ETCTN

Experimental Therapeutics Clinical Trials Network

Team Driven. Cancer Therapy Focused.

National Cancer Institute at the National Institutes of Health

NCI/DCTD/CTEP/CTMB

Summary of Changes to the ETCTN Monitoring Guidelines

[Revised: May 2022]

Effective: 7 June 2022

NOTE: A few revisions were made throughout the CTMB Audit Guidelines that are not reflected in this table if it did not change the meaning. This includes replacing 'an audit' with 'a review'. This was done specifically to maintain similar language between the auditing and monitoring guidelines, and to coincide with the CTMB-AIS database. Also, language that was added to the 'draft' audit guidelines related to critical non-compliance under the pharmacy section for product quality issues was removed after further consideration.

Summary of Changes to the ETCTN Monitoring Guidelines (7 June 2022)

Item #	Section	[Section Header Name] Previous Text	New/Current Text (Added/Revised)
1.	List of Appendices	**[List of Appendices]**	**Added Appendix 1:** Guidance for Allegations of Research Misconduct **Updated Appendices 2, 3 and 4:** Renamed, renumbered and updated
2.	2.1	**[Clinical Trials Monitoring Branch (CTMB)]**	**Added paragraph:** For reporting any allegation of research misconduct that is detected by site staff, LAO, and/or CTMS outside of a monitoring visit (i.e., through internal Quality Assurance review procedures), the CTMB must be notified immediately by telephone (240) 276-6545 or by email (NCICTMBResearchMisconductConcerns@mail.nih.gov). See 'Guidance for Allegations of Research Misconduct' under Appendix 1.
3.	3.1.1	**[Comprehensive Monitoring (CTMS-Monitored Trials)]** Protocols assigned for CTMS Comprehensive Monitoring (Phase 1 and early Phase 2, or trials where toxicities may be of concern), data is to be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11	**Revised paragraph as follows:** For protocols assigned for CTMS Comprehensive Monitoring (Phase 1 and early Phase 2, or trials where toxicities may be of concern), data is to be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Monitoring visits will be conducted three times annually (one annual site visit and two data reviews). Information on CTMS reporting is available at: http://theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11.
4.	3.1.2	**[Routine Monitoring (CTMS-Monitored Trials)]** Protocols assigned for CTMS Routine Monitoring (Phase 2), data is to be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11	**Revised paragraph as follows:** For protocols assigned for CTMS Routine Monitoring, data is to be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Monitoring visits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent reviews may be conducted if warranted by accrual or due to

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			concerns regarding data quality or timely submission. Information on CTMS reporting is available at: http://theradex.com/clinicalTechnologies/?National-Cancer Institute-NCI-11.
5.	4.2	**[Selection of the Monitor or Monitoring Team]**	**Section renumbered - moved to be Section 4.4**

6.	4.3	**[Off-site/Remote Monitoring]**	**Section Header renamed to:** Location of Monitoring Visit
			Section renumbered to: Section 4.2
			Added paragraph as follows:
			When scheduling the monitoring visit, below are the options to select from in the CTMB-AIS database:
			• On-Site Review: conducted at the institution being monitored
			• Off-Site/Remote Review:
			  ○ Review conducted at parent/affiliated site
			  ○ Review conducted remotely at CTMS location
			• Hybrid Review: combination of off-site and on-site review
			The use of the above approaches for off-site review is primarily intended for review of Patient Cases. It is at the discretion of the CTMS with consultation with CTMB on how the review of the Regulatory and Pharmacy documentation is conducted.

7.	5.0	**[Conducting the Visit]** In preparation for the monitoring visit, certain documents such as Regulatory Documentation and DARFs may be reviewed prior to the visit.	**Revised sentence as follows:** In preparation for the monitoring visit, certain documents such as Regulatory Documentation, informed consent documents, and DARFs may be reviewed prior to the visit.
8.	5.1	**[Assessing Findings from the Monitoring Visit – Critical]**	**Added paragraph:** **NOTE:** See 'Guidance for Allegations of Research Misconduct' (Appendix 1) for reporting any allegation of research misconduct that is detected by site staff, Lead Academic

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			Organization (LAO), and/or CTMS outside of a monitoring visit (i.e., through internal Quality Assurance review procedures).
9.	5.2.2	**[Review of the Local Institution Review Board (IRB) – IRB of Record]**	**Added sentence:** For studies reviewed/conducted at sites outside of the U.S., amendments must be approved within 120 days to allow for local regulatory authority review, applicable translations, and review by the IRB of record.
10.	5.2.3.1 5.2.3.2 5.2.4 5.2.5 5.3.5 5.4.1	**[CIRB – IRB of Record]** **[Local IRB – IRB of Record]** **[Critical ICC Deficiency]** **[Critical DTL Deficiency]** **[Assessment of the Pharmacy Review]** **[Deficiency Type by Category (IC, E, Rx, DR, AE and DQ)]** Any finding identified before or during an audit that is suspected to be fraudulent activity (see definition for Critical under Section 5.1)	**Revised paragraph as follows:** Any finding identified before or during the review that meets the definition of a critical finding as defined under Section 5.1.
11.	5.2.3.2	**[Local IRB – IRB of Record/ Major IRB Deficiencies]** Lack of documentation of IRB approval of a protocol amendment that affects more than minimal risk or IRB approval is greater than 90 calendar days after Network Group's notification; this includes a 'Request for Rapid Amendment (RRA)' resulting from an Action Letter indicating temporary suspension of accrual with expedited review permitted.	**Revised 9th bullet as follows:** Lack of documentation of IRB approval of a protocol amendment that affects more than minimal risk or IRB approval is greater than 90 calendar days (or 120 calendar days for sites outside of the U.S.) after Network Group's notification; this includes a 'Request for Rapid Amendment (RRA)' resulting from an Action Letter indicating temporary suspension of accrual with expedited review permitted.
12.	5.2.3.2	**[Local IRB – IRB of Record/ Lesser IRB Deficiencies]** Amendment/Investigator Brochure editorial revision or administrative in nature or other Network Group/NCORP Research Base specific document not submitted or not submitted timely to the local IRB	**Revised 3rd bullet as follows:** Amendment editorial revision or administrative in nature or other Network Group/NCORP Research Base specific document not submitted or not submitted timely to the local IRB

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13.	5.2.4	**[Review of the Informed Consent Content (ICC)]** The content of the local informed consent documents must be reviewed regardless of patient registration/ enrollment to ensure the informed consent forms contain the elements required by federal regulations and CTMB guidelines. Minimally, a consent form document must be reviewed for content for those protocols that a patient case was selected from for review under the Patient Case Review component.	**Revised paragraph as follows:** If the CIRB is utilized, a minimum of five (5) informed consent forms must be reviewed for content from the protocols selected for review. If there are more than ten (10) informed consent forms to review, then a random sample of at least 50% must be selected for review. Priority for selection must be given to registration trials. If deficiencies are noted, additional protocols may be reviewed for ICC at the monitor's discretion. If the local IRB is utilized, an informed consent form must be reviewed for all protocols selected for review regardless of patient registration/ enrollment. The review of informed consent content is to ensure all elements are included per the federal regulations.
14.	5.2.5	**[Review of the Delegation of Tasks Log (if applicable)]** To evaluate the roles and responsibilities of the individuals contributing efforts to a registration clinical trial or other clinical trial designated by CTEP, a Delegation of Tasks Log (DTL) must be maintained. The DTL is to list anyone who contributes significant trial-related duties. This log is generated and maintained by institution and by protocol, by the responsible Clinical Investigator. If applicable, the monitor will request the DTLs for the protocols being reviewed (for one or more institutions). The monitor will review the log to evaluate appropriate implementation and maintenance.	**Section Header revised to:** Review of the Delegation of Tasks Log (DTL) **Revised 2nd and 3rd paragraphs as follows:** To evaluate the roles and responsibilities of any individual contributing efforts to a clinical trial, a Delegation of Tasks Log (DTL) must be maintained. The DTL is to list anyone who contributes significant trial-related duties. This log is generated and maintained by institution and by protocol, by the responsible Clinical Investigator. The monitor will review a minimum of five (5) DTLs. If there are more than ten (10) DTLs, then a random sample of at least 50% must be selected for review. Priority for selection must be given to registration trials. The monitor will review the log to evaluate appropriate implementation and maintenance. If deficiencies are noted, additional DTLs may be reviewed at the monitor's discretion.
15.	5.3.4	**[NCI DARFs Completely and Correctly Filled Out]** Compliance: NCI-supplied study agents are not repackaged or reshipped to other investigators, patients, or locations by mail or express carrier	**Revised text as follows:** Compliance: [For NCI sponsored study] NCI-supplied study agents are not repackaged or reshipped to other investigators or locations by mail or express carrier, only shipment of oral

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		Non-Compliance: NCI-supplied study agents are repackaged and/or reshipped to other investigators, patients, or locations by mail or express carrier = = = Compliance: [For non-NCI sponsored study] Study agent final disposition of inventory is documented on DARF Non-Compliance: [For non-NCI sponsored study] Study agent final disposition of inventory is not documented on DARF	study agents directly to study subjects is allowed Non-Compliance: [For NCI sponsored study] NCI-supplied study agents are repackaged and/or reshipped to other investigator or locations by mail or express carrier = = = Compliance: Study agent final disposition of inventory is documented on DARF Non-Compliance: Study agent final disposition of inventory is not documented on DARF
16.	5.3.4	**[Return of Study Agent]** Compliance: Unused/un-dispensed NCI-supplied study agent is returned, transferred or locally destroyed within 90 calendar days when requested by the NCI, or when patients/study participants are in follow-up and no NCI-supplied agent is being administered Non-Compliance: 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 and no NCI-supplied study agent is being administered	**Revised text as follows:** Compliance: Unused/un-dispensed NCI-supplied study agent is returned, transferred or locally destroyed within 90 calendar days when requested by the NCI, and when patients/study participants are in follow-up**,** study is closed to enrollment and no NCI-supplied agent is being administered Non-compliance: 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
17.	5.4.1	**[Deficiency Type by Category – Disease Outcome/ Response]** Claimed response (i.e., partial response, complete response, stable) cannot be verified or monitor could not verify the reported response	**Revised 4th bullet as follows:** Claimed response (i.e., partial response, complete response, stable) cannot be verified, or auditor/monitor could not verify the reported response
18.	6.1.2.5	**[Monitoring Procedures]**	**Sentence added:** A summary may also be included if any component of the audit was not completed or not done, and reason.