Security • Authorized Prescription(s) <u>Participant Case Component</u>: • Informed Consent • Eligibility • Treatment • Disease Outcome/Response • Adverse Event • Correlative Studies, Tests, and Procedures • General Data Management Quality

Summary of Changes to the CTMB Audit Guidelines (15 August 2025)

Item #	Section	[Section Header Name] Previous Text	[Added, Revised, Moved or Deleted] New/Current Text
4.	2.1	**[Clinical Trials Monitoring Branch (CTMB)]**	**[Revised]** *Deleted 1st sentence of 3rd paragraph:* 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. *Deleted 4th paragraph:* For reporting any allegation of research misconduct that is detected by site staff and/or review by a Network Group/NCORP Research Base outside of an audit (i.e., through internal QA review procedures), the CTMB must be notified immediately by telephone (240) 276-6545 or by email (NCICTMBResearchMisconductConcerns@mail.nih.gov).
5.	2.2	**[Network Groups]** Section 2.2.1 Quality Control Section 2.2.2. Quality Assurance Section 2.2.2.1 Study Monitoring Section 2.2.2.2 Data Safety Monitoring Board Section 2.2.2.3 Auditing Program Section 2.2.2.4 CTMB – Audit Information System	**[Moved]** *Sections re-ordered and re-numbered* Section 2.2.1 Quality Assurance Section 2.2.1.1 Auditing Program Section 2.2.1.2 Monitoring Program Section 2.2.2 Quality Control Section 2.2.3 Data Safety Monitoring Board Section 2.2.4 CTMB – Audit Information System
6.	2.4.1		**[Added]** Section title: Site Audit Portal (SAP) The Site Audit Portal (SAP) is an application in the auditing area of the CTSU website that serves as the communications link between CTMB- AIS and Medidata Rave. The SAP seamlessly coordinates audit activities with Medidata using the visit information provided by CTMB-AIS. It displays visit information, tracks the visit process, and provides a direct link to study participants, visit-associated queries in Rave, Delegation of Tasks Logs (DTLs), and study participant-level source documentation uploaded to the Source Document Portal (SDP). Furthermore, it manages the invitation of volunteer auditors and cross-network

Item #	Section	[Section Header Name] Previous Text	[Added, Revised, Moved or Deleted] New/Current Text
			auditors to studies in Rave for Targeted Source Data Verification (TSDV), which is described in the next section. *Note: SAP is not available to site staff.* For auditor access to the SAP to view visit details and access study participant cases and other items go to (login required): https://www.ctsu.org/RAVE/SiteAudit.aspx For instructions on navigating the SAP (log-in required): https://www.ctsu.org/master/simplepage.aspx?ckey=HELP-AUDITING-NAVIGATION
7.	3.3	**[Auditable and Non-Auditable Institutions]** *4th paragraph, 1st sentence:* Tier 3 sites (sub affiliates and NCORP sub affiliates) are routinely 'non-auditable' (auditable flag set to 'no' in the CTMB-AIS).	**[Revised]** All institutions designated as a Sub Affiliate (Tier 3) site are listed with a non-auditable flag in the CTMB-AIS
8.	3.11	**[Auditing of Withdrawn or No Longer Funded (NLF) Institutions]** If an institution's membership or participation in a Network Group or NCORP Research Base is withdrawn, continued long-term follow-up of registered/enrolled patients and the collection of good quality data according to the study schedule are required. Therefore, these institutions remain eligible for an audit. If the NCORP is "defunded" by DCP, or the LAPS is no longer funded by CTEP, their membership status will be set to 'NLF' in the CTMB-AIS until the patients/study participants are off treatment/study intervention, the patient case(s) are transferred to another investigator/institution and/or follow-up is no longer required. The LAPS Aligned Affiliate is not part of the LAPS grant. The Group will need to change the Aligned Affiliate by either assigning a new Main Member, changing their role (to a Main Member) or withdrawing them. The Group remains responsible for auditing the NCORP Affiliate, NCORP Sub Affiliate, LAPS Main Member, LAPS Integrated Component, LAPS Affiliates/Aligned Affiliates, and LAPS Affiliates/Aligned Sub Affiliates.	**[Moved]** *Moved to Section 4.8*

Summary of Changes to the CTMB Audit Guidelines (15 August 2025)

Item #	Section	[Section Header Name] Previous Text	[Added, Revised, Moved or Deleted] New/Current Text
		For NCORPs and LAPS in NLF or withdrawn status, a close-out audit should be considered by the Network Group/NCORP Research Base. The decision whether to conduct an audit is based on the following: • The number of patient cases enrolled since the previous audit. • The number of active protocols with emphasis on registration or pivotal trials. • If there is a high number of patients/study participants in follow-up. • Site performance is not meeting acceptable quality standards for audit and/or submitting follow-up data. If there is accrual and the institution has never been audited, it must have a close out audit conducted. A decision not to audit these institutions must first be discussed with CTMB.	
9.	3.12	**[Off-Cycle Audits]** 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. • An Off-Cycle/For Cause Audit may be warranted when there are concerns or irregularities found through quality control procedures or when there are allegations of possible scientific misconduct. • More frequent auditing may also be scheduled, if requested by CTEP/CTMB due to the nature of the study (Special Protocols, registration trials, etc).	**[Moved][Revised]** *Similar text added under Section 4.3*

10.	4.1	**[CTMB-AIS Generated Notifications/Emails]** 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 five (5) business days of receiving the notification. The Group/NCORP Research Base response should be directed to the appropriate CTMB liaison via the Email Notification Response Management module in the CTMB-AIS.	**[Moved]** *Moved to Section 6.1*
11.	4.1		**[Added]** Section title: Scheduling and Arranging the Audit Audits are scheduled in the CTMB-AIS by the Group/NCORP Research Base. If there was a previous audit for the same institution for the same Group/NCORP Research Base in the CTMB-AIS, the prior audit must be considered complete (i.e., audit report and CAPA plan reviewed and acknowledged by CTMB in the CTMB-AIS) before a new audit can be scheduled. The audit date must be entered into the CTMB-AIS at least six (6) weeks in advance. This will ensure sufficient notification to the institution and will allow CTMB staff to decide which audits they or their designee will attend. The Group/NCORP Research Base must obtain CTMB approval prior to scheduling any audit with less than six weeks of notice. The request should be directed to the appropriate CTMB liaison via the Email Notification Response Management module in the CTMB-AIS. The request to CTMB must include written documentation from the institution to be audited stating they are aware of the minimum six week requirement and agree with the proposed date. The institution is to be provided with a list of protocols and study participant cases selected for review at least four but no more than six weeks prior to the audit. This will allow the institution staff sufficient time to collect, prepare, assemble and label the required materials. In the event of a for-cause audit, advance notice of the selection of protocols and/or study participant cases to be reviewed may be limited due to the nature of the review.

12.	4.2	**[Arranging the Audit]** An audit date must be entered into the CTMB-AIS at least six (6) weeks in advance of the scheduled routine audit or re-audit. This will ensure sufficient notification to the institution and will allow CTMB staff to decide which audits they or their designee will attend. The Group/NCORP Research Base must contact CTMB for approval prior to scheduling any audit within six weeks. At the time of contacting CTMB, the Group/NCORP Research Base must forward written documentation to CTMB from the institution to be audited (routine or re-audit) stating they are aware of the minimum six (6) week requirement and agree with the proposed date. The institution must be supplied with a list of protocols and patient cases selected for review at least four but no more than six weeks prior to the audit. This will allow the institution staff sufficient time to collect, prepare, assemble and label the required materials. If the Group/NCORP Research Base needs to cancel an audit within three business days prior to the audit for unforeseen circumstances, they must notify the CTMB liaison. If a Clinical Trials Monitoring Service (CTMS) co-site visitor was assigned to the audit, the Group/NCORP Research Base must also contact CTMS.	**[Moved]** *Text moved to Sections 4.1 and 4.3.*
13.	4.2		**[Added]** Section Title: Audit Not Scheduled or Cancellation of an Audit If the Group/NCORP Research Base Audit Coordinator/ designee receives an AIS generated email related to an audit that has not been scheduled timely per the audit guidelines, the Audit Coordinator/designee must provide a response/ explanation in writing within five (5) business days of receiving the notification. The response should be directed to the appropriate CTMB liaison via the Email Notification Response Management module in the CTMB-AIS. If the Group/NCORP Research Base needs to cancel an audit for unforeseen circumstances and it is within three business days prior to the audit date, they must notify the CTMB liaison. If a Clinical Trials Monitoring Service (CTMS) co-site visitor was

			assigned to the audit, the Group/NCORP Research Base must also contact CTMS.
14.	4.3		**[Added]** Section Title: Type of Audits in CTMB-AIS Audits may be scheduled in the CTMB-AIS as a Routine, Reaudit or Off-cycle. Routine audits are scheduled for routine reviews and can occur within 18 to 36 month intervals. The frequency of audits may depend on whether a particular site(s) is considered a high enrolling site, or the rate of accrual is unusually high. Reaudits are scheduled when there are concerns based on the prior audit (by component) and oversight is required usually within 12 months from the prior audit. Off-cycle audits are scheduled based on the below circumstances: • More frequent auditing may be warranted if requested by CTMB due to the nature of the study (registration trial, etc.), or • A for-cause audit may be warranted when there are concerns or significant irregularities found through quality control procedures or if there are allegations of possible scientific misconduct. If an audit at an institution is for a protocol designated as a Special Protocol, it can be scheduled in the CTMB-AIS database as an Initial, Semi-Annual or Annual review.

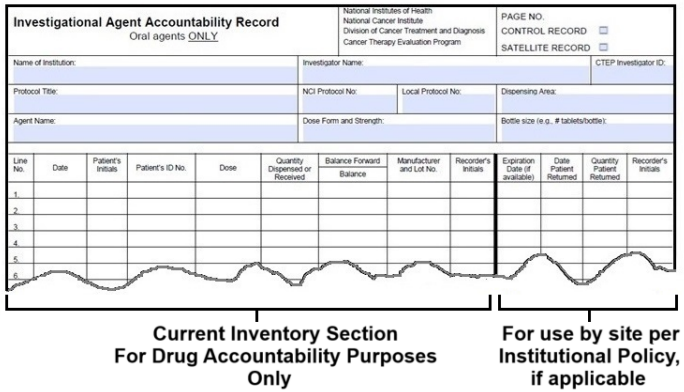
15.	4.4	**[Audit Location]**
		Previously Section 4.3
		When scheduling the audit, below are the options to select from in the CTMB-AIS database:
		• On-Site Review: conducted at the institution being audited
		• Off-Site/Remote Review:
		  ○ Review conducted at parent/affiliated site
		  ○ Review conducted remotely at Network Group/Research Base
		• Hybrid Review: combination of off-site and on-site review
		The use of the above approaches is at the discretion of the Network Group/Research Base. The address to enter in the AIS
			[Revised]
			The location of the audit is at the discretion of the Network Group/Research Base.
			• On-Site Review: conducted at the institution being audited
			• Off-Site/Remote Review:
			  ○ Review conducted at parent/affiliated site
			  ○ Review conducted remotely at Network Group/Research Base

		database when scheduling an Off-site or Hybrid review is as follows: • Off-site/Remote Review – enter address of Network Group/Research Base *or* Parent Institution • Hybrid Review – enter address of the where the component(s) being reviewed off-site is taking place. For example, if regulatory documents are reviewed at the Network Group and patient cases are review on-site at the institution, enter the 'off-site' address for the review of the regulatory documents. Note: Location of review by component must be identified under the Audit Procedures section of the audit report.	
16.	4.5	**[Selection of Protocols and Patient Cases for On-site or Off-site Audits]** *Previously Section 4.4* 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 four (4) 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. Specific trials (e.g., prevention, screening trials, etc.) with very high accrual may be audited under a different mechanism with CTMB approval. These trials may be excluded from the selection process. A minimum of 10% of the patient cases accrued since the last audit will be reviewed by the Network Group/NCORP Research Base. For Tier 1 and Tier 2 sites, patient cases accrued must be selected from each accruing institution. For Tier 3 sites, a representative sampling is to be audited at the 'parent' institution. For selection purposes, the 10% of chosen cases must be rounded up (e.g., if 12 patient cases are eligible for audit selection, at least two cases must be audited). In summary, when selecting the patient cases for audit, the following selection process applies, where appropriate: • Select 10% of treatment cases where the auditing Group is	**[Revised]** 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. While most cases will be selected from study participants accrued since the previous audit, any study participant case may be audited at any time. A minimum of four (4) 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. Specific trials (e.g., registration, prevention, advanced imaging, screening trials, etc.) with very high accrual may be audited under a different mechanism with CTMB approval. These trials may be excluded from the selection process. For Tier 1 and Tier 2 sites, a minimum of 10% of the participant cases accrued by site since the last audit will be reviewed by the Network Group/NCORP Research Base. For Tier 3 sites (Sub Affiliates), the Group is expected to select a representative sampling from each Sub Affiliate to audit under the parent institution. Selecting 10% of participant cases from each Sub Affiliate is not required. Under certain circumstances, CTMB may mandate an independent audit of any Sub Affiliate site. For selection purposes, the 10% of chosen cases must be rounded up (e.g., if 12 participant cases are eligible for audit

		the protocol lead or credited with the enrollment; and • Select 10% of patient cases from protocols with advanced imaging studies/imaging studies embedded in treatment protocols; and • Select 10% of patient cases enrolled onto DCP cancer control/prevention trials. 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 audited. Depending on the volume of patients enrolled onto a registration trial, auditing additional patient cases may be required. While most cases will be selected from patients accrued since the previous audit, any patient case may be audited at any time. In addition, the Network Group/NCORP Research Base must select at least one or more unannounced cases to be reviewed, if the total accrual warrants selection of unannounced cases. The audited institution(s) may learn of the unannounced case(s) the day before or the day of the audit. These cases may have a limited review consisting of minimally reviewing the patient informed consent document and patient eligibility to be counted as part of the selection process noted above. Note: If unannounced cases receive a limited review, these patient cases do not count towards the required minimum of 10% to be reviewed. Selection of unannounced cases for review does not apply when conducting an off-site/remote audit. In the event of a patient case transfer, the receiving/accepting institution should ensure that complete documentation is provided as part of the transfer process. Any audit taking place after the date of transfer will occur at the receiving/accepting institution. This is because only the accepting institution will have access to the subject's information after the transfer takes place.	selection, at least two cases must be audited). In summary, when selecting the participant cases for audit, the following selection process applies, where appropriate: • Select at least one participant case for every registration trial, at every institution selected for audit. Depending on volume of enrolled onto a registration trial, auditing additional participant cases may be required; and • Select 10% of treatment cases where the auditing Group is the protocol lead or credited with the enrollment; and • Select 10% of participant cases from protocols with advanced imaging studies/imaging studies embedded in treatment protocols; and • Select 10% of participant cases enrolled onto DCP cancer control/prevention trials. A participant case must not be counted towards the minimum 10% rule when: • The participant case is only evaluated under a Screening Step of the study. • No categories (i.e., Informed Consent, Eligibility, Treatment, etc.) were reviewed for a participant case at the time of the audit. In this scenario, the case must be removed from the audit report.
17.	4.5.1		**[Added]** Section title: Selection of Unannounced Participant Case(s) If the total accrual warrants selection of unannounced cases, the Group must select at least one unannounced participant case to review. The audited institution may learn of the unannounced case(s) the day before or the day of the audit. These cases may

			have a limited review consisting of minimally participant informed consent and participant eligibility and cannot count towards the required 10% rule unless an unannounced case is reviewed in full (i.e., all categories reviewed). Selection of unannounced cases for review does not apply when conducting an off-site/remote audit due to system limitations.
18.	4.5.2		**[Added]** Section title: Review of Transferred Participant Cases In the event of a participant case transfer, the receiving/ accepting institution should ensure that complete documentation is provided as part of the transfer process. Any audit taking place after the date of transfer will occur at the receiving/accepting institution. This is because only the accepting institution will have access to the study participant's information after the transfer takes place.
19.	4.8		**[Added]** Section title: Auditing of Withdrawn or No Longer Funded (NLF) Institutions If an institution's membership or participation in a Network Group or NCORP Research Base is withdrawn, continued long-term follow-up of registered/enrolled participants and the collection of good quality data according to the study schedule are required. Therefore, these institutions remain eligible for an audit. If the NCORP is "defunded" by DCP, or the LAPS is no longer funded by CTEP, their membership status will be set to 'NLF' in the CTMB-AIS until the study participants are off treatment/study intervention, the participant case(s) are transferred to another investigator/ institution and/or follow-up is no longer required. The LAPS Aligned Affiliate is not part of the LAPS grant. The Group will need to change the Aligned Affiliate by either assigning a new Main Member, changing their role (to a Main Member) or withdrawing them. The Group remains responsible for auditing the NCORP Affiliate, NCORP Sub Affiliate, LAPS Main Member, LAPS Integrated Component, LAPS Affiliates/Aligned Affiliates, and LAPS Affiliates/Aligned Sub Affiliates. For NCORPs and LAPS in NLF or withdrawn status, a close-out audit should be considered by the Network Group/NCORP Research Base. The decision whether to conduct an audit is based on the following:

			• The number of participant cases enrolled since the previous audit • The number of active protocols with emphasis on registration or pivotal trials • If there is a high number of study participants in follow-up • Site performance is not meeting acceptable quality standards for submitting follow-up data If there is accrual and the institution has never been audited, it must have a close out audit conducted. A decision not to audit these institutions must first be discussed with CTMB.
20.	5.1	**[Assessing Audit Findings]** 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]** Any condition, practice, process or pattern that adversely affect the rights, safety or well-being of the study participant and/or the quality and integrity of the data; includes serious violation of safeguards in place to ensure safety of a study participant and/or manipulation and intentional misrepresentation of data (see: https://www.ema.europa.eu/en/documents/other/classification-and-analysis-good-clinical-practice-gcp-inspection-findings-gcp-inspections-conducted-request-chmp_en.pdf). *Link updated*
21.	5.2.5	**[Review of the Delegation of Tasks Log (DTL)]** 4th Bullet: Performing study-related activities without an approved DTL	**[Revised]** • Major: Individual performing study-related activities with DTL unapproved greater than 30 calendar days • Lesser: Individual performing study-related activities with DTL unapproved 30 calendar days or less
22.	5.2.6 5.3.5 5.4.2	**[Assessment of the Regulatory Documentation Review]** *Under Acceptable rating paragraph* 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.	**[Revised]** In either case, *the major deficiency(s) must still be cited and described in the audit report and* 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.
23.	5.3	**[Review of Accountability of Investigational Agents and Pharmacy Operations]**	**[Revised]** Agent accountability and storage procedures described in this section are required under federal regulations and NCI policy for

		Agent accountability and storage procedures described in this section are required under federal regulations and NCI policy for study-supplied agents. See PMB policies under: https://ctep.cancer.gov/branches/pmb/agent_management.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.	NCI IND studies where agents are provided by CTEP. See CTEP policies under: https://dctd.cancer.gov/research/ctep-trials/for-sites/agent-management. Investigational agent accountability instructions for agents supplied under a non-NCI IND studies are available in the corresponding protocol. The NCI does not endorse any commercial electronic accountability 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. NCI launched the electronic accountability module in AURORA, known as the eDARF on December 27, 2024. A DARF is an inventory accountability log, not a study participant compliance document. For non-oral agents, study participant returns should therefore, not be documented on the DARF. Separate study participant compliance documentation may be maintained at the site if required by institutional policy. For NCI Oral DARFs, study participant returns are considered waste pharmaceuticals and not part of agent accountability. The study participant return section of the DARF is for the convenience of the site (if required by site SOP) and is not part of study agent accountability for protocol auditing purposes (see Figure 2). **Figure 2 Example of NCI Oral DARF**  Investigational Agent Accountability Record Oral agents ONLY National Institutes of Health National Cancer Institute Division of Cancer Treatment and Diagnosis Cancer Therapy Evaluation Program PAGE NO. CONTROL RECORD SATELLITE RECORD Name of Institution: Investigator Name: CTEP Investigator ID: Protocol Title: NCI Protocol No: Local Protocol No: Dispensing Area: Agent Name: Dose Form and Strength: Bottle size (e.g., # tablets/bottle): Line No. Date Patient's Initials Patient's ID No. Dose Quantity Dispensed or Received Balance Forward Balance Manufacturer and Lot No. Recorder's Initials Expiration Date (if available) Date Patient Returned Quantity Patient Returned Recorder's Initials Current Inventory Section For Drug Accountability Purposes Only For use by site per Institutional Policy, if applicable

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<u>Types of NCI DARFs</u>:

NCI DARF – paper or non-NCI eDARF that prints to match NCI DARF
NCI Oral DARF – paper or non-NCI eDARF that prints to match NCI Oral DARF
eDARF – AURORA accountability log

Site may choose which DARF type to use:
<table>
<tr><td>CTEP IND study - NCI supplied study agent</td><td rowspan="2">NCI DARF - Required
(see above)</td></tr>
<tr><td>CTEP IND study – Study agent not directly supplied by NCI repository (including radiopharmaceuticals)</td></tr>
<tr><td>Study utilizing non-CTEP IND agent and study agent not supplied by NCI</td><td rowspan="2">*NCI paper DARF
(AURORA eDARF not available)</td></tr>
<tr><td>Study utilizing non-CTEP IND agent and study agent is supplied by NCI</td></tr>
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* The NCI DARF is not required to be the form used for drug accountability. Refer to protocol for specific drug accountability instructions.
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24.	5.3.3	**[Imaging Studies/Cancer Control]** Imaging and radiopharmaceutical therapy agents may or may not be managed by the pharmacy depending on the protocol. Imaging and radiopharmaceutical therapy agents are usually delivered directly to the imaging, radiation oncology, nuclear medicine or nuclear pharmacy department or center that is performing the imaging study or radiopharmaceutical therapy. Cancer control/prevention and imaging study and radiopharmaceutical therapy are usually manufactured on-site or purchased from and distributed by commercial vendors. Even though these study agents are not usually distributed by the NCI, cancer control/imaging and radiopharmaceutical therapy studies should abide by the same NCI/CTEP policies. It is strongly suggested that NCI DARFs be utilized to track these study agents. If NCI DARFs are not utilized, the imaging study agent/radiopharmaceutical accountability logs must at least capture the same information as on the NCI DARFs. Some protocols will describe the record-keeping processes.	**[Revised]** Imaging and radiopharmaceutical therapy agents may or may not be managed by the pharmacy depending on the protocol. Imaging and radiopharmaceutical therapy agents are usually delivered directly to the imaging, radiation oncology, nuclear medicine or nuclear pharmacy department or center that is performing the imaging study or radiopharmaceutical therapy. Cancer control/prevention and imaging study and radiopharmaceutical therapy are usually manufactured on-site or purchased from and distributed by commercial vendors. Even though these study agents are not usually distributed by the NCI, cancer control/imaging and radiopharmaceutical therapy studies must abide by the same NCI/CTEP policies. NCI DARFs must be utilized to track these study agents as described in the protocol.
25.	5.3.4	**[Guidelines for Conducting the Pharmacy Review]** **NCI DARFs Completely and Correctly Filled Out**	**[Revised]**

		Non-Compliance • NCI DARF not maintained or not maintained completely, accurately or on a timely basis • Oral NCI DARF not maintained for oral study-supplied agents, not maintained completely, accurately or on a timely basis • DARF not maintained to verify cancer control/imaging study supplied agents are administered to patients/study participants • Paper and/or electronic DARFs (eDARFs) are not completed as required; paper printout of eDARF is not identical to the NCI DARF • Erasures or whiteout used on paper DARF • Corrections are not lined out, initialed and dated on paper DARF • Corrections are not appropriately documented on eDARF in electronic inventory system • Study-supplied agent is dispensed to a registered patient/study participant is not recorded on the appropriate DARF • Multiple dose vials not used for more than one patient/study participant and/or doses not documented correctly on separate lines of the DARF • Dispensing of study-supplied agent to a non-registered patient/study participant recorded on the DARF • Patient/study participant returns of oral study-supplied agents not documented on the Oral DARF • Patient/study participant returns of non-oral, non-patient-specific agent supplies are documented on the DARF • Patient/study participant returns of non-oral, patient-specific agent supplies are not documented on the DARF • [For NCI sponsored study] NCI-supplied study agents are repackaged and/or reshipped to other investigators or locations by mail or express carrier • Study agent final disposition of inventory is not documented on DARF	**Non-Compliant** NCI DARF/Oral DARF/eDARF not maintained or not maintained completely, accurately or in real-time basis Paper and/or eDARF are not completed as required; paper printout of eDARF is not identical to NCI DARF Erasures or whiteout used on paper DARF Corrections are not lined out, initialed, and dated on paper DARF Corrections are not appropriately documented on eDARF in electronic inventory system Study-supplied agent dispensed to a registered study participant is not recorded on the appropriate DARF Multiple dose vials not used for more than one study participant and/or doses not documented correctly on separate lines of the DARF Study-supplied agent dispensed to a non-registered study participant recorded on the DARF Study participant return of oral agents are documented as part of 'current inventory' section on DARF Study participant returns of non-oral study agent are documented on NCI DARF Study agent final disposition of undispensed inventory is not documented on DARF NCI DARF not maintained to verify cancer control/imaging study-supplied agents is administered to study participant

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DARFs Protocol and Study Agent Specific

<u>Non-Compliance</u>

Substitution of any study-supplied agent, with non-study supplied study agent, including commercial agents
DARF maintained by Lot #
Single DARF used for more than one protocol
Single DARF used for a protocol using multiple study agents
Single DARF used for multiple agent strengths, dosage forms, or ordering investigators
Single DARF used for multiple patients/study participants when patient-specific DARF must be maintained
Study-supplied agent used for pre-clinical or laboratory studies without written approval by NCI

NCI DARFs Kept as Primary Transaction Record

<u>Non-Compliance</u>

Study-supplied agent order receipts/ documentation (paper or electronic) are not retained or not available for review
No documentation on Control DARF of study-supplied agent transactions and local destruction
Quantities not accounted for in physical inventory; quantities do not match DARF

</td>
<td>
[Revised]
<table>
<tr><th>Non-Compliant</th></tr>
<tr><td>Non-study drug is dispensed and/or administered to study participant when NCI study agent is supplied by protocol</td></tr>
<tr><td>DARF maintained by Lot #, when multiple lots have been received</td></tr>
<tr><td>Separate DARF not maintained by protocol, study agent, strength, formulation and ordering investigator when agent is supplied by protocol</td></tr>
<tr><td>Separate DARF not maintained for each study participant on participant-specific supply studies as dictated by protocol</td></tr>
<tr><td>Study-supplied agent used for pre-clinical or laboratory studies without written approval from NCI</td></tr>
</table>

[Revised]

Title: Agent Inventory and Accountability Documentation
<table>
<tr><th>Non-Compliant</th></tr>
<tr><td>Study-supplied agent order receipts/ documentation (paper or electronic) are not retained or not available for review</td></tr>
<tr><td>No documentation on Control DARF of study-supplied agent transactions including local destruction of undispensed inventory</td></tr>
<tr><td>Quantities not accounted for in inventory; quantities do not match DARF</td></tr>
<tr><td>[For NCI-sponsored study] NCI oral study agent shipment policy is not followed when shipping directly to study participant</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td>Return of Study Agent [NCI-sponsored studies]

<u>Non-Compliance</u>

• Study agent is transferred to investigator or protocol without NCI written approval
• Study agent returned to PMB that should have been destroyed on-site or study agent returned to PMB that was not supplied by PMB
• Return Form or documentation of local destruction not maintained
• Unused/un-dispensed NCI-supplied study agents not returned, transferred or locally destroyed within 90 calendar days when requested by the NCI, or when patients/study participants are in follow-up, study is closed to enrollment and no NCI-supplied study agent is being administered</td>
<td>[Revised]

Title: Return of Undispensed Study Agent (NCI sponsored study)

<table><tr><th>Non-Compliant</th></tr><tr><td>Study agent is transferred to another site, investigator or protocol without NCI written approval</td></tr><tr><td>Undispensed study-provided agent returned to NCI when supplied by another source</td></tr><tr><td>Return Form or documentation of local destruction for undispensed inventory is not maintained</td></tr><tr><td>Undispensed NCI-supplied study agent not returned, transferred or locally destroyed within 90 calendar days when requested by the NCI</td></tr><tr><td>Undispensed NCI-supplied study agent remains on inventory greater than 90 days after all study participants are in follow-up, or study is closed to enrollment and no NCI-supplied study agent is being administered</td></tr></table></td>
</tr>
<tr>
<td>26.</td>
<td>5.4.1</td>
<td>[Deficiency Type by Category] Treatment

<u>Treatment – Major Deficiencies</u>
• 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)</td>
<td>[Revised]

<u>Treatment – Major Deficiencies</u>
• 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; or not administered correctly
• Timing and sequencing of treatment/intervention not per protocol
• Unjustified delays in treatment/intervention
• Treatment/intervention not documented in source documentation; or not documented correctly[1]
• Treatment/intervention not reported; or not reported correctly on Case Report Forms[2]
• Other (explain)</td>
</tr>
</table>

		[Deficiency Type by Category] Disease Outcome/Response Disease Outcome/Response – Major Deficiencies • Inaccurate documentation of initial sites of involvement • Tumor measurements/evaluation of 'status of 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/monitor could not verify the reported response • Failure to detect cancer (as in a prevention study) or failure to identify cancer progression • Other (explain)	**[Revised]** Disease Outcome/Response – Major Deficiencies • Inaccurate documentation of initial sites of involvement • Tumor measurements/evaluation of 'status of disease' not performed • Tumor measurements/evaluation of 'status of disease' not documented in source documentation; or not documented correctly[3] • Tumor measurements/evaluation of 'status of disease' not reported; or not reported correctly on Case Report Forms[4] • Protocol-directed response criteria not followed • Claimed response (i.e., partial response, complete response, stable) cannot be verified • Failure to identify cancer progression or failure to detect cancer in adjuvant or prevention study • Other (explain)
		[Deficiency Type by Category] Adverse Events 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)	**[Revised] Adverse Event** Adverse Event – 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 • Grades, types, or dates/duration of serious adverse events inaccurately recorded • Adverse events not assessed by the investigator in a timely manner per protocol • Serious adverse events reported on Case Report Forms but cannot be substantiated in source documentation • Routine adverse events not documented in source documentation; or not documented correctly[5] • Adverse events not reported; or not reported correctly on Case Report Forms[6] • Follow-up studies necessary to assess adverse events not performed • Recurring under- or over-reporting of adverse events • Other (explain)

			[Added] Correlative Studies, Tests, and Procedures Correlative Studies, Tests, and Procedures – Critical Deficiency • Any finding identified before or during the review that meets the definition of a critical finding Correlative Studies, Tests, and Procedures – Major Deficiencies • Protocol-specified diagnostic studies including baseline assessments not done, not reported or not documented • Protocol-specified laboratory tests or other parameters not done, not reported, or not documented • Protocol-specified research (Quality of Life forms, collection of research samples, etc.)/advanced imaging studies not done, not submitted or submitted inappropriately • Other (explain)
		[Deficiency Type by Category] General Data Management Quality General Data Management Quality – Major Deficiencies • Recurrent missing documentation in the patient/study participant records • Protocol-specified laboratory tests or other parameters not done, not reported, or not documented • Protocol-specified diagnostic studies including baseline assessments not done, not reported or not documented • Protocol-specified research (Quality of Life forms, collection of research samples, etc.)/advanced imaging studies not done or submitted appropriately • Frequent data inaccuracies; un-redacted data[a] • Errors in submitted data; data cannot be verified • Delinquent data submission[b] • Other (explain)	**[Revised]** General Data Management Quality – Major Deficiencies • Recurring missing documentation in the study participant records • Frequent data inaccuracies in primary source documentation[7]; unredacted data[8] • Significant number of errors in submitted data[7]; data cannot be verified • Delinquent data submission[9] • Other (explain)
27.	6.1	**[CTMB-AIS Generated Notifications/Emails]** *Previously Section 4.1*	**[Moved to Section 6.1]** 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 via the Email Notification Response Management module in the CTMB-AIS.
28.	6.2.1	**[Submission of Preliminary Report of Audit Findings]** 1st paragraph: 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 misrepresentation 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.	**[Revised]** The Preliminary Report of Audit Findings Form must be uploaded into the CTMB-AIS within one business day of completing the audit. The CTMB must be notified immediately by telephone (240) 276-6545 and by email (ReportingResearchMisconductConcerns@nih.gov) 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 Participant Case Review) of an audit.
29.	6.3.2.1	**[General Information – Final Audit Report]** • 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	**[Revised]** • On the front page of the report, provide information specific to the institution such as number of cases audited, and average annual accrual • List the site staff names and titles involved or present at the audit • List the names, titles and affiliations each member of the audit team • List Co-site visitor(s) and affiliation, if applicable

30.	6.3.2.2	**[Review of the Regulatory Documentation]**	**[Deleted]** • 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
31.	6.3.2.3	**[Review of the Pharmacy]**	**[Added]** *Last Bullet* • Provide an overall assessment for this component (Acceptable, Acceptable needs F/U, Unacceptable, Limited Review Needs F/U or No Assessment Required), and indicate if a reaudit is required, including timeframe
32.	6.3.2.4	**[Review of the Patient Cases]** • 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-AIS pre-populates and summarizes the deficiencies for each patient/study participant and category in a table; this table calculates the total number of critical, major and lesser deficiencies for the total patient cases reviewed • Provide an overall assessment for this component and indicate if a re-audit is required, including timeframe	**[Revised]** • For each category in the audit report, indicate if critical, major or lesser deficiency is being cited, and describe; otherwise indicate OK or Not Reviewed • If a category is designated as 'Not Reviewed' for a participant case selected for audit (i.e., announced case), an explanation (rather than a deficiency description) must be summarized by participant ID and category in the audit report • For findings related to documentation or reporting, ensure the deficiency is captured by category (i.e., Informed Consent; Eligibility; Treatment; Disease Response/Outcome; Adverse Event; Correlative Studies, Tests, and Procedures) where appropriate, rather than under General Data Management Quality • The CTMB-AIS pre-populates and summarizes the deficiencies for each study participant and category in a table embedded in the report; this table calculates the total number of critical, major and lesser deficiencies for the total participant cases reviewed; if a participant case was selected for review but no categories were reviewed, it must not be listed in the table of the final report • Under the Participant Case Review Assessment section of the final report in the CTMB-AIS, provide a brief summary for each category if a CAPA plan is being requested. The brief summary should include a description of items that need to be addressed in the CAPA plan/response

<table>
<tr><td></td><td></td><td></td><td>• Provide an overall assessment for this component (Acceptable, Acceptable needs F/U, or Unacceptable), and indicate if a reaudit is required, including timeframe</td></tr>
<tr><td>33.</td><td>6.4</td><td>[Corrective and Preventative Action (CAPA) Plan]
As outlined under Sections 5.2.6, 5.3.5 and 5.4.2, CAPA plans/follow-up responses are uploaded in the CTMB-AIS by the Group/NCORP Research Base. Other pertinent correspondence or documentation related to the audit may also be uploaded. It must be uploaded to the Document Management tab (in the CTMB-AIS) by corresponding CTEP Site Code and audit date.</td><td>[Revised]
As outlined under Sections 5.2.6, 5.3.5 and 5.4.2, CAPA plan/follow-up response must be uploaded into the CTMB-AIS within 45 calendar days from the date the final audit report is uploaded in the CTMB-AIS by the Group/NCORP Research Base. Other pertinent correspondence or documentation related to the audit may also be uploaded. The CAPA plan must include a cover letter from the auditing Group stating that the auditing Group has reviewed the CAPA plan/response(s) and find response(s) adequate. It must be uploaded to the Document Management tab in the CTMB-AIS by corresponding CTEP Site Code and audit date.</td></tr>
<tr><td>34.</td><td>6.5</td><td></td><td>[Added]
[Timeline for Uploading Preliminary Forms, Final Reports and CAPA Plans into the CTMB-AIS]
<table><tr><th>Submission Type</th><th>Due Date to Upload into CTMB-AIS</th></tr><tr><td>Preliminary Report for Audit Findings</td><td>Within 1 business day of completing the audit</td></tr><tr><td>Final Audit Report</td><td>Within 70 calendar days of Day 1 of the audit date</td></tr><tr><td>CAPA Plan*</td><td>Within 45 calendar days from the date the final audit report is uploaded in the CTMB-AIS</td></tr></table>* CAPA plan must be uploaded into the CTMB-AIS within 45 days by the Group/ Research Base, therefore the site should provide their CAPA plan to the Group/ Research Base sooner, per the requirements set by the Group/Research Base.</td></tr>
<tr><td>35.</td><td>6.11</td><td>[Withdrawal of a Participating Institution]
Previously Section 6.10
If improved performance is not documented at the time of the second re-audit, the institution may be withdrawn by the Network Group or NCORP Research Base. Any such action will be done in consultation with CTMB. An off-cycle (for cause) audit may take place if patient/study participant safety or scientific misconduct is suspected.</td><td>[Revised]
If improved performance is not documented after reaudits have taken place, the institution may be withdrawn by the Network Group or NCORP Research Base. Any such action will be done in consultation with CTMB. A for-cause (i.e., off-cycle audit) may take place at any site, at any time, if study participant safety or scientific misconduct is suspected.</td></tr>
</table>