NCI Cancer Prevention Clinical Trials Network

A program of the National Cancer Institute of the National Institutes of Health

CP-CTNetDMACC
Cancer Prevention Clinical Trials Network
Data Management, Auditing, and Coordinating Center

CP-CTNET MANUAL OF STANDARD OPERATING PROCEDURES (M-SOP)

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Cancer Prevention Clinical Trials Network (CP-CTNet)
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REVISION HISTORY (most recent first)

Version	Effective Date	Summary of Changes
3.0	JAN-26-2024	Updated the file format, title page, SOP 01-01, SOP 01-02, SOP 01-03, SOP 02-01, SOP 02-02, SOP 02-04, SOP 02-05, SOP 02-06, SOP 02-07, SOP 03-03, and SOP 04-01.
2.0	JUL-13-2023	Updated the title page, SOP 01-01, SOP 02-03, SOP 02-04, SOP 02-05, and SOP 03-03.
1.0	FEB-21-2023	Original version of document.

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Title: Essential Documents Submission for Sponsor's Record

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REVISION HISTORY (most recent first)

Version	Effective Date	Summary of Changes
8.0	JAN-26-2024	Added HC requirements; Added requirements of DTL documents.
7.0	JUL-13-2023	Clarification on the collection of laboratory documents and laboratory certifications for those institutions not certified by CLIA, and clarification on the submission of laboratory normal values.
6.0	FEB-21-2023	Renamed document. Major rewrite of the entire document.
5.0	APR-27-2022	Additional clarification was added regarding RCR and the documents collected from RCR. Minor edits were made throughout the document to provide clarification on documents collected from LAOs and AOs.
4.0	JAN-25-2022	The required essential site documents in section 3 were reordered and updated. Additional clarification was added to the sections on Form FDA 1572 and the DTL.
3.0	SEP-02-2021	Additional information about CTEP-IAM, and clarification of DTL requirements.
2.0	JUN-01-2021	DTL changes.
1.0	AUG-17-2020	Original version of the document.

1. INTRODUCTION AND PURPOSE

"Essential documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of Good Clinical Practice (GCP) and with all applicable regulatory requirements. Trial Master Files (TMFs) should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office" as per *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry*. These documents should be available for sponsor audits and inspection by regulatory authorities. Lead Academic Organizations (LAOs) and Affiliated Organizations (AOs) are required to prepare, submit, and maintain essential documents throughout the duration of each study in accordance with GCP guidelines. This document provides the essential documents requirements for the sponsor's TMF. The Cancer Prevention Clinical Trials Network (CP-CTNet) is developed and sponsored by the National Cancer Institute's (NCI's) Division of Cancer Prevention (DCP). Each accruing site must submit the full complement of essential documents required for Drug Shipment Authorization (DSA) before they will be allowed to open to accrual. Once these documents have been received and reviewed, The DCP Regulatory Contractor will issue DSA.

A number of essential documents require updates throughout the course of the study. Refer to the section describing each document to determine if and when submission of updates is required.

The final close out of the study at each accruing site requires confirmation that all essential documents are current and complete. All essential documents and communication should be maintained at each site during the study and for at least three years after its completion.

2. SCOPE

This document details the submission of essential documents required from LAOs and AOs for the sponsor's TMF. The DCP Regulatory Contractor maintains the sponsor's TMF.

3. DEFINITIONS

Term	Definition
A	Associate
AO	Affiliated Organization
AP	Associate Plus
APIW	Annual Principal Investigator Worksheet
ASIW	Annual Signatory Institution Worksheet
CAP	College of American Pathologists
CI	Clinical Investigator
CIRB	Central Institutional Review Board
CITI	Collaborative Institutional Training Initiative
CLIA	Clinical Laboratory Improvement Amendments
CLP	Clinical Laboratory Permit
CP-CTNet	Cancer Prevention Clinical Trials Network
CPC	Cancer Prevention and Control
CRA	Clinical Research Associate
CTEP	Cancer Therapy Evaluation Program

Term	Definition
DCP	Division of Cancer Prevention
DMACC	Data Management, Auditing, and Coordinating Center
DO	Doctor of Osteopathic Medicine
DSA	Drug Shipment Authorization
DTL	Delegation of Tasks Log
DTLA	Delegation of Tasks Log Administrator
FDA	Food and Drug Administration
FDF	Financial Disclosure Form
FWA	Federal wide Assurance
GCP	Good Clinical Practice
H&P	History and Physical
IAM	Identity and Access Management
IB	Investigator's Brochure
ICD	Informed Consent Document
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IVR	Investigator
LAO	Lead Academic Organization
LNV	Laboratory Normal Value
M-SOP	Manual of Standard Operating Procedures
MD	Doctor of Medicine
ML	Medical License
MM	Medical Monitor
NC	Nurse Consultant
NCI	National Cancer Institute
NIH	National Institutes of Health
NP	Nurse Practitioner
NPIVR	Non-Physician Investigator
NTF	Note-to-File
OHRP	Office for Human Research Protections
PA	Physician's Assistant
PhD	Doctor of Philosophy
PI	Principal Investigator
PIO	Protocol Information Office
RCR	Registration and Credential Repository
RN	Registered Nurse

Term	Definition
SL	Scientific Lead
SSW	Site Specific Worksheet
TMF	Trial Master File
US	United States
HC	Health Canada
QI	Qualified Investigator

4. REQUIRED ESSENTIAL DOCUMENTS FOR SPONSOR'S TMF

DCP's list of required essential documents for the sponsor's TMF is provided below, followed by guidelines for completion and submission of each document type.

1. NCI Biosketch*
2. Professional Licensure*
3. GCP Training Certification*
4. Statement of Investigator (Form FDA 1572)*
5. Financial Disclosure Form (FDF)*
6. Delegation of Tasks Log (DTL)
7. Principal Investigator (PI) Acknowledgement of Investigator's Brochure (IB) or Package Insert
8. Office of Human Subject Protections (OHRP) Assurance
9. Current Lab Certification
10. Laboratory Normal Values (LNVs)
11. Central Institutional Review Board (CIRB) or Independent Ethics Committee (IEC) Approval
12. Informed Consent Document (ICD)
13. CIRB- or IEC-approved Patient/Recruitment Materials
14. CIRB Annual Signatory Institution Worksheet (ASIW) Approval Letter
15. CIRB Annual Principal Investigator Worksheet (APIW) Approval Letter
16. CIRB Approval of the Site Specific Worksheet (SSW)
17. Local Site IRB Acknowledgements or Approvals (US Sites)
18. Certificates of Translation (if applicable)

*Documents collected from RCR

5. NCI REGISTRATION AND CREDENTIAL REPOSITORY (RCR)

NCI policy requires all persons participating in the conduct of an NCI-sponsored clinical trial be registered in the NCI Registration and Credential Repository (RCR). Investigators and all study staff listed on the Delegation of Tasks Log (DTL) are required to register. The RCR provides a self-service online person registration application with electronic signature and submission capability.

Individuals must use their Cancer Therapy Evaluation Program (CTEP)-Identity and Access Management (IAM) account username and password to log into the RCR.

1. Individuals registering in the RCR should choose one of the following four registration types depending on their credentials and the task(s) they have been assigned on the DTL:
    1.1. Investigators holding a medical license (MD or DO) register as an Investigator (IVR).
    1.2. Investigators who are an advanced practice provider such as a Nurse Practitioner or Physician's Assistant or a graduate level researcher (PhD) without a medical degree register as a Non-Physician Investigator (NPIVR).
    1.3. Clinical site staff (study coordinators, regulatory coordinators, study nurses, data managers, etc.) register as an Associate Plus (AP).
    1.4. Other clinical site staff who are not generating study data or accessing data entry applications may be registered as an Associate (A).
2. All study staff designated must provide the following in the RCR:
    2.1. NCI Biosketch
    2.2. Professional Licensure (e.g., medical, nursing, and/or pharmacy), as applicable
    2.3. GCP Training Certification
    2.4. FDF
    2.5. Study staff registered in RCR as **IVR** or **NPIVR** must, in addition, complete a Form FDA 1572

Study staff registered in RCR as A are not required to be added to the DTL. However, if they are added to the DTL, DCP requires them to have proof of GCP training. The GCP training certificate must be provided to the DCP Regulatory Contractor for each A added to the DTL.

Study level Statistician listed on the protocol cover page may not be added to the DTL, they must be registered in RCR and should have an active account. The DCP Regulatory Contractor will check for RCR status and download the documents for the sponsor's record at the time of study initiation and prior to the LAO audit if not included in any of the site DTL.

The RCR serves as the official repository for the above documents for the DCP Regulatory Contractor and auditors. Study staff must maintain an ACTIVE RCR account status. The RCR is an annual registration, therefore, the ACTIVE or NOT ACTIVE status of the registration will determine whether the credentials of the individual are acceptable. This includes acceptable for DSA and audit status as well. To issue DSA, all staff listed on the DTL must have ACTIVE status in the RCR. In addition, the RCR status of staff will be reviewed prior to an audit.

Sites are not required to maintain "shadow" copies of the documents uploaded in the RCR in their regulatory binder or submit copies of these documents to the DCP Regulatory Contractor or LAO.

6. REQUIRED ESSENTIAL DOCUMENTS GUIDELINES

1. **NCI Biosketch**
    1.1. An NCI Biosketch is required for study staff who participate in the clinical investigation and hold an RCR registration type of IVR, NPIVR, or AP, including international site staff. The purpose of the NCI Biosketch is to document that the individual who is assigned a task on

the DTL is qualified by training, experience, and/or education to perform their assigned task(s).

1.2. The NCI Biosketch should display the study staff's current affiliation and dates of involvement with the institution.

1.3. The DCP Regulatory Contractor will download the NCI Biosketch from the RCR when staff is initially added to the DTL. The downloaded document will be maintained for the sponsor's record.

2. **Professional Licensure**

2.1. Each study staff member listed on the DTL who holds a professional license (e.g., MD, DO, RN, NP, PA, PharmD, etc.) should provide their license number. A controlled substance license is not an accepted form of professional licensure.

2.2. The staff member's name should match the Form FDA 1572 or NCI Biosketch.

2.3. The DCP Regulatory Contractor will download the professional licensure from the RCR when staff is added to the DTL and prior to an audit. This downloaded document will be maintained for the sponsor's record.

3. **GCP Training Certification**

3.1. GCP training certification is required for all personnel listed on the DTL.

3.2. A GCP training certificate will need to be uploaded into the RCR for those who hold an RCR registration type of IVR, NPIVR, or AP. For 'A' registration type, a GCP training certificate must be provided to the DCP Regulatory Contractor separately via email, if not uploaded in RCR.

3.3. Collaborative Institutional Training Initiative (CITI) GCP training comes in two versions, FDA and ICH. The FDA version is preferred, though the ICH version is also acceptable.

3.4. GCP training certification from NIH, Trancelerate GCP Mutual Recognition Program, or the staff member's own institution is acceptable.

3.5. Expiration of GCP training certification is based on the training provider/institution. Expiration dates should be listed on training certificates and should not exceed three years from the date of completion.

3.6. The DCP Regulatory Contractor will download the GCP training certificate from the RCR when staff is added to the DTL and prior to an audit. This downloaded document will be maintained for the sponsor's record.

4. **Statement of Investigator (Form FDA 1572)**

4.1. DCP requires all investigators (IVR and NPIVR) conducting clinical investigations to complete Form FDA 1572 within the RCR and to provide accurate and current information. Form FDA 1572 provides documentation of Principal Investigator (PI) oversight; therefore, a Protocol Signature Page or PI Statement of Responsibility is not needed.

4.2. Instructions for the completion of Form FDA 1572 are provided in the RCR. Of note for Cancer Prevention Clinical Trials Network (CP-CTNet) studies:

4.3. **Section 5:** NCI's Cancer Prevention and Control (CPC) Central IRB (CIRB) is the IRB of record for LAO and AO sites in the US and its territories (e.g., Puerto Rico) and should be

included in this section. For international sites, the name and address of their Independent Ethics Committee (IEC) or equivalent should be included instead.

4.4. The DCP Regulatory Contractor will download Form FDA 1572 from the RCR for all IVR and NPIVR staff listed on the DTL and as necessary for Food and Drug Administration (FDA) submissions. This downloaded document will be maintained for the sponsor's record.

4.5. If an investigator at an international site cannot submit Form FDA 1572, an agreement equivalent to Form FDA 1572 is required to be submitted. For studies conducted under a DCP-held Investigational New Drug (IND), an approved waiver from FDA, submitted to FDA by the DCP Regulatory Contractor, is also required.

5. **Financial Disclosure Form (FDF)**

5.1. The FDF must be signed and dated electronically by staff who hold an RCR registration type of IVR, NPIVR, or AP and are listed on the DTL.

5.2. If any financial interests are indicated, they should be disclosed on the FDF in the RCR.

5.3. The DCP Regulatory Contractor will download the FDF from the RCR for IVR, NPIVR, and AP registration types when they are added to the DTL. In addition, FDF will be reviewed in the RCR by the DCP Regulatory Contractor annually or prior to an audit, whichever occurs first from date of issuing DSA. FDF will be downloaded if any changes are made.

5.4. The downloaded FDF will be reviewed by DCP for conflict of interest and maintained for the sponsor's record. If any potential conflict is identified, DCP will discuss with the LAO.

6. **Delegation of Tasks Log (DTL) (template provided to the LAO by the DCP Regulatory Contractor upon DCP "Approval on Hold" of the protocol).**

6.1. The DTL is the primary source for tracking staff who perform study-related duties, site and lab locations used in the study. Each LAO and AO will provide either:

- A protocol specific DCP DTL listing all study staff members, including the PI, who are registered as IVR, NPIVR, AP, and A.
- A protocol-specific Site PI DTL, along with an Individual Staff DTL. In this case, an Individual Staff DTL may be provided for each study staff member, or all staff (except the PI) may be listed on one Individual Staff DTL. The DTL must be signed by each study staff member next to their designated task codes, and the site PI. Signatures must be 21 CFR Part 11 compliant.

6.2. The site can choose either the protocol specific DCP DTL or the Site PI plus Individual Staff DTLs at the beginning of the study. The site should adhere to this DTL format throughout the duration of the study.

6.3. Once a protocol has received DCP "Approval on Hold" status, the DCP Regulatory Contractor will request that the LAO determines with each site which DTL template they plan to use. The DCP Regulatory Contractor then completes the appropriate template with protocol and site information (excluding the CTEP-Site ID) and sends the DTL to the LAO. The LAO distributes to the sites, who will complete the remaining sections in the DTL.

6.4. The study staff CTEP Person ID and tasks on the DTL must align with the individual's RCR registration type. Tasks assigned to study staff must be appropriate for their level of training and qualifications.

6.5. Tasks assigned to study staff listed on the DTL should be indicated as described below:

Site Principal Investigator	Patient Screening/Recruiting
DTL Administrator (DTLA)	Primary Study/Site Contact
Agent Prescribing	Rave CRA
Consenting Person	Rave Investigator
Eligibility Assessments	Regulatory Contact
End Point Assessments	RT/Imaging Support
Enrolling Person/Treating Investigator	Source Documentation Completion
History and Physical (H&P) Assessments	Study-related Interventions
IND Prescribing	Toxicity Assessment
Investigational Product Accountability	Unblinded Study Personnel
Pathology Lab Support	Other (Specify)

6.6. Unblinded Study Personnel is required to be assigned only for blinded studies. When this task is assigned, a plan or SOP should be in place at the site that articulates the steps to be followed to prevent possible unblinding to others. This must be included in the site's Trial Master File (TMF) and need not be provided to the DCP Regulatory Contractor.

6.7. Only one site principal investigator can be assigned at each site.

Note: For sites in Canada, if the QI is not the same personnel as the PI. Both QI and PI are required to sign the DTL.

6.8. At least one of the site information, IRB of record and laboratory information listed on the DTL should match the staff IVR/NPIVR 1572. For biostatisticians and pharmacists, lab is not required to match as they are not expected to use the lab for study.

6.9. The first and last name of the staff on the DTL must match the RCR CTEP ID registration name.

6.10. The lab information on the DTL should be verifiable. It is highly recommended to match the lab name and the address on the DTL as it is provided on the RCR 1572 and/or CLIA (US labs using CLIA) or lab certificate.

6.11. Assignment minimum as specified on the 'Delegation of Task Log – Master log' must be met for the site to receive DSA.

6.12. Study staff performing non-protocol-specific research (e.g., biomarker analysis, gene expression, etc.) are not required to be added to the DTL. Examples include nurses, residents, pharmacists (except for a specific pharmacist who is compounding the study agent, monitoring compliance, or needs access to Stars), fellows, and office staff who provide only ancillary or intermittent care. No essential documents are collected for these staff.

Note: Pharmacists can still register in RCR as an A, however, if performing duties that require them to be on the DTL, DCP requires them to have proof of GCP training. The GCP training certificate must be provided to the DCP Regulatory Contractor.

6.13. The site PI's signature or initials acknowledging the staff member's role may not precede the staff member's signature date. The end date for the performance of the tasks should be entered when the staff member leaves the study.

6.14. The DTL can be signed electronically (preferred), or wet ink and then scanned. The signed DTL does not need to be an original.

6.15. An updated DTL should be provided when a staff member changes responsibility or leaves or joins the study.

6.16. LAOs will provide the DTLs to the DCP Regulatory Contractor who will review and maintain the documents for the sponsor's record. the DCP Regulatory Contractor will send the signed DTL to the Data Management, Auditing, and Coordinating Center (DMACC).

- Requirements for Providing Site PI DTL
    - Along with an Individual Staff DTL, a Site PI DTL is also required.
    - The Site PI DTL will capture protocol information, site information, clinical investigator information, IRB of record, laboratory information, and DSA information.
    - If the LAO PI is at the accruing site, then task codes for the LAO PI are listed and the site PI initials against the LAO tasks. If the LAO PI is at a non-accruing site, they will not be listed with task codes on a DTL.

7. **PI Acknowledgement of IB or Package Insert**

7.1. The DCP Regulatory contractor provides the IB or Package Insert acknowledgement form.

7.2. The LAO PI and PI at each site must sign an acknowledgement form provided by the DCP Regulatory Contractor, stating that he/she has reviewed each version of the IB or package insert provided for each agent under investigation in the study.

7.3. LAOs will provide the signed acknowledgement form to the DCP Regulatory Contractor who will review and maintain the document for the sponsor's record.

8. **OHRP Assurance**

8.1. All sites participating in federally funded studies are required to have Federal-wide Assurance (FWA).

8.2. LAOs will provide the OHRP assurance for the site to the DCP Regulatory Contractor who will review and maintain the document for the sponsor's record.

9. **Lab Certification**

9.1. CLIA and CAP certification for labs in the US is highly recommended. When CLIA and or CAP is not available state licenses or other recognized certificates (e.g., Joint Accreditation, COLA) acceptable. At least one certification is required to be provided for a lab. If there are no certifications available (e.g., research labs) an NTF confirming the same is required on the institutional letterhead signed and dated by site staff.

9.2. For International labs, when CLIA/CAP is not available, provide certification pertinent to the country or state.

9.3. LAO will provide copy of certification(s) to the DCP Regulatory Contractor who will review and maintain the document for the sponsor's record.

- Current CLIA Certification

- The majority of laboratories have CLIA certification. The laboratory name and address should match the information on the DTL and the certification must be current.

- Current CAP Certification
  - The laboratory name on the CAP certificate does not always match that on the DTL or the CLIA certificate; however, the CLIA number should match. Not all sites are certified by CAP; if this is the case, an NTF, on institutional letterhead, should be provided.
  - If CAP renewed certificate is not available, CAP extension letter provided by the laboratory is acceptable.

10. **Laboratory Normal Values (LNVs)**

10.1. A set of LNVs is required for each laboratory listed on the DTL. The LNVs should be from the correct laboratory and be current.

10.2. LNVs for local and central laboratories (if applicable) should be updated every two years.

10.3. The laboratory for which LNVs are provided should be uniquely identifiable with the information provided on the document such as laboratory name, address, CLIA number, or any other unique identifiable local laboratory certification number.

10.4. A NTF specifying the location of the LNVs or where the ranges can be found is acceptable instead of a full list of LNVs. The laboratory in reference should be uniquely identifiable with the information provided on the document such as laboratory name, address, CLIA number, etc. The NTF must be signed and dated.

10.5. LAOs will provide the LNVs and/or NTF to the DCP Regulatory Contractor who will review and maintain the document for the sponsor's record.

11. **CIRB or IEC Approval**

11.1. CIRB approval of the protocol is required; this is obtained from the DCP Protocol Information Office.

11.2. For international sites, protocol approval, and annual review approval, if applicable, is required from the IEC or equivalent only. The exception is for sites in US territories (e.g., Puerto Rico), which are overseen by the CIRB.

12. **Informed Consent Document (ICD)**

12.1. CIRB (or IEC or equivalent for international sites) approval must be provided for each ICD. The ICD version on the form must match the approval memo.

12.2. The CIRB approved version of the ICD template is provided to sites. The sites (within US and US territories) will incorporate the boilerplate language and formatting (including any local IRB approval stamps, if required) from their institution's own CIRB ASIW approval letter, CIRB SSW, and/or CIRB APIW approval letter into the CIRB approved template to create their own "localized version" of the ICD. This localized version is the one that must be used for participant enrollment. A copy of the localized version of the ICD (including any versions translated into another language) must be provided to the DCP Regulatory Contractor for review and approval before the DSA for the site will be issued.

12.3. The localized version of the ICD may require local IRB approval. Each institution has individual guidelines for versioning IRB submissions for local review. If required by the local IRB, the localized ICD version and date may be included in addition to the ICD template version and date.

12.4. If the institution has an approval stamp, the ICD with the incorporated template language should be stamped and provided to the DCP Regulatory Contractor.

12.5. CIRB template of short form consents need not be provided to the DCP Regulatory Contractor.

12.6. International sites will make necessary changes to the CIRB approved ICD template as per local requirements and must provide the IEC or equivalent approved localized ICD to The DCP Regulatory Contractor.

12.7. During the course of the study, localized versions of ICD amendments (including all applicable translations) must be provided to The DCP Regulatory Contractor who will maintain the document for the sponsor's record.

Note: A stand-alone HIPAA document need not be provided to the DCP Regulatory Contractor.

13. **CIRB- or IEC-approved Site-Specific Patient/Recruitment Materials**

13.1. DCP obtains approval for all study-level Participant/Recruitment Materials, and they are provided to the DCP Regulatory Contractor, LAO, and AO by the DCP PIO.

13.2. CIRB (or IEC or equivalent for international sites) approval must be provided for any site (LAO/AO) specific patient/recruitment materials (drug diaries, quality of life questionnaires, local advertising, etc.) for sites in the US and its territories.

13.3. The patient/recruitment materials version should match the approval memo.

13.4. Some sites will utilize a local version of the patient/recruitment materials. . The modified document (and any translated versions of the document) should be sent to the LAO for submission to the DCP. Once DCP approval is obtained, the document (and any translations) is submitted to the CIRB for review/approval via the SSW. Submit any modified documents to the DCP Regulatory Contractor to maintain for the sponsor's records.

Note: Information sheets provided to participants, which are not specific to the study do not require DCP or CIRB review and approval.

13.5. The patient/recruitment material version and date may be included if approved as part of the institution's boilerplate language. The date may be a different date than the version date on the CIRB-approved document, as each institution has individual guidelines for versioning IRB submissions.

13.6. LAO provides a copy of CIRB approved local Participant/Recruitment materials to the DCP Regulatory Contractor for sponsor's record.

14. **Other CIRB Approvals**

14.1. The CIRB ASIW approval letter must be provided to the DCP Regulatory Contractor to issue DSA. During the course of the study, all ASIW amendments approved by the CIRB must be provided to the DCP Regulatory Contractor for the sponsor's record.

14.2. The CIRB APIW approval letter must be provided to the DCP Regulatory Contractor to issue DSA. During the course of the study, all APIW amendments approved by the CIRB must be provided to the DCP Regulatory Contractor for the sponsor's record.

14.3. The CIRB approval of the SSW for the study must be provided to the DCP Regulatory Contractor when the LAO obtains it for the sponsor's record. This approval letter is not required for DSA. Any document approved with the SSW must be provided to the DCP Regulatory Contractor for the sponsor's record.

15. **Local Site IRB Acknowledgement or Approvals (US Sites)**

15.1. According to CIRB policies and procedures, the local IRBs in the US give authority to the CIRB for review and approval of protocols. Collection of any local IRB acknowledgement letters for those sites that produce them will be managed by the LAOs.

15.2. LAOs are to notify the DCP Regulatory Contractor if a site's local IRB will be providing any acknowledgment or approval letters and the time point at which these letters will be provided. This information must be provided at the time of confirming the site's DTL preference. All approvals and/or acknowledgments issued by the local IRB must be provided to the DCP Regulatory Contractor.

15.3. IRB acknowledgement or approval of protocol and ICD must include the version number in the letter. If information is not provided in the letter, the site must confirm the version date.

15.4. When a site's local IRB provides a letter prior to initiating the study at the site, the LAO must provide this letter to the DCP Regulatory Contractor for the site to obtain DSA.

16. **Certificates of Translation**

16.1. Certificates of translation should be provided for ICDs, IRB or IEC approvals, patient/ recruitment materials, or any other documents that are translated from one language to another.

16.2. A NTF attesting to the accuracy and completeness of the translated document with information about the person who translated the document can be submitted in lieu of certificates of translation. This document must be signed by either the translator or the site PI.

7. LAO, AO, AND THE DCP REGULATORY CONTRACTOR RESPONSIBILITIES

1. **Document Submission for DSA**

1.1. Check Appendix I *DSA Documents Checklist* on the list of documents that must be submitted to the DCP Regulatory Contractor to obtain DSA for a site.

1.2. Prior to forwarding essential documents to the LAO, an inspection of materials by the AO is recommended to reduce the submission of expired, illegible, and invalid paperwork.

1.3. Upon receipt from the AO, the LAO should forward the essential documents to the DCP Regulatory Contractor, who will conduct a full quality review based on the criteria for each document type described in section 5 of this document. As detailed above, except for documents downloaded from the RCR by the DCP Regulatory Contractor, all other essential documents should be submitted to the DCP Regulatory Contractor in electronic format at regulatory@ccsainc.com.

1.4. Upon receipt of essential documents, the DCP Regulatory Contractor will confirm that each investigator providing a Form FDA 1572 is not listed on the FDA Disqualification Proceedings and Warning Letters websites.

- FDA Disqualification Proceedings
- Warning Letters

1.5. If an investigator is listed on either website, he/she may not participate in the study.

1.6. The DCP Regulatory Contractor will request the LAO to communicate any quality review comments and/or requests for revised documents to the submitting AO.

1.7. When all essential documents for the sponsor's TMF have been received, reviewed, and approved, the DCP Regulatory Contractor will email a DSA to the DCP Protocol Information Office, LAO, AO, Medical Monitor (MM), Scientific Monitor (SM), Nurse Consultant (NC), Scientific Lead (SL), DMACC, and drug distributor (e.g., NCI repository contractor).

2. **Document Submission for Non-accruing and Administrative Sites**

2.1. The following essential documents are required for non-accruing and administrative site activation, if applicable:

- PI's NCI Biosketch, professional licensure, GCP training certification, and FDF.
- PI's Form FDA 1572.
- PI's acknowledgement of IB or package insert.
- OHRP assurance.
- CIRB or IEC approval of the protocol (no ICD).

2.2. As detailed above, except for documents downloaded from the RCR by the DCP Regulatory Contractor, all other essential documents should be submitted to the DCP Regulatory Contractor in electronic format at regulatory@ccsainc.com.

3. **Document Submission During Course of Study**

3.1. Each LAO and AO is responsible for submitting updated essential documents throughout the duration of the study except for documents that are downloaded from the RCR. All updated documents should be forwarded to the DCP Regulatory Contractor.

3.2. **Canadian sites**: Post-DSA prior to activation of all protocol amendments, the LAO must confirm with the DCP Regulatory Contractor if the protocol amendment can be activated at the site(s).

3.3. The following essential documents expire and require submission of updated versions to the DCP Regulatory Contractor:

- OHRP assurance
- Lab Certification*
- LNVs, every two years*
- CIRB or IEC approval of the protocol, ICD, and participant/recruitment materials
- Local IRB approval or acknowledgement, if applicable

*Laboratory certifications and LNVs will need to be provided while the laboratory is in use for the study.

4. **DTL Updates**

4.1. A DTL must be updated when there are updates to site information, laboratory information, drug shipment address, study staff, or role of study staff. The DCP Regulatory Contractor must be informed of any updates made to the DTL and a copy of the DTL must be provided to the DCP Regulatory Contractor who will review and maintain the document for the sponsor's record.

4.2. If an individual site study staff no longer performs study-related tasks, the end date can be added to the DTL for those study staff. The updated DTL is submitted to the DCP Regulatory Contractor. No further updated documents will be required for the staff after the end date is added to the DTL.

4.3. When a laboratory is no longer in use for the study, the DCP Regulatory Contractor must be updated with the laboratory's end date. No further updated documents will be required for the laboratory after the end date is added to the DTL.

8. ADDITIONAL INFORMATION

Please send questions and comments to regulatory@ccsainc.com.

9. REFERENCES

Note: All CP-CTNet SOPs are included in the *CP-CTNet Manual of Standard Operating Procedures (M-SOP)*, which is available on the CP-CTNet DMACC public website.

Document	ID	Location
CTEP Identity and Access Management	Application	CTEPcore.nci.nih.gov
DCP Delegation of Tasks Log	Form	Program Resources
DCP Delegation of Tasks Log – Individual Staff	Form	Program Resources
DCP Delegation of Tasks Log – Site Principal Investigator	Form	Program Resources
DCP Delegation Task Log Master Task List	Reference	Program Resources
FDA Disqualification Proceedings	Reference	Accessdata.fda.gov
Good Clinical Practice: Integrated Addendum to ICH E6(R1)	E6(R2)	FDA.gov
NCI Registration and Credential Repository	Application	CTEPcore.nci.nih.gov
OHRP Website	Reference	OHRP.cit.nih.gov
Warning Letters	Reference	FDA.gov

10. APPENDICES

1. Appendix I *DSA Documents Checklist*

Appendix I

DSA Documents checklist

Following is the checklist of documents to provide the DCP Regulatory Contractor to obtain DSA for a site.

- ☐ Signed DTL.
- ☐ Staff listed on the DTL must have active RCR registration.
- ☐ LAO PI signed IB/PI Acknowledgement Form (if not already provided for study).
- ☐ PI signed IB/PI Acknowledgment Form.
- ☐ Current Laboratory Certifications for all labs added to the DTL.
- ☐ Current LNV for all labs added to the DTL.
- ☐ Federal Wide Insurance (OHRP).
- ☐ Local ICF (including other languages).
- ☐ Local IRB letters (if applicable).
- ☐ Site Specific or stamped by local IRB Patient/Recruitment Materials (if applicable).
- ☐ CIRB ASIW.
- ☐ CIRB APIW.
- ☐ Certificate of Translation (if appliable).

Title: Study Initiation Meeting

Document ID:	CP-CTNet SOP 01-02
Version:	5.0
Version Date:	January 26, 2024

REVISION HISTORY (most recent first)

Version	Effective Date	Summary of Changes
5.0	JAN-26-2024	Replaced references to sites with accruing LAOs and AOs and added references to the *CP-CTNet Study Initiation Meeting Agenda Template*. Made minor updates throughout the document.
4.0	FEB-21-2023	Added a section about study initiation meetings for new sites that are added to existing studies.
3.0	JUL-18-2022	Updated the DMACC role and contact information for scheduling and conducting study initiation meetings, added references to accruing LAOs, and made minor updates throughout document.
2.0	SEP-13-2021	Updated the action item documentation procedure and added a section about storing and sharing the study initiation meeting recording.
1.0	AUG-17-2020	Original version of document.

1. INTRODUCTION AND PURPOSE

It is the Lead Academic Organization's (LAO's) responsibility to conduct the study initiation meeting (SIM). The purpose of the SIM is to meet with Division of Cancer Prevention (DCP) staff, Data Management, Auditing, and Coordinating Center (DMACC) staff, and key staff from each accruing LAO and Affiliated Organization (AO) who will conduct the study. This meeting provides an opportunity to:

1. Provide an orientation to the study and review study-specific details (e.g., the procedures for investigational agent management, reporting requirements, and data and specimen management).
2. Confirm all roles, responsibilities, and performance expectations.
3. Highlight that the following items need to occur before each accruing LAO and AO may begin enrolling participants:
    - 3.1. Staff at each accruing LAO and AO have received the required access and training for DMACC systems (e.g., Medidata Rave, Stars, etc.).
    - 3.2. All regulatory requirements have been completed for each accruing LAO and AO.
    - 3.3. Each accruing LAO and AO has met all other accruing LAO or AO activation requirements as per SOP 01-03 *Accruing LAO and AO Activation*.

2. SCOPE

This document details the responsibilities of the LAO Investigators, LAO Coordinators, and their designees regarding the SIM.

3. DEFINITIONS

Term	Definition
AO	Affiliated Organization
CIRB	Central Institutional Review Board
CP-CTNet	Cancer Prevention Clinical Trials Network
DCP	Division of Cancer Prevention
DMACC	Data Management, Auditing, and Coordinating Center
LAO	Lead Academic Organization
M-SOP	Manual of Standard Operating Procedures
MM	Medical Monitor
NC	Nurse Consultant
NCI	National Cancer Institute
SIM	Study Initiation Meeting
SL	Scientific Lead

4. ROLES AND RESPONSIBILITIES OF LAOS

1. The LAO Investigator, LAO Coordinator, and/or their designee(s) are responsible for conducting the SIM for each study.
2. Key staff members from each accruing LAO and AO are responsible for attending the SIM before consenting or enrolling participants.

5. PROCEDURES

The LAO Investigator, LAO Coordinator, and/or their designee(s):

1. Schedule the SIM:
    1.1. The meeting is typically scheduled after:
        - DCP issues a "Notice of Study Approved on Hold" letter to the LAO; and
        - The NCI CIRB has approved the protocol.
    1.2. The meeting is scheduled as close to the anticipated study activation date as possible.
    1.3. The meeting may be held at the LAO institution, accruing LAO or AO institution, other location, or remotely. If held onsite, remote conferencing for participants unable to attend in person is scheduled.
    1.4. The meeting is typically scheduled for a three-hour time period.
    1.5. Schedule a meeting date that is mutually convenient for LAO staff, key staff from each accruing LAO and AO, DCP staff, and DMACC staff. Consider the following list of staff from the LAO, each accruing LAO and AO (as applicable to the study), DCP, and DMACC:
        - Investigator(s)
        - LAO Coordinator(s)
        - Accruing LAO and AO Coordinator(s)
        - Study pathologist(s)
        - Study statistician(s)
        - Study pharmacist(s)
        - Data management team
        - Other staff with study responsibilities, such as key laboratory staff
        - DCP MM, SL, NC, and other representatives
        - DMACC staff (via DMACC_SIM_CP-CTNet@frontierscience.org)

          Note: If there are many accruing LAOs and AOs participating in a study, separate SIMs may need to be conducted to accommodate all accruing LAO and AO staff. If separate SIMs are not feasible, access to a recording of the original SIM is provided to staff from accruing LAOs and AOs who are unable to attend or whose accruing LAO or AO is added as a new enrolling institution at a later date.
    1.6. Send an email confirmation of the meeting date to all participants.

2. Prepare for the SIM:

    2.1. Prepare an agenda prior to the meeting that outlines all relevant discussion topics and designates a facilitator for each topic. Refer to the *CP-CTNet Study Initiation Meeting Agenda Template* and the *CP-CTNet Study Initiation Meeting Report* to review the list of topics that may be applicable.

    - DMACC participates in the preparation process for each SIM by working with the LAO Coordinator to develop a study-specific training topic list, and provides training during the SIM based on the DMACC responsibilities outlined in the *CP-CTNet Study Initiation Meeting Report Template*. The LAO coordinates with DMACC (via DMACC_SIM_CP-CTNet@frontierscience.org) before scheduling the SIM to ensure that DMACC trainers are available to present at the SIM.

    2.2. Prepare meeting materials and distribute to participants.

    2.3. Confirm with the DCP Regulatory Contractor (via regulatory@ccsainc.com) that all or most of the essential documents are on file and complete for each accruing LAO and AO.

3. Conduct the SIM:

    3.1. Complete an attendance record to document the name, institutional affiliation, and study role for all meeting participants. Maintain the original attendance record in the LAO essential documents file and provide a copy to accruing LAO and AO staff for their records.

    3.2. During the meeting, document items that are identified as action items or that require follow-up. Review the action items with the meeting participants prior to concluding the meeting.

    3.3. Complete the *CP-CTNet Study Initiation Meeting Report*, including a description of action items.

    - Distribute the completed report via email to the accruing LAOs and AOs, DCP, and DMACC within 15 business days of the meeting.

    Note: If accruing LAO or AO follow-up of action items is required, the accruing LAO(s) and/or AO(s) must return the updated *CP-CTNet Study Initiation Meeting Report* to the LAO Coordinator within 30 business days upon receipt of the completed report.

    - Document the resolution of all action items in the *CP-CTNet Study Initiation Meeting Report* prior to participant enrollment, and forward the updated *CP-CTNet Study Initiation Meeting Report* to the accruing LAOs and AOs, DCP, and DMACC.

4. Record the SIM:

    4.1. Store the SIM recording on a preferred secure internal storage system.

    4.2. Share the SIM recording with relevant LAO and/or accruing LAO and AO staff (e.g., staff that missed the original SIM, new accruing LAO or AO staff, etc.).

Maintain an attendance record for LAO and/or accruing LAO and AO staff who reviewed and signed off on the training included in the SIM. The DMACC Audit team verifies that the appropriate documentation for SIMs is available during DMACC quality assurance audits.

6. DOCUMENTATION REQUIREMENTS

The LAO is responsible for maintaining the following documentation related to the SIM: attendance record, meeting agenda, *CP-CTNet Study Initiation Meeting Report*, SIM recording, and any other related communications (e.g., resolution of action items). This documentation must be readily accessible and may be requested by DCP, the DCP Regulatory Contractor, and/or the DMACC Audit team at any time during the duration of the study. The accruing LAOs and AOs must file the completed *CP-CTNet Study Initiation Meeting Report* in their essential documents file.

7. SIMS FOR NEW ACCRUING LAOS OR AOS ADDED TO EXISTING STUDIES

The LAO is responsible for determining the best way to convey important SIM information to accruing LAOs or AOs that are added to a study after the initial SIM is conducted. The LAO considers the training needs of each new accruing LAO or AO while determining the agenda and format for conveying this SIM information (e.g., via a full-length SIM, an abbreviated SIM with limited presenters and presentations, a documented review of the original SIM recording, etc.). The DMACC Audit team verifies that the appropriate documentation related to any SIM for new accruing LAO(s) or AO(s) added to an existing study is available during DMACC quality assurance audits.

8. ADDITIONAL INFORMATION

Please send questions and comments to DMACC_SIM_CP-CTNet@frontierscience.org.

9. REFERENCES

Note: All CP-CTNet SOPs are included in the *CP-CTNet Manual of Standard Operating Procedures (M-SOP)*, which is available on the CP-CTNet DMACC public website.

Document	ID	Location
CP-CTNet Study Initiation Meeting Agenda Template	Template	Program Resources
CP-CTNet Study Initiation Meeting Report Template	Template	Program Resources
Accruing LAO and AO Activation	SOP 01-03	Program Resources

10. APPENDICES

- None

Title:	**Accruing LAO and AO Activation**
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Version:	4.0
Version Date:	January 26, 2024

REVISION HISTORY (most recent first)

Version	Effective Date	Summary of Changes
4.0	JAN-26-2024	Updated the document to clarify the approval and document submission requirements for accruing LAO and AO activation. Replaced the term "site" with “accruing LAOs and AOs” (as appropriate) throughout the document.
3.0	FEB-21-2023	Added section 3 Definitions and updates to procedures throughout document.
2.0	JAN-06-2022	Major rewrite of entire SOP.
1.0	AUG-17-2020	Original version of document.

1. INTRODUCTION AND PURPOSE

The purpose of this document is to provide accruing Lead Academic Organization (LAO) and Affiliated Organization (AO) activation requirements for Cancer Prevention Clinical Trials Network (CP-CTNet) studies. Accruing LAO or AO activation means an accruing LAO or AO can enroll participants and enter data for a given study.

The following must be in place for an accruing LAO or AO to be activated to a study:

- The study has Final Approval from the Division of Cancer Prevention (DCP).
- The study setup in the Medidata Rave Electronic Data Capture (EDC) system is completed by the Data Management, Auditing, and Coordinating Center (DMACC).
- The study implementation in the Stars registration/randomization system has been completed by DMACC. Stars is the web-based enrollment system hosted at DMACC and is used to pre-screen, screen, and enroll participants to a study.
- The LAO has confirmed to DMACC that the accruing LAO or AO has met all accruing LAO and AO activation requirements (see the *CP-CTNet Accruing LAO and AO Activation Checklist for LAOs* for more information).

The steps for activating an accruing LAO or AO can begin prior to database and systems setup being completed by DMACC. Each accruing LAO and AO must meet several requirements, including receipt of local Institutional Review Board (IRB) acknowledgement, submission of documents to the DCP Regulatory Contractor, registration of appropriate staff to the National Cancer Institute (NCI) Registration and Credential Repository (RCR), etc. (refer to SOP 01-01 *Essential Documents Submission for Sponsor's Record* for additional information). The accruing LAO's or AO's site open date (site activation date) is the date that DMACC sends a ***Confirmation of Site Activation*** email to PIO, the LAO, the accruing LAO or AO, the DCP Regulatory Contractor, and the DCP Study Team (Medical Monitor (MM), Nurse Consultant (NC), and Scientific Lead (SL)). If multiple accruing LAOs and/or AOs are participating in a study, each accruing LAO and/or AO may have a different site open date, depending on when requirements are met.

LAOs are responsible for study oversight, including conducting Study Initiation Meeting(s) (SIM(s)), assisting accruing LAOs and AOs with meeting all regulatory and documentation requirements before activation at their accruing LAO or AO, and informing DMACC when an accruing LAO or AO meets all requirements for activation.

2. SCOPE

This document details the requirements and steps for LAOs, accruing LAOs and AOs, and DMACC that must be completed before activating an accruing LAO or AO to begin enrollment onto a study.

3. DEFINITIONS

Term	Definition
AO	Affiliated Organization
CIRB	Central Institutional Review Board
CP-CTNet	Cancer Prevention Clinical Trials Network
DCP	Division of Cancer Prevention
DMACC	Data Management, Auditing, and Coordinating Center
eCRF	Electronic Case Report Form

Term	Definition
EDC	Electronic Data Capture
IBC	Institutional Biosafety Committee
IRB	Institutional Review Board
LAO	Lead Academic Organization
M-SOP	Manual of Standard Operating Procedures
MM	Medical Monitor
NC	Nurse Consultant
NCI	National Cancer Institute
PID	Participant Identification Number
PIO	Protocol Information Office
RCR	Registration and Credential Repository
SIM	Study Initiation Meeting
SL	Scientific Lead
SOP	Standard Operating Procedure
SSW	Study Specific Worksheet
SVAR	System Variable Attribute Report

4. REQUIRED STEPS FOR ACCRUING LAO OR AO ACTIVATION

The process of accruing LAO or AO activation involves the accruing LAO or AO meeting all regulatory requirements, as well as accruing LAO or AO users having appropriate access to Stars (including all applicable modules) and Medidata Rave. An accruing LAO or AO cannot be activated or begin pre-screening, screening, and enrolling participants to a study until they receive a ***Confirmation of Site Activation*** email from DMACC. This email indicates that an accruing LAO or AO has met all requirements for activation and now has permissions to begin pre-screening, screening, and enrolling participants to a study. The date that DMACC sends the ***Confirmation of Site Activation*** email is the accruing LAO's or AO's site open date.

The LAO is responsible for ensuring all requirements for accruing LAO and AO activation are met. A *CP-CTNet Accruing LAO and AO Activation Checklist for LAOs* is provided as a guideline. There is no need to submit the checklist to DMACC. These requirements include:

1. All regulatory approvals are in place (e.g., CIRB, local IRB, SSW, IBC, in-country approvals for international sites (if applicable)), and the DCP Regulatory Contractor has collected all necessary regulatory documents (refer to SOP 01-01 *Essential Documents Submission for Sponsor's Record*).
2. Contracts/sub-contracts are in place.
3. The LAO conducted the SIM(s) onsite or virtually with the accruing LAOs and AOs who are named as "Accrual Organizations" for the study (refer to SOP 01-02 *Study Initiation Meeting*).
4. If applicable, Drug Shipment Authorization has been received and drug availability is confirmed onsite.
5. The LAO Coordinator or designee accessed the CP-CTNet DMACC Portal Gateway to proxy-request appropriate access for accruing LAO or AO staff based on their study role, and DMACC has granted access. There are several study roles that may be requested within the Portal Gateway and the most common applications associated with the requested study role are selected by default. The available study roles include Audit System User, Clinical Research

Coordinator, DCP Staff, LAO Staff, Medical Monitor, Pharmacist, Scientific Lead, and Site Investigator. For information about the CP-CTNet DMACC Portal Gateway account registration process, refer to USRMAN02 *Public Website and Portal Gateway Overview and User Registration Guide*.

5.1. DMACC User Support processes each access request within two days. DMACC User Support (UserSupport_CP-CTNet@frontierscience.org) is available to assist with any questions.

6. DMACC contacted the LAO Coordinator or designee to confirm the name(s) and email address(es) of the personnel at the LAO who have permission to reserve PIDs for each accruing LAO and AO (usually the LAO Coordinator).

   6.1. DMACC User Support will process each access request within two days.

   6.2. The LAO must access the Reserve PIDs module in Stars to reserve PIDs for a given accruing LAO or AO before that accruing LAO or AO can enroll participants. For more information about the process that LAOs follow to reserve PIDs in Stars, refer to USRMAN01 *CP-CTNet Stars User Guide*, QKREFGD02 *Summary of Enrollment Process*, and the Reserving Participant IDs for CP-CTNet video tutorial that is available on the Stars dashboard item page on the CP-CTNet DMACC Portal Gateway.

7. The LAO sent an email to DMACC, confirming the accruing LAO or AO has met all activation requirements.

5. CONFIRMATION OF ACCRUING LAO OR AO ACTIVATION

1. Once the first accruing LAO or AO has met all activation requirements outlined in Section 4 above, with the exception of SSW and IBC (if applicable) approvals, the LAO completes a *Protocol Status Update Form* and submits it to PIO to indicate that the study is active. PIO submits the *Protocol Status Update Form* to the CIRB. Once the CIRB is notified that the study is active, then all accruing LAOs and AOs can submit their SSW.
2. Once DMACC receives notification from the LAO that an accruing LAO or AO has met all activation requirements outlined in Section 4 above, including SSW and IBC (if applicable) approvals, and the study has been implemented in Stars and set up in Medidata Rave, DMACC then activates the accruing LAO or AO in its Protocol Approval module in Stars.
3. DMACC sends a ***Confirmation of Site Activation*** email to PIO, the LAO, the accruing LAO or AO, the DCP Regulatory Contractor, and the DCP Study Team (MM, NC, and SL) to indicate that the accruing LAO or AO site is officially open to accrual in Stars and the accruing LAO or AO may now begin pre-screening, screening, and enrolling participants to the study. The LAO and accruing LAO or AO file this email in their electronic or paper essential documents binder for the study. After pre-screening its first participant, a newly activated accruing LAO or AO should update the CP-CTNet AQuIP Recruitment Journal in Medidata Rave with the site open date, which is the date that the accruing LAO or AO was activated to the study as per the ***Confirmation of Site Activation*** email sent by DMACC.

6. ACCRUING LAO OR AO ACTIVATION TO AN AMENDMENT

1. Depending on the nature of the amendment, all the steps involved in activating an accruing LAO or AO to the initial study protocol may not need to be followed. For example, new or revised contracts are generally not required (unless a new accruing LAO or AO is added), additional or updated regulatory documents may not be needed (e.g., in case of an administrative amendment), etc.

2. DMACC will implement the CIRB and DCP approved amendment in Stars and Medidata Rave (as needed). During the amendment process, the initial and amended version will be in Stars, and accruing LAOs and AOs will continue to enroll under the initial version until they are activated to the amended version.
3. The LAO confirms that all necessary accruing LAO and AO activation requirements have been completed for the amendment (see the *CP-CTNet Accruing LAO and AO Activation Checklist for LAOs* for more information). Once an accruing LAO or AO has met all amendment activation requirements, the LAO sends a confirmation email to DMACC.
4. Once the amendment has been implemented in Stars and set up in Medidata Rave (as needed), DMACC activates the accruing LAO or AO to the amendment in the Protocol Approval module in Stars. This is required before the accruing LAO or AO can use any updated eligibility checklists in Stars or apply/enact any modifications included in the amendment.
5. DMACC sends a ***Confirmation of Site Activation to Amendment*** email to PIO, the LAO, the accruing LAO or AO, the DCP Regulatory Contractor, and the DCP Study Team (MM, NC, and SL) to indicate that the accruing LAO or AO site is officially open to accrual to the amendment in Stars and the accruing LAO or AO may now begin pre-screening, screening, and enrolling participants to the amendment. The LAO and accruing LAO or AO file this email in their electronic or paper essential documents binder for the study.

7. ADDITIONAL INFORMATION

Please send questions and comments to DataManagement_CP-CTNet@frontierscience.org.

8. REFERENCES

Note: All CP-CTNet SOPs are included in the *CP-CTNet Manual of Standard Operating Procedures (M-SOP)*, which is available on the CP-CTNet DMACC public website.

Document	ID	Location
CP-CTNet Program Guidelines	Reference	Program Resources
CP-CTNet Accruing LAO and AO Activation Checklist for LAOs	Form	Program Resources
CP-CTNet Stars User Guide	USRMAN01	Program Resources
Essential Documents Submission for Sponsor's Record	SOP 01-01	Program Resources
NCI Registration and Credential Repository	Application	CTEPcore.nci.nih.gov
Protocol Status Update Form	Form	Program Resources
Public Website and Portal Gateway Overview and User Registration Guide	USRMAN02	Program Resources
Reserving Participant IDs for CP-CTNet	Video Tutorial	Stars Dashboard Page
Study Initiation Meeting	SOP 01-02	Program Resources
Summary of Enrollment Process	QKREFGD02	Program Resources

9. APPENDICES

- None

Title: Reporting Serious Adverse Events

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Version Date:	January 26, 2024

REVISION HISTORY (most recent first)

Version	Effective Date	Summary of Changes
5.0	JAN-26-2024	Updated the text and flowchart to include the notification procedures for Protocol PIs, the CIRB, and CNTs. Minor updates were made throughout the document.
4.0	FEB-21-2023	Added section 3 Definitions, minor clarifications on timelines for reporting SAEs.
3.0	DEC-02-2021	Updated SAE definition and reporting requirements to be consistent with FDA guidance, updated response to queries in Appendix I.
2.0	SEP-10-2020	Clarified inpatient hospitalization, updated DCP Regulatory Contractor phone number, clarified query response submittal, updated contact information in Appendix I.
1.0	AUG-17-2020	Original version of document.

1. INTRODUCTION AND PURPOSE

Investigators, Co-Investigators, Coordinators, and designees at Cancer Prevention Clinical Trials Network (CP-CTNet) accruing Lead Academic Organizations (LAOs) and Affiliated Organizations (AOs) are responsible for the proper and timely reporting of all serious adverse events (SAEs) that occur during the conduct of a study.

For all SAEs, the accruing LAO or AO where the SAE occurred is responsible for reporting the SAE to the Division of Cancer Prevention (DCP) Medical Monitor (MM) and DCP Regulatory Contractor's Safety Department by phone or email within 24 hours of knowledge and on the *DCP Serious Adverse Event Report Form* within 48 hours of knowledge. The accruing LAO or AO must also report the SAE to the Protocol Principal Investigator (PI) and LAO Coordinator. The Food and Drug Administration (FDA) or other regulatory authority, and/or the pharmaceutical sponsor, may also have other reporting requirements.

For Cross-Network Trials (CNTs), in addition to the above, the accruing LAO or AO where the SAE occurred must also send the *DCP Serious Adverse Event Report Form* to the Lead LAO Coordinator and Collaborating LAO Coordinator within 48 hours of knowledge (see REFGD06 *Cross-Network Trials Guidelines* for more information).

Note: The DCP protocol numbering convention for CP-CTNet CNTs is INT, which stands for "inter-network trial" (e.g., INT21-05-01).

An SAE is defined by the Code of Federal Regulations (CFR) as any untoward medical occurrence associated with the use of a drug in humans that, at any dose, has one or more of the following outcomes:

1. Death.
2. A life-threatening adverse event:
    - 2.1. Per FDA regulations, a life-threatening adverse event places the participant at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization or prolongation of existing hospitalization:
    - 3.1. The FDA does not define what constitutes inpatient hospitalization. The National Cancer Institute (NCI), DCP uses admission or stay (including emergency room) equal to or greater than 24 hours as the definition of hospitalization. Exceptions are hospitalization for treatment of a pre-existing condition (unless the condition increased in severity on study), outpatient surgery, planned/elective procedures, and procedures described in the protocol (e.g., pharmacokinetic sampling, surgery). These events ***should not*** be reported by the Investigator/Co-Investigator on the *DCP Serious Adverse Event Report Form* even if the hospital stay is equal to or greater than 24 hours.
    - 3.2. In contrast, an event occurring during any hospitalization, even during protocol-defined procedures, that prolongs the hospitalization or has another serious outcome should be considered an SAE and reported by the Investigator/Co-Investigator on the *DCP Serious Adverse Event Report Form*. The DCP MM, DCP Regulatory Contractor's Safety Department, Protocol PI, and LAO Coordinator should also be notified by phone or email.
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. A congenital anomaly or birth defect.

6. Important medical events that may not result in death, are not life-threatening, and do not require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the other outcomes listed above.

    6.1. FDA's examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

2. SCOPE

This document details the responsibilities of the CP-CTNet accruing LAO and AO Investigators, Co-Investigators, Coordinators, and designees regarding the reporting of SAEs, including initial reporting, follow-up, and documentation.

3. DEFINITIONS

Term	Definition
AO	Affiliated Organization
CFR	Code of Federal Regulations
CIRB	Central Institutional Review Board
CNT	Cross-Network Trial
Collaborating LAO	An LAO that is involved in a CNT that has oversight responsibilities for its own accruing LAO and AOs
CP-CTNet	Cancer Prevention Clinical Trials Network
DCP	Division of Cancer Prevention
FDA	Food and Drug Administration
INT	Inter-Network Trial or INT is the DCP protocol numbering convention for CP-CTNet trials (e.g., INT21-05-01).
IRB	Institutional Review Board
LAO	Lead Academic Organization
Lead LAO	An LAO that takes primary responsibility for the administrative aspects of the CNT and has oversight responsibilities for its own accruing LAO and AOs
M-SOP	Manual of Standard Operating Procedures
MM	Medical Monitor
NCI	National Cancer Institute
PI	Principal Investigator
PT	Pacific Time Zone
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
UP	Unanticipated Problem

4. RESPONSIBILITIES FOR REPORTING SAES

Investigators, Co-Investigators, Coordinators, and designees at each accruing LAO and AO will report SAEs as follows:

1. Contact the DCP MM (phone and email as listed in the protocol), DCP Regulatory Contractor's Safety Department (phone: 650-691-4400 x133 and email: safety@ccsainc.com), Protocol PI (phone and email as listed in the protocol), and LAO Coordinator within 24 hours of knowledge of the SAE, and communicate the following information:
    1.1. Participant ID.
    1.2. Date and time of SAE onset.
    1.3. Date and time the accruing LAO or AO was notified about the SAE by the study participant or other person(s).
    1.4. Name of the person who is reporting the SAE.
    1.5. Call-back phone number and email.
    1.6. Accruing LAO or AO at which the participant is enrolled.
    1.7. DCP protocol number.
    1.8. Title of protocol.
    1.9. Suspected drug (if any).
    1.10. Description of SAE, including attribution to the investigational agent.
2. Email a copy of the completed *DCP Serious Adverse Event Report Form* to the DCP MM (email as listed in the protocol) and DCP Regulatory Contractor's Safety Department (safety@ccsainc.com) within 48 hours of knowledge of the SAE. The information must be entered into the Word form; the form should then be signed with a wet ink or electronic signature, scanned (as needed), and emailed. For guidance or assistance, the DCP Regulatory Contractor's Safety Department may also be reached by phone at 650-691-4400 x133 during regular business hours (PT).
    2.1. Reference the *Serious Adverse Event Report Form: Instructions for Completion and Submission* for assistance in completing the *DCP Serious Adverse Event Report Form*.
    2.2. Ensure that an Investigator or Co-Investigator for the accruing LAO or AO where the SAE occurred signs the form.
    2.3. Forward the completed form to the Protocol PI and LAO Coordinator. For CNTs, also forward the completed form to the Lead LAO Coordinator and Collaborating LAO Coordinator (see REFGD06 *Cross-Network Trials Guidelines* for more information).
3. Comply with all institutional requirements and all CIRB requirements related to the reporting of SAEs. Specifically, if an SAE meets the definition of a UP (i.e., requires expedited reporting to the FDA or manufacturer as a safety report [serious, unexpected, and related to a study agent]), then it needs to be reported to the CIRB by the Signatory Institution PI at the accruing LAO or AO where the SAE occurred (see SOP 02-02 *Reporting Protocol Deviations* for more information). In addition to CIRB requirements, UPs must be reported to the accruing LAO's or AO's local IRB per local requirements.
    3.1. Accruing LAOs and AOs must discuss UPs with the DCP Study Team, Protocol PI, and LAO (or Lead and Collaborating LAOs for CNTs) prior to CIRB submission.
    3.2. The Signatory Institution PI or designee should share a copy of the UP CIRB submission with the DCP Study Team.
4. Respond to any queries from the DCP Regulatory Contractor's Safety Department.
5. When applicable (e.g., revised information, new follow-up information), complete a follow-up report using the previously submitted *DCP Serious Adverse Event Report Form* as soon as

additional information is available. The Investigator or Co-Investigator should also sign and date each follow-up report.

6. Send follow-up reports to the following:
   6.1. DCP Study Team.
   6.2. DCP Regulatory Contractor's Safety Department.
   6.3. Protocol PI.
   6.4. LAO Coordinator.
   6.5. Lead LAO Coordinator and Collaborating LAO Coordinator if the study is a CNT.
7. Comply with the instructions listed in the protocol regarding the length of time for follow-up of an SAE.

5. DOCUMENTATION REQUIREMENTS

1. Each accruing LAO and AO will retain in their study files a copy of each *DCP Serious Adverse Event Report Form*, supporting documentation, and communication related to the reporting of the SAE. All participant identifiers should be redacted from copies of the supporting documentation.
2. The LAO Coordinators and/or designees will retain in the LAO study files a copy of each *DCP Serious Adverse Event Report Form*, supporting documentation, and communication related to the reporting of the SAE from all accruing LAOs and AOs.
3. The Protocol PI will retain in the study Trial Master File a copy of each *DCP Serious Adverse Event Report Form*, supporting documentation, and communication related to the reporting of the SAE from all accruing LAOs and AOs.
4. For CNTs, the Lead LAO Coordinator and/or designees will retain in the LAO study files a copy of each *DCP Serious Adverse Event Report Form*, supporting documentation, and communication related to the reporting of the SAE from all accruing LAOs and AOs. The Collaborating LAO Coordinator and/or designees will retain in the LAO study files a copy of each *DCP Serious Adverse Event Report Form*, supporting documentation, and communication related to the reporting of the SAE from their accruing LAO and all of their AOs.

6. ADDITIONAL INFORMATION

Questions related to the reporting of SAEs may be directed to the DCP Regulatory Contractor's Safety Department at safety@ccsainc.com.

7. REFERENCES

Note: All CP-CTNet SOPs are included in the *CP-CTNet Manual of Standard Operating Procedures (M-SOP)*, which is available on the CP-CTNet DMACC public website.

Resource	ID	Location
Algorithm to Assess a Potential Unanticipated Problem	Website	ncicirb.org
Cross-Network Trials Guidelines	REFGD06	Program Resources
DCP Serious Adverse Event Report Form	Form	Program Resources
Reporting Protocol Deviations	SOP 02-02	Program Resources

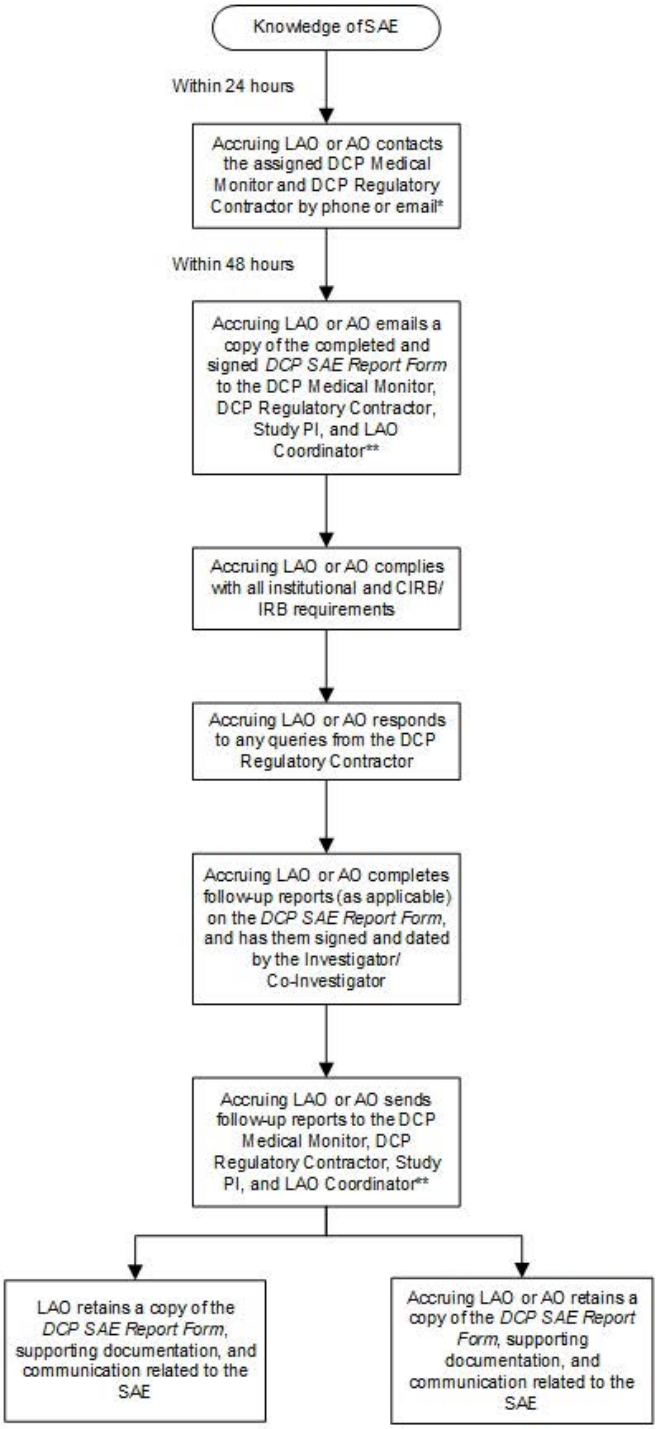
Resource	ID	Location
Serious Adverse Event Report Form: Instructions for Completion and Submission	Reference	Program Resources

8. APPENDICES

1. Appendix I – Reporting Serious Adverse Events

Appendix I

Reporting Serious Adverse Events



*Contact Information:
- DCP Medical Monitor: Refer to the phone number and email address as listed in the protocol.
- DCP Regulatory Contractor: Phone number (650-691-4400 x133), email address (safety@ccsainc.com).

**For Cross-Network Trials (CNTs), the accruing LAO or AO must send the SAE and any follow-up reports to both the Lead LAO Coordinator (LAO Coordinator at the Lead LAO) and Collaborating LAO Coordinator (LAO Coordinator at the accruing LAO's or AO's LAO).

v5.0 27Sep23

Title: Reporting Protocol Deviations

Document ID:	CP-CTNet SOP 02-02
Version:	4.0
Version Date:	January 26, 2024

REVISION HISTORY (most recent first)

Version	Effective Date	Summary of Changes
4.0	JAN-26-2024	Updated the text to include a timeframe for reporting PDs in Rave, the updated DCP MM/NC review process, and the notification procedures for Study PIs, the CIRB, and CNTs. Major updates were made throughout the document to clarify the protocol deviation reporting and review workflow.
3.0	FEB-21-2023	Added information to Section 6 to clarify that the LAO Administrative Team is responsible for monitoring protocol deviation trends at their accruing LAO and AOs. Updated the protocol deviation grade definitions. Minor editorial edits were made as well.
2.0	JUL-11-2022	Major rewrite of entire SOP to reflect the updated protocol deviation reporting and review procedure in Medidata Rave.
1.0	AUG-17-2020	Original version of document.

1. INTRODUCTION AND PURPOSE

A protocol deviation is any noncompliance with the study design and/or procedures of a Division of Cancer Prevention (DCP)- and Central Institutional Review Board (CIRB)-approved protocol. Protocol deviations may result from the actions of the study participant, the Investigators, or the clinical staff conducting the study.

Investigators, Coordinators, and designees at accruing Lead Academic Organizations (LAOs) and Affiliated Organizations (AOs) are responsible for recording and reporting protocol deviations as soon as they are identified.

Note: DCP does not allow any protocol waivers or exceptions for the enrollment of a participant in violation of protocol inclusion/exclusion criteria.

2. SCOPE

This document details the responsibilities of the Investigators, Coordinators, and designees at accruing LAOs and AOs regarding the reporting of protocol deviations, as well as the responsibilities of the LAO Administrative Teams and DCP Study Teams (Medical Monitors (MMs), Nurse Consultants (NCs), and Scientific Leads (SLs)) regarding the review of protocol deviations.

3. DEFINITIONS

Term	Definition
AE	Adverse Event
AO	Affiliated Organization
CIRB	Central Institutional Review Board
CNT	Cross-Network Trial
Collaborating LAO	An LAO that is involved in a CNT that has oversight responsibilities for its own accruing LAO and AOs.
CP-CTNet	Cancer Prevention Clinical Trials Network
DCP	Division of Cancer Prevention
DM	Data Manager
DMACC	Data Management, Auditing, and Coordinating Center
eCRF	Electronic Case Report Form
ICF	Informed Consent Form
INT	Inter-Network Trial. The DCP protocol numbering convention for CP-CTNet CNTs is INT (e.g., INT21-05-01).
IRB	Institutional Review Board
LAO	Lead Academic Organization
LAO Administrative Team	The LAO Coordinator and other LAO staff at the Lead LAO and each Collaborating LAO that provide oversight for their own accruing LAO and AOs.
Lead LAO	An LAO that takes primary responsibility for the administrative aspects of a CNT and has oversight responsibilities for its own accruing LAO and AOs.
M-SOP	Manual of Standard Operating Procedures
MM	Medical Monitor
NC	Nurse Consultant
NCI	National Cancer Institute

Term	Definition
OTC	Over The Counter
PI	Principal Investigator
PID	Participant Identifier
SAE	Serious Adverse Event
SL	Scientific Lead

4. RESPONSIBILITIES FOR PROMPT REPORTING OF PROTOCOL DEVIATIONS

Investigators, Coordinators, and designees at accruing LAOs and AOs report protocol deviations using the *CP-CTNet Protocol Deviation Notification* eCRF in Medidata Rave (Rave) as soon as a protocol deviation is identified.

1. Protocol Deviation Entry:

    1.1. The accruing LAO or AO where the protocol deviation originated must comply with all institutional, CIRB, and international requirements related to reporting protocol deviations (as applicable).

    1.2. To start the process of entering a protocol deviation into Rave, the accruing LAO or AO uses the Add Event dropdown on the participant's subject page and selects "Protocol Deviation Notification" to add the *CP-CTNet Protocol Deviation Notification* eCRF to the record of the participant who is impacted by the protocol deviation.

    - The accruing LAO or AO completes the first section of the *CP-CTNet Protocol Deviation Notification* eCRF (up to and including the "By checking this box, I confirm that the site investigator has reviewed this form" field). The help text associated with each question on the eCRF can be used to assist with completing the eCRF. Help text in Rave is accessed by clicking the question mark icon next to the associated question on the eCRF.

    1.3. Only one protocol deviation per PID should be recorded on a single eCRF.

    - If another protocol deviation occurs for the same participant, a separate *CP-CTNet Protocol Deviation Notification* eCRF should be added and completed.
    - If the same protocol deviation occurs for two (2) to nine (9) participants, a separate *CP-CTNet Protocol Deviation Notification* eCRF should be added and completed for each PID.
    - If the same protocol deviation occurs for 10 or more participants, the information for all participants can be documented on one *CP-CTNet Protocol Deviation Notification PDF*, which is available on the CP-CTNet DMACC public website. The completed PDF should be sent to the DMACC DMs via DataManagement_CP-CTNet@frontierscience.org. The DMACC DMs route the PDF for LAO Administrative Team and DCP Study Team review and enter the protocol deviations into the database on behalf of the accruing LAO or AO, LAO Administrative Team, and DCP Study Team.
        - Each PID and associated protocol deviation date must be noted on the PDF.
        - DCP does not require prior approval or a Note to File.

    1.4. Rave automatically sends the LAO Administrative Team an email indicating that there is a protocol deviation to be reviewed.

Note: For CNTs, Rave automatically sends the DMACC DMs an email notification that there is a protocol deviation to be reviewed, and the DMACC DMs forward the email to the appropriate LAO Administrative Team.

Note: The DCP protocol numbering convention for CP-CTNet CNTs is INT, which stands for "inter-network trial" (e.g., INT21-05-01).

2. LAO Administrative Team Review:

   2.1. As a function of their oversight role, the LAO Administrative Team (LAO Coordinator and/or designee(s)) is responsible for reviewing protocol deviations reported by their accruing LAO and AOs. For CNTs, the LAO Administrative Team at the Lead LAO and each Collaborating LAO is responsible for reviewing protocol deviations reported by its own accruing LAO and AOs (see REFGD06 *Cross-Network Trials Guidelines* for more information).

   2.2. The LAO Administrative Team verifies the accuracy and completeness of the *CP-CTNet Protocol Deviation Notification* eCRF, and confirms that appropriate details were provided and the eCRF was completed according to the help text.

   2.3. The LAO Administrative Team answers the "CIRB notified? (for CIRB-approved studies)" question as appropriate. See Section 5 below for more information.

   2.4. If queries are required, the LAO Administrative Team checks "Yes" for the "Does LAO review require queries?" question and enters the query/queries into Rave.

   2.5. The accruing LAO or AO responds to the query/queries directly in Rave as part of their routine data management activities. The accruing LAO or AO addresses each query by either correcting the data and providing a reason for correction, or by indicating that the data are correct and providing an explanation. In order to facilitate timely review, the DMACC DMs email the LAO Administrative Team if they see (as part of their routine data management) that the accruing LAO or AO has addressed the query/queries, but the query response(s) have yet to be reviewed by the LAO Administrative Team.

   - Queries should be addressed by accruing LAOs or AOs within 14 calendar days. See REFGD03 *CP-CTNet Master Data Management Plan* for more information.

   2.6. The LAO Administrative Team logs into Rave to review the accruing LAO's or AO's query responses. The LAO Administrative Team can re-query, if necessary. Once the queries are resolved, the LAO Administrative Team changes their response for the "Does LAO review require queries?" question from "Yes" to "No."

   2.7. If there are no queries, or once the query/queries from the LAO Administrative Team are resolved, the LAO Administrative Team checks the "LAO Review Complete" box and saves the eCRF.

3. DCP Protocol Deviation Review:

   3.1. The DCP MM/NC reviews minor (grade 1) protocol deviations on/near the 1st of each month. For minor protocol deviations where the LAO Administrative Team review is complete, the DMACC DMs enter what is already in Rave into the *CP-CTNet Protocol Deviation Notification PDF*, send the PDF to the DCP MM/NC, and ask that the DCP MM/NC complete their review on this PDF within 10 business days of receipt. If the same protocol deviation is entered into Rave for more than one participant per study, DMACC may combine these protocol deviations on the same PDF to streamline the DCP MM/NC review. **Note:** This is different from the procedure outlined in Section 1.3 above for the

initial reporting of the protocol deviation by the accruing LAO or AO (i.e., using this PDF to report the same protocol deviation for 10 or more participants).

3.2. The DCP MM/NC reviews moderate (grade 2)/major (grade 3) protocol deviations in real time. For moderate/major protocol deviations where the LAO Administrative Team review is complete, the DMACC DMs enter what is already in Rave into the *CP-CTNet Protocol Deviation Notification PDF*, send the PDF to the DCP MM/NC, and ask that the DCP MM/NC complete their review on this PDF within 10 business days of receipt. If the same protocol deviation is entered into Rave for more than one participant per study, DMACC may combine these protocol deviations on the same PDF to streamline the DCP MM/NC review. **Note:** This is different from the procedure outlined in Section 1.3 above for the initial reporting of the protocol deviation by the accruing LAO or AO (i.e., using this PDF to report the same protocol deviation for 10 or more participants).

3.3. The DCP MM/NC reviews each *CP-CTNet Protocol Deviation Notification PDF*.

3.4. If queries are required, the DCP MM/NC sends them to the DMACC DMs via DataManagement_CP-CTNet@frontierscience.org, and the DMACC DMs proxy enter them into Rave on behalf of the DCP MM/NC. The DMACC DMs indicate that each query is from the DCP MM/NC in the query text.

3.5. The accruing LAO or AO responds to the query/queries directly in Rave as part of their routine data management activities. The accruing LAO or AO addresses each query by either correcting the data and providing a reason for correction, or by indicating that the data are correct and providing an explanation.

- Queries should be addressed by accruing LAOs and AOs within 14 calendar days. See REFGD03 *CP-CTNet Master Data Management Plan* for more information.

3.6. The DMACC DMs provide the accruing LAO or AO query response(s) and updated *CP-CTNet Protocol Deviation Notification PDF*, if necessary, to the DCP MM/NC via email. The DCP MM/NC works with the DMACC DMs to re-query, if necessary.

3.7. If there are no queries, or once the query/queries from the DCP MM/NC are resolved, the DCP MM/NC completes the “DCP MM/NC Use Only” section on the *CP-CTNet Protocol Deviation Notification PDF*.

3.8. The DCP MM/NC sends each completed *CP-CTNet Protocol Deviation Notification PDF* to the DMACC DMs via DataManagement_CP-CTNet@frontierscience.org.

Note: If the same minor protocol deviation occurs consistently within an accruing LAO or AO or across accruing LAOs and AOs, the DCP MM/NC may determine the grade of the protocol deviation(s) to be moderate (grade 2)/major (grade 3). This protocol deviation grade escalation may need to be reported to the CIRB as potential serious or continuous noncompliance. See Section 5 CIRB Requirements for Reporting Protocol Deviations for more information.

3.9. The DMACC DMs enter the DCP MM/NC review into Rave, check the “DCP MM/NC Review Complete” box, and save the eCRF. Rave automatically sends an email to the accruing LAO or AO study staff with the *Clinical Research Coordinator - IVRS* role in Rave, LAO Administrative Team, and DMACC DMs to indicate that the protocol deviation has been finalized.

3.10. The accruing LAO or AO reviews the completed “For DCP MM/NC Use Only” section of the eCRF.

3.11. Per the accruing LAO's or AO's protocol deviation procedures, the accruing LAO or AO completes the "For Site Use Only" section of the eCRF to confirm that the accruing LAO or AO Investigator acknowledges the DCP MM/NC review and saves the eCRF.

3.12. The review process for the protocol deviation is complete.

5. CIRB REQUIREMENTS FOR REPORTING PROTOCOL DEVIATIONS

1. The Signatory Institution PI is responsible for reporting all required protocol deviations to the CIRB that occur at their accruing LAO or AO (see algorithms linked below). In addition, these protocol deviations should be reported to the study PI, LAO Administrative Team, and DCP Study Team prior to CIRB submission. For CNTs, the protocol deviations should be reported to the study PI, Lead LAO Administrative Team (LAO Administrative Team at the Lead LAO), Collaborating LAO Administrative Team (LAO Administrative Team at the accruing LAO's or AO's LAO), and DCP Study Team prior to CIRB submission (see REFGD06 *Cross-Network Trials Guidelines* for more information).
2. The LAO Administrative Team reports any study-wide issues or protocol deviations (per the algorithm) to the CIRB. For CNTs, the Lead LAO Administrative Team reports any study-wide issues or protocol deviations (per the algorithm) to the CIRB (see REFGD06 *Cross-Network Trials Guidelines* for more information).
3. The following protocol deviation categories must be reported to the CIRB via the IRB Manager:

    3.1. Serious or continuous noncompliance:

    - Further details regarding whether a protocol deviation is reportable as serious or continuous noncompliance may be found on the NCI CIRB webpage: Algorithm to Assess Noncompliance.

    3.2. Unanticipated problem:

    - Further details regarding whether a protocol deviation is reportable as an unanticipated problem may be found on the NCI CIRB webpage: Algorithm to Assess a Potential Unanticipated Problem.

4. The LAO Administrative Team records that the serious or continuous noncompliance/unanticipated problem has been reported to the CIRB on the *CP-CTNet Protocol Deviation Notification* eCRF. For CNTs, the Collaborating LAO Administrative Team records that the serious or continuous noncompliance/unanticipated problem has been reported to the CIRB on the *CP-CTNet Protocol Deviation Notification* eCRF (see REFGD06 *Cross-Network Trials Guidelines* for more information).
5. In addition to CIRB requirements, protocol deviations (including those not reportable to the CIRB) must be reported to the accruing LAO's or AO's local IRB as per local requirements.
6. The Signatory Institution PI or designee should share copies of the CIRB submissions with the DCP Study Team (if possible).

6. PROTOCOL DEVIATION TRENDS

The LAO Administrative Team is responsible for monitoring protocol deviation trends at their accruing LAO and AOs. As trends are identified, the LAO Administrative Team should notify the study PI, DCP Study Team, and DMACC of the trend, and maintain consistent communication about any corrective and/or preventative action(s) implemented to address the identified trend (as needed). For CNTs, the Collaborating LAO Administrative Team should notify the study PI, Lead LAO Administrative Team,

DCP Study Team, and DMACC of the trend, and maintain consistent communication about any corrective and/or preventative action(s) implemented to address the identified trend (as needed). Protocol deviation trends and the LAO oversight of these trends are reviewed during DMACC quality assurance audits.

The Data Listing Report in Rave can be used by the LAO Administrative Team to help monitor and identify protocol deviation trends. This report is useful for reviewing/downloading bulk data reported on the *CP-CTNet Protocol Deviation Notification* eCRF for all participants in a selected study. The LAO Administrative Team can run this report at any time. For more information on generating Rave reports, please refer to QKREFGD01 Medidata Rave Reports and USRMAN03 Rave Reports Resource Guide for the CP-CTNet Project. Accruing LAOs and AOs, LAOs, and DCP may also submit a request for a report by emailing the DMACC DMs via DataManagement_CP-CTNet@frontierscience.org. DMACC will send an encrypted email with the report as an attached Excel file.

The DMACC DMs also send a cumulative protocol deviation report for each study to the LAO Administrative Team and DCP Study Team on/near the 1st of each month.

7. ADDITIONAL INFORMATION

Please send questions and comments to DataManagement_CP-CTNet@frontierscience.org.

8. REFERENCES

Note: All CP-CTNet SOPs are included in the CP-CTNet Manual of Standard Operating Procedures (M-SOP), which is available on the CP-CTNet DMACC public website.

Resource	ID	Location
Algorithm to Assess a Potential Unanticipated Problem	Reference	ncicirb.org
Algorithm to Assess Noncompliance	Reference	ncicirb.org
CP-CTNet DMACC Website	Website	cp-ctnet-dmacc.org
CP-CTNet Master Data Management Plan	REFGD03	Program Resources
Cross-Network Trials Guidelines	REFGD06	Program Resources
IRB Manager	Application	nci.my.irbmanager.com
CP-CTNet Protocol Deviation Notification PDF	Form	Program Resources
Medidata Rave Reports	QKREFGD01	Program Resources
Rave Reports Resource Guide for the CP-CTNet Project	USRMAN03	Program Resources

9. APPENDICES

1. Appendix I - Protocol Deviation Grade Definitions and Category Descriptions

Appendix I

Protocol Deviation Grade Definitions and Category Descriptions

Protocol Deviation Grade Definitions:

1. **Grade 1/Minor:** No meaningful effect on the integrity or reliability of research data and no meaningful risk to participant rights or safety.
2. **Grade 2/Moderate:** Has the potential to affect the integrity or reliability of research data or poses potential risk to participant rights or safety.
3. **Grade 3/Major:** Will affect the integrity or reliability of research data or will affect participant rights or safety. This includes all deviations related to inclusion/exclusion criteria, deviations related to data necessary for primary endpoints, and deviations related to data necessary for key secondary endpoints.

Protocol Deviation Category Descriptions:

1. **AE/SAE Reporting:** Any adverse or serious adverse event that was not reported.
2. **Biospecimen:** Tissue, Blood, Urine: Any deviation impacting biospecimen collection, integrity (processing/storing), and/or analysis (both pre- and post-intervention).
3. **Concomitant Medication:** Any OTC (over the counter)/prescription drug that is prohibited per protocol.
4. **Consent Procedures:** Any deviation from compliance with Human Subject Protection regulations including any deviation from Informed Consent Form (ICF) version, signature, date, or other requirements.
5. **Pre-Intervention Procedure:** Any deviation related to eligibility (inclusion/exclusion criteria), registration or randomization (other than biospecimen-related deviations).
6. **Schedule: Incomplete Visit Assessment/Call:** Some or part of visit assessment/call was not completed (other than biospecimen-related deviations).
7. **Schedule: Missed Visit Assessment/Call:** Visit assessment/call did not occur (other than biospecimen-related deviations).
8. **Schedule: Out of Window Visit Assessment/Call:** Visit assessment/call was not held within study-designated time points (other than biospecimen-related deviations).
9. **Study Drug Accountability:** Any deviation related to study drug requirements (e.g., pharmacy documentation, study drug integrity, distribution, administration error by study staff, or missing study drug).
10. **Study Drug Administration:** Any deviation related to the participant not taking the drug per protocol.
11. **Documentation Error:** An error or absence in documenting any research-related activity.
12. **Removal from Study Error:** Deviation related to the erroneous removal of a participant from the study.

Title: System Variable Attribute Report (SVAR) and Electronic Case Report Form (eCRF) Development

Document ID:	CP-CTNet SOP 02-03
Version:	4.0
Version Date:	July 13, 2023

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REVISION HISTORY

Version	Effective Date	Summary of Changes
4.0	JUL-13-2023	Major updates to entire document.
3.1	FEB-21-2023	Title change – formerly “Electronic Case Report Form Development.”
3.0	AUG-02-2022	Addition of Definition and References sections, major rewrite of section 4, replaced original Appendix I with current Appendix I.
2.0	JUN-07-2021	Major updates to entire document.
1.0	AUG-17-2020	Original version of document.

1. INTRODUCTION AND PURPOSE

Electronic Case Report Forms (eCRFs) are developed to collect and record the data required to answer the research question(s) for a specific protocol, to create the study build in the Medidata Rave clinical database management system, and to serve as a description of the expected content of the final dataset for the study.

The System Variable Attribute Report (SVAR) Template is a customizable tool that is used to create or revise protocol-specific eCRFs. The SVAR Template contains both mandatory and recommended content, and should be used as the basis for developing the protocol-specific eCRFs.

eCRFs should be created to collect data in a consistent manner to assure quality, completeness, and accuracy of the final data sets, and to ensure that data collection is done in compliance with Good Clinical Practice, the standards for National Cancer Institute (NCI) Common Data Elements (CDEs), and federal regulations, including but not limited to 21 CFR Part 11 and the Health Insurance Portability and Accountability Act (HIPAA).

2. SCOPE

This document details the responsibilities of the Principal Investigators (PIs), Lead Academic Organization (LAO) Coordinators, and designees regarding the creation of eCRFs for new and amended protocol submissions.

3. DEFINITIONS

Term	Definition
CDE	Common Data Element
DCP	Division of Cancer Prevention
DMACC	Data Management, Auditing, and Coordinating Center
eCRF	Electronic Case Report Form
LAO	Lead Academic Organization
M-SOP	Manual of Standard Operating Procedures
MDS	Minimum Data Set
NCI	National Cancer Institute
PI	Principal Investigator
PIO	Protocol Information Office
SVAR	System Variable Attribute Report

4. RESPONSIBILITIES

DMACC is responsible for drafting eCRFs for each new protocol submission and any applicable amended protocol submissions. The PI, LAO Coordinator, and/or designee is responsible for reviewing and approving these eCRFs and collaborating with DMACC to ensure that these eCRFs accurately reflect the protocol and contain all necessary data elements for data collection, analysis, and reporting.

1. Procedures for SVAR development include:

    1.1. DMACC begins drafting the study-specific SVAR Workbook after DMACC receives the first Approval on Hold letter for the protocol from PIO.

1.2. The *CP-CTNet SVAR Template*, including instructions for use of the SVAR, is posted on the CP-CTNet DMACC public website. The SVAR Template is a spreadsheet used to create the study-specific SVAR Workbook. The study-specific SVAR Workbook should document all questions and data elements required for a given protocol.

- Each tab in the SVAR Workbook represents an eCRF and contains questions, their corresponding attributes (e.g., field length, response value, data type), and other additional elements. The columns in each eCRF tab include the following:
  - Change Indicator
  - Question Name
  - Data Type
  - Field Length (including decimal places, if applicable)
  - Field Type
  - Valid Values
  - Field Help Text
  - MDS Field?
  - MDS Collection Table
  - Site Comments
  - DMACC Comments
  - Curator Comments
  - caDSR Public ID: Version
  - csDSR Definition
  - caDSR Representation (Value Domain Public ID)
- The SVAR Template contains “generic” eCRFs that can be used across CP-CTNet studies, if applicable. Generic/standard fields on each eCRF tab that should not be changed across studies are highlighted gray. Fields that can be modified according to a study’s protocol are not highlighted gray. Notes to the Study Build Team may be included at the top of each eCRF tab and serve as a guide for modifying these fields.
- Study-specific eCRFs can be designed and added to the SVAR Workbook.
- The SVAR also includes the Schedule of Forms, which describes which eCRFs should be completed at each visit/event according to the protocol, a Minimum Data Set (MDS) Checklist to identify MDS fields, and a Versions tab used to track each version of the protocol and SVAR Workbook.

1.3. The Versions tab of the SVAR Workbook should contain the protocol version number and date as well as the SVAR version number and date.

- The initial draft of the SVAR Workbook is version 1.0. It remains version 1.0 while DMACC and the LAO work on it until it is sent out for initial eCRF Review Team review.
- During the review process, if minor updates (e.g., spelling, grammar, minor formatting updates) are made, the SVAR Workbook is not up-versioned. If major updates (e.g.,

adding/removing eCRFs) are made, the SVAR Workbook is up-versioned by a whole number (e.g., 2.0 → 3.0).

- When a protocol amendment receives final approval, the SVAR Workbook must be updated (as needed) and up-versioned. Subsequent versions are incremented by .1 (e.g., 4.1, 4.2, 4.3, etc.) and will remain this version number throughout the review process.
- Each version is tracked in the Versions tab of the SVAR Workbook.

  Note: The version date of the SVAR Workbook is not required to match the version date of the protocol and informed consent form.

1.4. After DMACC receives the first Approval on Hold letter for the protocol from PIO and drafts the initial SVAR Workbook, DMACC sends this draft to the LAO. The LAO should follow the SVAR Workbook review process as outlined in CP-CTNet REFGD03 *Master Data Management Plan for Lead Academic Organizations and Affiliated Organizations*.

- When sending the initial draft of the SVAR Workbook to the LAO, DMACC can request to schedule a meeting with the LAO to discuss the SVAR Workbook. This meeting can occur before or after LAO review of the initial draft of the SVAR Workbook, depending on LAO preference.

1.5. The LAO reviews the SVAR Workbook to ensure all information specified in the protocol is captured on an eCRF. DMACC tracks any changes based on LAO comments in the appropriate tab of the SVAR Workbook. These tracked changes will be removed before the SVAR Workbook is sent out for initial eCRF Review Team review.

1.6. Once the DMACC Data Management team and LAO determine the SVAR Workbook is ready for wider review, the DMACC Data Management team submits the SVAR Workbook to the eCRF Review Team (DCP Regulatory Contractor, DCP CDE Contractor, and DMACC Statisticians) for their initial review, along with the current version of the protocol.

- The eCRF Review Team confirms that all mandatory questions, including those that are used to collect data for MDS reporting, are included in the SVAR Workbook. The eCRF Review Team also confirms compliance with the standards for the CDEs. Information regarding these standards is available at https://wiki.nci.nih.gov/display/CRF/Case+Report+Forms+Wiki. The DCP CDE Curator works with DMACC and each LAO to ensure all questions and valid values are CDE-compliant.

  Note: The DMACC Statisticians review the protocol for internal consistency and share any comments with the DMACC Data Management team as part of this process. The DMACC Data Management team then relays these comments to the LAO and/or DCP Study Team on behalf of the DMACC Statisticians so that the comments can be considered by the PI. If the DMACC Statisticians have no comments on the protocol or SVAR Workbook, they email the DMACC Data Management team to confirm the completion of their review.

1.7. DMACC compiles the eCRF Review Team comments and works with the LAO, if needed, to resolve the comments. If revision is required, DMACC tracks any updates in the appropriate tabs of the SVAR Workbook and summarizes the updates in a Change Memo. The SVAR Workbook is revised and resubmitted until the eCRF Review Team finds the SVAR Workbook to be acceptable.

1.8. Once the SVAR Workbook is found to be acceptable by the eCRF Review Team, DMACC removes any tracked updates. Once DMACC receives the CIRB Approval letter for the protocol version from PIO, DMACC submits the SVAR Workbook to the DCP Study Team for their initial review. The DCP Study Team sends any comments they have to DMACC. DMACC works with the LAO and eCRF Review Team, if needed, to resolve the comments. If revision is required, DMACC tracks any updates in the appropriate tabs of the SVAR Workbook and summarizes the updates in a Change Memo. The SVAR Workbook is revised and resubmitted until the DCP Study Team grants approval.

1.9. Once DCP Study Team approval is granted, DMACC notifies PIO and sends the final SVAR Workbook to them. PIO sends DMACC an official approval letter. PIO also notifies the LAO and provides them with the final SVAR Workbook and approval letter for their records.

1.10. The SVAR Workbook may be revised due to protocol amendments. When DMACC receives a protocol amendment from PIO, they will review the protocol amendment and determine if any updates are needed to the SVAR Workbook.

- If no updates are needed, only the Versions tab of the SVAR Workbook will be updated to reflect the updated protocol version. This updated SVAR Workbook will then be sent to PIO per step 1.9 above.
- If updates are needed, DMACC tracks any updates in the appropriate tabs of the SVAR Workbook and summarizes the updates in a Change Memo. The revised SVAR Workbook and Change Memo are submitted to the LAO, followed by the eCRF Review Team, followed by the DCP Study Team for their review. Approval of the revised SVAR Workbook follows the same steps as noted above (LAO, eCRF Review Team, DCP Study Team).

1.11. The SVAR Workbook may also be revised to address administrative issues at the site and/or to address site errors. If an update is identified by the LAO, they should contact the DMACC Data Management team (DataManagement_CP-CTNet@frontierscience.org) with details.

5. DOCUMENTATION REQUIREMENTS

Each LAO is responsible for maintaining the following documentation in their files:

1. Current CP-CTNet REFGD03 *Master Data Management Plan for Lead Academic Organizations and Affiliated Organizations* and any related documents that reflect the current data collection practices for each protocol.
2. The approval letter from DCP regarding all approved SVAR Workbooks for each protocol.
3. All approved SVAR Workbooks for each protocol.

6. ADDITIONAL INFORMATION

Please send questions and comments to DMACC at:
DataManagement_CP-CTNet@frontierscience.org

7. REFERENCES

Note: All CP-CTNet SOPs are included in the *CP-CTNet Manual of Standard Operating Procedures (M-SOP)*, which is available on the CP-CTNet DMACC public website.

Resource	ID	Location
Case Report Forms (NCI restricted)	--	NCI Wiki
CP-CTNet REFGD03 Master Data Management Plan for Lead Academic Organizations and Affiliated Organizations	REFGD03	Program Resources
CP-CTNet SVAR Template	Template	Program Resources
CP-CTNet DMACC public website	Website	cp-ctnet-dmacc.org

8. APPENDICES

1. Appendix 1: CP-CTNet SVAR Change Memo

Appendix I

CP-CTNet SVAR Change Memo

Protocol Number	
Protocol Title	
Protocol Version and Date	
SVAR Version and Date	

SVAR [version] dated [date] has been updated to [include brief summary of updates]. The updates made are outlined below. Tabs highlighted in [color] in the SVAR include these updates. Tabs highlighted in [color] in the SVAR include comments for the CDE Curators.

Tab Name	Change

Title:	**Participant Recruitment, Retention, Adherence, and Reporting Requirements**
Document ID:	CP-CTNet SOP 02-04
Version:	5.0
Version Date:	January 26, 2024

REVISION HISTORY (most recent first)

Version	Effective Date	Summary of Changes
5.0	JAN-26-2024	Updated to clarify the process for submitting study-wide and accruing LAO or AO-specific participant-facing recruitment materials for typical trials and CNTs. Additional minor clarifying updates were made throughout the document.
4.0	JUL-13-2023	Added detail about accruing LAO and AO responsibilities when completing the *CP-CTNet AQuIP Recruitment Journal - Site-Specific Events* eCRF, clarified the section on recruitment materials and protocol submissions, added detail about the RRA plan, and made other clarifying updates throughout the document.
3.0	FEB-21-2023	Editorial modifications to clarify procedures.
2.0	SEP-20-2021	This version of the SOP includes updated information about CP-CTNet procedures, resources, and eCRFs used to collect AQuIP-related data. Proofing and formatting updates were applied throughout the SOP.
1.0	AUG-17-2020	Original version of document.

1. INTRODUCTION AND PURPOSE

The Cancer Prevention Clinical Trials Network (CP-CTNet) Participant Recruitment, Retention, Adherence, and Reporting Requirements Standard Operating Procedure (SOP) pertains to the National Cancer Institute (NCI) Division of Cancer Prevention's (DCP's) Accrual Quality Improvement Program (AQuIP) and the required CP-CTNet Data Management, Auditing, and Coordinating Center (DMACC) systems for recording accrual information. The overall purpose of AQuIP is to facilitate efficient implementation of clinical trials through well-planned and carefully monitored participant accrual. AQuIP supports NCI DCP's mission to lead, conduct, and support cancer research across the nation, advance scientific knowledge, and help all people to live longer, healthier lives, while ensuring proper stewardship of public funds.

AQuIP is a multi-component, continuous quality improvement program that entails systematic study- and site-specific recruitment planning with data-driven accrual rate goals and detailed real-time reporting of accrual activity and actual recruitment rates. Frequent monitoring and analysis of accrual data enables a better understanding of performance factors and continuous identification of opportunities for modification of study characteristics and outreach methods.

2. SCOPE

This document provides information for Investigators and Coordinators of Lead Academic Organizations (LAOs) as well as accruing LAOs and Affiliated Organizations (AOs) regarding planning, implementing, monitoring, and adjusting participant recruitment, retention, and adherence (RRA) strategies as well as documenting recruitment-related information. AQuIP RRA planning covers the enrollment trajectory from study design, to accruing LAO and AO selection, to identification of potential participants (pre-screening) through first contact, consent, screening, enrollment, and start of study intervention. Detailed instructions for completing the RRA Plan are embedded in the fillable PDF planning form. All activities should be consistent with Good Clinical Practice (GCP).

3. DEFINITIONS

Term	Definition
AO	Affiliated Organization
AQuIP	Accrual Quality Improvement Program
CIRB	Central Institutional Review Board
CNT	Cross-Network Trial
Collaborating LAO	An LAO that is involved in a CNT that has oversight responsibilities for its own accruing LAOs and AOs.
CP-CTNet	Cancer Prevention Clinical Trials Network
DCP	Division of Cancer Prevention
DM	Data Manager
DMACC	Data Management, Auditing, and Coordinating Center
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
INT	Inter-Network Trial or INT is the DCP protocol numbering convention for CP-CTNet trials (e.g., INT21-05-01).
LAO	Lead Academic Organization
Lead LAO	An LAO that takes primary responsibility for the administrative aspects of the CNT and has oversight responsibilities for its own accruing LAOs and AOs.

Term	Definition
M-SOP	Manual of Standard Operating Procedures
NCI	National Cancer Institute
PI	Principal Investigator
PIO	Protocol Information Office
RRA	Recruitment, Retention, and Adherence
SOP	Standard Operating Procedure

4. AQUIP TOOLS AND PROCEDURES

AQuIP provides LAOs as well as accruing LAOs and AOs with six complementary tools. ***All tools are available on the CP-CTNet DMACC Public Website and Portal Gateway***:

1. RRA Plan: A comprehensive fillable PDF planning form.

    1.1. Use the RRA Plan to formulate and document study- and site-specific plans for ensuring appropriate recruitment, retention, and adherence for each study.

    1.2. Each study RRA Plan includes site-specific strategies for each accruing LAO and AO (as developed in consultation with each accruing LAO and AO PI and Coordinator for implementation by each accruing LAO and AO).

    1.3. The planned enrollment of participants from underrepresented racial and ethnic populations must be defined and justified.

    - Refer to the RRA Plan for additional recommendations regarding the specific plan of action to enroll and retain diverse participants.

    1.4. RRA Plans are submitted with the first revision (e.g., version 2.0) of the protocol.

    1.5. The RRA Plan is revised per DCP recommendation, if needed.

    1.6. The approved RRA Plan is distributed to each accruing LAO and AO by the LAO.

2. AQuIP Toolkit: A user-friendly library of recruitment resources including a recruitment instruction manual, templates for recruitment materials, media templates, and an image library that may be used by recruitment staff.

    2.1. Recruitment materials include items designed to inform potential participants or referral sources about a specific study in the form of letters, brochures, telephone scripts, advertisements, websites, social media announcements, videos, and other modes of communication.

    2.2. Policies and guidance related to submission of recruitment materials are included in the AQuIP Toolkit.

    2.3. Recruitment materials, including their content and mode of communication, intended for presentation to potential participants (at the public-level or participant-level) must be approved by DCP and the CIRB.

    - All study-wide and accruing LAO- or AO-specific participant-facing recruitment materials should be submitted by LAOs to DCP for approval prior to CIRB submission. This includes any participant-facing recruitment materials that are only applicable to one accruing LAO or AO which are unique or have significantly changed from analogous study-wide CIRB-approved materials (e.g., a phone script with significantly

different wording from the study-wide CIRB-approved phone script), but not those which have been updated to only add institutional contact information.

- If an LAO needs additional clarification about whether accruing LAO- or AO-specific participant-facing recruitment materials should be reviewed by DCP for approval prior to CIRB submission, they should contact their DCP Study Team.

- For CNTs, accruing LAO- or AO-specific participant facing recruitment materials should be submitted to the Collaborating LAO (the accruing LAO's or AO's LAO) for review and submission to DCP. The Lead LAO (has primary responsibility for the administrative aspects of the CNT and has oversight responsibilities for its own accruing LAOs and AOs) should be copied on each email correspondence related to the accruing LAO- or AO-specific participant-facing recruitment materials (see REFGD06 *Cross-Network Trials Guidelines* for more information).

  Note: The DCP protocol numbering convention for CP-CTNet CNTs is INT, which stands for "inter-network trial" (e.g., INT21-05-01).

2.4. Recruitment materials require distribution plans when submitted for CIRB review.

- The protocol document should NOT reference or include recruitment materials, as they are not considered a required component of the protocol submission.
  - However, if this guidance is not followed, and the protocol document refers to recruitment materials, those materials must be submitted as a separate part of the same protocol submission for DCP and CIRB approval.
  - If the protocol document refers to recruitment materials that are not included in the protocol submission, the CIRB tables those protocols until those materials are submitted. For more information about CIRB requirements for submission of recruitment materials, refer to the CIRB SOPs.

2.5. Recruitment materials may be submitted for DCP review and approval, in order to proceed to CIRB review, any time after the protocol and other associated documents are submitted/approved.

- Recruitment materials* are submitted to DCP for review through PIO (nci_dcp_pio@mail.nih.gov). Once the materials are approved by DCP, PIO forwards the materials to the CIRB for review.
  - *Different types of recruitment materials for the same study may be submitted to DCP for review via PIO simultaneously, or at different times. However, every effort should be made to consolidate submissions.

3. Training and Resources: A library of recorded webinars as well as links to additional clinical trial resources and accrual support tools to aid LAOs as well as accruing LAOs and AOs in their ongoing research staff training responsibilities.

4. Systems to Record Accrual Information:

4.1. The Stars registration/randomization system (Stars) is the system that accruing LAOs and AOs use to obtain *Pre-Screen ID*, *Screening ID*, and *Participant ID* assignments for Pre-Screening, Screening, and Enrollment, respectively. Stars is also used to generate participant records in the Medidata Rave (Rave) clinical database. Please see USRMAN01 *CP-CTNet Stars User Guide* for more information.

4.2. Rave is the Electronic Data Capture system that holds the clinical database that accruing LAOs and AOs use to enter participant-level and site-specific recruitment information.

4.3. Participant-level recruitment information is entered into several Rave eCRFs during the participant's enrollment trajectory, including the *CP-CTNet Pre-Screening Form*, *CP-CTNet Screening Form*, *Demography, Intervention Administration*, *Registration*, and *Off Study* eCRFs (as applicable). Participant-level recruitment information includes:

- Strategies used to identify and/or contact and inform each study candidate in order to track the implementation and effectiveness of recruitment strategies for each individual.
- Reasons that individual study candidates do not proceed to the next stage of the enrollment process – in order to identify study components or recruitment strategies that may be modified to improve accrual.
- Participant demographic data including race, ethnicity, gender, date of birth, and zip code – in order to determine if the characteristics of the potential participant pool change at each stage of the enrollment process (e.g., pre-screening, first contact, consent, screening, enrollment, and start of study intervention). Please see the *AQuIP Guide to the Enrollment Trajectory: I-SCORE 2023* brochure for more information about the participant enrollment trajectory.

4.4. Site-specific and study-wide recruitment information, referred to as AQuIP Recruitment Journal data, is entered into the AQuIP Recruitment Journal in Rave and is intended to chronicle the "life story" of the study.

- The AQuIP Recruitment Journal in Rave includes eCRFs that are used to enter AQuIP Recruitment Journal data.
- Examples of these data (events, conditions, or efforts (with dates of occurrence) that may, or are expected to, affect accrual (either positively or negatively)) include the following:
    - Protocol amendments, study agent updates, availability of new recruitment strategies or materials, holidays, staffing issues, and any activities, events, situations, clinic conditions, and/or efforts at a particular accruing LAO or AO or all accruing LAOs and AOs (as opposed to those that affect an individual participant).
- *Study-wide* recruitment information refers to the subset of AQuIP Recruitment Journal data that may, or is expected to, impact all accruing LAOs and AOs (e.g., protocol amendments, study agent updates, national holidays, etc.) and is entered and maintained in the *CP-CTNet AQuIP Recruitment Journal - Study-Wide Events* eCRF by DMACC.
    - DMACC receives information about study-wide events from several sources, including event notification emails from the LAOs and/or DCP Study Teams, study active notifications, protocol amendment notifications, protocol status update documents, protocol submission worksheets and documents, agent calls, and study staff changes/turnover notifications (as applicable).
    - Accruing LAOs and AOs can view, but not edit, study-wide recruitment information on this eCRF.
- *Site-specific* recruitment information refers to the subset of AQuIP Recruitment Journal data that may, or is expected to, impact a single accruing LAO or AO and is entered

and maintained in the *CP-CTNet AQuIP Recruitment Journal - Site-Specific Events* eCRF by the accruing LAO or AO where the event occurred. Accruing LAOs and AOs are responsible for regularly updating the *CP-CTNet AQuIP Recruitment Journal - Site-Specific Events* eCRF and should include any site-specific events that may affect recruitment (either positively or negatively) for their accruing LAO or AO. Accruing LAOs and AOs and are not responsible for entering study-wide recruitment information.

- Accruing LAOs and AOs should add a new log line on the *CP-CTNet AQuIP Recruitment Journal - Site-Specific Events* eCRF for each site-specific *Study Event*.
- The first site-specific *Study Event* that should be added for each accruing LAO and AO is "A3 - Site Open (provide date in *Event Description*)." The *Study Event Start Date* and *Study Event End Date* should be the date that the accruing LAO or AO was activated to the study based on receipt of the ***Confirmation of Site Activation*** email sent by DMACC.
- Anytime the accruing LAO or AO is activated to an amendment, the site-specific *Study Event* "A29 - Amendment Activated at Accrual Site" should be entered in a new log line. The *Study Event Start Date* and *Study Event End Date* should be the date that the accruing LAO or AO was activated to the amendment based on receipt of the ***Confirmation of Site Activation to Amendment*** email sent by DMACC.
- An *Event Description* should always be entered to provide more detail about the selected event.
- Since the events added to this eCRF are site-specific, the *AOs Affected* dropdown should always be completed. The selected accruing LAO or AO should match the AQuIP Recruitment Journal that is being updated.
- DMACC DMs send monthly AQuIP Recruitment Journal email reminders to each LAO. The purpose of these reminders is to ensure that accruing LAOs and AOs add site-specific events (if any) to the *CP-CTNet AQuIP Recruitment Journal - Site-Specific Events* eCRF.

Note: LAOs have view only permission for both the study-wide and site-specific AQuIP Recruitment Journal eCRFs for their accruing LAOs and AOs. LAOs are not responsible for entering, editing, or querying AQuIP Recruitment Journal data for their accruing LAOs and AOs.

Note: Documentation and training materials for Stars and Rave can be found in the Stars and Rave sections of the CP-CTNet DMACC Portal Gateway.

5. AQuIP Accrual Tracking and Monitoring Reports: This set of data analytics and visualizations is produced by DMACC based on real-time accrual data entered into Stars and Rave by accruing LAO and AO staff. The reports provide visual goals and motivation for timely accrual as well as a basis for monitoring accrual rates by DCP, LAO staff, and accruing LAO and AO staff, facilitate prompt identification of improvement opportunities, and provide guidance for responsive interventions to address shortfalls in accrual. The AQuIP Recruitment Journal events are reported on the AQuIP Accrual Tracking and Monitoring Reports to illustrate associations (if any) with accrual changes.

6. AQuIP Think Tank: A group of CP-CTNet representatives (including DCP) with expertise in clinical trial management and coordination, assembled as a community of practice to facilitate discussion of real-world clinical trial implementation challenges and solutions, collaboratively identify knowledge and training gaps, and provide practical feedback to DCP leadership.

5. AQUIP DOCUMENTATION, REPORTING, AND OVERSIGHT REQUIREMENTS

1. Data should be entered on a continual basis, and all required data fields should be completed.
    1.1. Data are reviewed carefully by DMACC staff, who aggregate the data, perform data integrity checks, and send data queries back to the accruing LAOs and AOs.
    1.2. Each accruing LAO and AO is responsible for entering data and resolving data queries within 14 calendar days.
2. An escalation process is defined for data and/or query responses that are overdue:
    2.1. If an accruing LAO or AO has not responded to requests for overdue data/queries, DMACC escalates to the LAO. If there is no resolution, the LAO escalates to DCP, keeping DMACC in copy.
    2.2. If an LAO has not responded to requests for overdue data/queries for their accruing LAO or AOs, DMACC escalates to DCP.
3. DCP, DMACC, and LAOs (as applicable) work with accruing LAOs and AOs to determine the reason for the delinquency and create a plan to address the issue and prevent further issues.
4. DMACC generates monthly AQuIP Accrual Tracking and Monitoring Reports.
    4.1. The LAOs provide oversight of accrual and participant-level and site-level recruitment information documentation for their respective accruing LAOs and AOs to assure timely and accurate data entry.
    4.2. The LAOs must review and proactively evaluate the study-specific AQuIP Accrual Tracking and Monitoring Reports and distribute the reports to their accruing LAOs and AOs.
    4.3. The LAOs must assure that the recruitment impediments, strategic corrective actions, and favorable factors are well-documented via accruing LAO and AO AQuIP Recruitment Journal event entries.
    4.4. DCP may require additional recruitment barrier analysis and a corrective action plan for review by the DCP Medical Monitor, Nurse Consultant, and Scientific Lead, and approval by DCP leadership. Depending on the recruitment issues, interventions for improvement will be devised and/or study design modifications or discontinuation will be considered.

    Please send questions and comments to DataManagement_CP-CTNet@frontierscience.org.

6. REFERENCES

Note: All CP-CTNet SOPs are included in the *CP-CTNet Manual of Standard Operating Procedures (M-SOP)*, which is available on the CP-CTNet DMACC public website.

Document	ID	Location
AQuIP Guide to the Enrollment Trajectory: I-SCORE 2023	Brochure	Program Resources
AQuIP Toolkit	Manual	Program Resources
CP-CTNet Stars User Guide	USRMAN01	Program Resources
Cross-Network Trials Guidelines	REFGD06	Program Resources

Document	ID	Location
RRA Plan	Form	Program Resources

7. APPENDICES

- None

Title: Policy on Standard Operating Procedures

Document ID: CP-CTNet SOP 02-05

Version: 4.0

Version Date: January 26, 2024

REVISION HISTORY (most recent first)

Version	Effective Date	Summary of Changes
4.0	JAN-26-2024	Updated the M-SOP release schedule from up to three times per year to up to two times per year. Updated the DTL descriptions based on the updated DTL Master Task List. Minor updates were made throughout the document. Updated the document title.
3.0	JUL-13-2023	Updated to clarify that LAO staff should review and sign off on the M-SOP. Updated the links to documents hosted on the DCP website to ensure that documents download as expected.
2.0	FEB-21-2023	Total re-write to reflect implementation of the M-SOP.
1.0	AUG-17-2020	Original version of document.

1. INTRODUCTION AND PURPOSE

The Division of Cancer Prevention (DCP) Cancer Prevention Clinical Trials Network (CP-CTNet) Standard Operating Procedures (SOPs) are written standard procedures that describe the responsibilities of staff from DCP, the Data Management, Auditing, and Coordinating Center (DMACC), Lead Academic Organizations (LAOs), accruing LAOs, and Affiliated Organizations (AOs).

The CP-CTNet SOPs are maintained as one master manual, referred to as the Manual of Standard Operating Procedures (M-SOP). The M-SOP is located on the *Program Resources* page on the CP-CTNet DMACC public website.

2. SCOPE

This document details the responsibilities of DCP, DMACC, LAOs, accruing LAOs, and AOs throughout the creation, update, review, sign-off, and amendment process for CP-CTNet SOPs.

3. DEFINITIONS

Term	Definition
AE	Adverse Event
AERS	Adverse Event Reporting System
AO	Affiliated Organization
CP-CTNet	Cancer Prevention Clinical Trials Network
CRA	Clinical Research Associate
CRF	Case Report Form
CTEP	Cancer Therapy Evaluation Program
DCP	Division of Cancer Prevention
DMACC	Data Management, Auditing, and Coordinating Center
DTL	Delegation of Tasks Log
H&P	History and Physical
IND	Investigational New Drug
LAO	Lead Academic Organization
M-SOP	Manual of Standard Operating Procedures
PI	Principal Investigator
QA	Quality Assurance
SOP	Standard Operating Procedure

4. SOP CREATION, UPDATE, AND REVIEW

1. Creation and Update:

1.1. The first iteration of a CP-CTNet SOP is written by DCP and DMACC.

1.2. The draft SOP is then reviewed by the LAOs, as applicable. Each LAO determines the reviewer(s).

1.3. The draft SOP is then sent to the CP-CTNet Steering Committee for final approval.

1.4. DMACC integrates the approved individual SOP into the M-SOP. The new SOP and changes to any existing SOPs will be documented in the M-SOP's revision history table alongside the M-SOP version number and effective date. See the Versioning section below for more information about M-SOP and individual SOP versioning.

1.5. Any new or updated individual SOPs are included as part of the next M-SOP release. See the Release Frequency section below for more information.

1.6. The M-SOP is posted to the *Program Resources* page on the CP-CTNet DMACC public website.

1.7. The initial/new version of the SOP becomes effective within five (5) business days after DMACC sends an announcement email to DCP and the LAOs indicating that a new version of the M-SOP is available. The LAOs then forward the announcement to their accruing LAOs and AOs.

2. Review:

2.1. All SOPs require review by DCP and DMACC annually, and ad hoc, with the latest version superseding earlier versions. The annual review is formally performed by DMACC. Every January, a new version of the M-SOP will be released and will include changes made to the individual SOPs during the annual review.

2.2. All changes to SOPs made during the annual and ad hoc reviews are sent to DCP for review and approval before they are finalized and integrated into the M-SOP. The changes from the annual and ad hoc reviews are announced to the network as part of one of the M-SOP releases (up to two (2) times per year). See the Release Frequency section below for more information.

2.3. LAO and CP-CTNet Steering Committee review is requested for major changes to individual SOPs.

2.4. The LAOs discuss the M-SOP with their accruing LAOs and AOs annually, and each time the M-SOP is released (up to two times per year) to ensure understanding.

5. M-SOP

After individual SOPs are created, reviewed, and finalized, they are integrated and maintained within the M-SOP by DMACC. The M-SOP contains all current CP-CTNet SOPs in one file, which is posted to the *Program Resources* page on the CP-CTNet DMACC public website. The M-SOP includes a clickable table of contents to allow for quick navigation to individual SOPs. DMACC releases the M-SOP up to two times per year (e.g., January and June) if there have been updates to individual SOPs since the last release of the M-SOP. See the Release Frequency section below for more information. Each M-SOP release includes all new and revised CP-CTNet SOPs, with a *CP-CTNet M-SOP Acknowledgement Sign-Off Log*.

Note: The M-SOP does not include related documentation (e.g., reference guides, quick reference guides, templates, forms, etc.). All related, publicly available CP-CTNet documentation is reviewed by DMACC on an annual basis, and ad hoc, and is available on the *Program Resources* page on the CP-CTNet DMACC public website.

1. **Initial Rollout:**

    1.1. When the initial M-SOP is distributed to the network members, the LAO communicates to their accruing LAOs and AOs that this is the collection of CP-CTNet SOPs, referred to as the M-SOP.

    1.2. The LAO distributes the M-SOP to any new accruing LAOs and AOs that join the network after the initial M-SOP is released and communicates that this is the collection of CP-CTNet SOPs, referred to as the M-SOP.

    1.3. Each LAO, accruing LAO, and AO is responsible for obtaining documented evidence of training/sign-off on the M-SOP for current and new relevant staff at their site. See the M-SOP Sign-off section below for more information about the relevant staff that are required to sign off on the M-SOP.

2. **Release Frequency:**

    2.1. DMACC, in collaboration with DCP, releases the M-SOP with relevant individual SOP changes up to two times per year to alleviate constant SOP updates.

    - If an individual SOP is updated after the M-SOP is released, posted, and announced, that individual SOP is included as part of the next M-SOP release.
    - It is possible that individual SOPs as part of the M-SOP may require updates outside of the release schedule (up to two times per year), as procedures change, or new processes are added. If an individual SOP containing major revisions requires an expedited update and cannot wait until the next M-SOP release, the plan of action is determined collaboratively by DCP and DMACC.

    2.2. Documented evidence of communication and training or sign-off for each M-SOP version at each LAO, accruing LAO, and AO is required. See the M-SOP Sign-off section below for more information on the relevant staff that are required to sign off on the M-SOP.

    2.3. All LAOs, accruing LAOs, and AOs should maintain the most recent version of the M-SOP on file at each site.

    2.4. If there are no updates to individual SOPs prior to an M-SOP release, then the M-SOP is not released and DMACC sends a notification to LAOs indicating that there are no changes to the M-SOP. LAOs notify their accruing LAOs and AOs that there are no changes to the M-SOP. No additional action is needed from DCP, DMACC, LAOs, accruing LAOs, or AOs.

3. **Versioning:**

    3.1. The entire M-SOP is assigned a version number, starting at version 1.0, which is increased by a whole number each time the M-SOP is released to the network. If no SOP updates have occurred since the last release, the M-SOP version will not change until the next release containing an SOP update.

    3.2. Individual SOPs also maintain their own cover tracking sheet and revision history table to track historical changes made to individual SOPs.

    3.3. The M-SOP version date is equal to or greater than the last revised individual SOP date (e.g., the SOP with the most recent date).

    - For example, if an individual SOP was updated on 02/28/2023, the M-SOP has a version date of 02/28/2023 or later.

4. M-SOP Sign-off:

4.1. All LAO staff need to review and sign off on the M-SOP as part of their oversight of their accruing LAOs and AOs. Accruing LAO and AO staff that are listed on the *DTL* with the task names listed below are required to review and sign off on the M-SOP as well. The M-SOP does not apply to the other DTL task names.

- Agent Prescribing: Responsible for writing an order for a patient that is not a DCP IND agent.
- Site PI: Investigator at the site responsible for signing the DTL for a given protocol, and with overall responsibility for the study conduct at the site.
- Consenting Person: Person having responsibility for consent.
- Eligibility Assessments: Verification of eligibility.
- End Point Assessment: Assess study endpoints.
- Enrolling Person/Treating Investigator: Investigator having responsibility for subject treatment (e.g., Enrolling investigator).
- H&P Assessments: Conducts physical exam and assessments.
- IND Prescribing: Responsible for writing an order for a patient that is an IND agent.
- Patient Screening/Recruiting: Responsible for screening and recruiting of subjects.
- Primary Study/Site Contact: The point of contact for the study.
- Rave CRA: Rave write access; responsible for data management and uploads of Central Monitoring documents; and using Rave CTEP - AERS safety reporting tools.
- Rave Investigator: Investigator assigned to sign-off on the CRFs in Rave.
- Regulatory Contact: Site staff responsible for regulatory submissions and maintaining essential documents.
- Source Documentation Completion: Responsible for collecting data on study-related assessments.
- Study-Related Interventions: Responsible for coordinating and/or administering study-related interventions and procedures.
- Toxicity Assessment: Assesses AEs.
- Unblinded Study Personnel: Study personnel responsible for handling, preparing, and labeling study agents to ensure blinded study randomization is protected at the site. A copy of the pharmacy's plan or SOP for unblinded study personnel to be included in the site Trial Master File. At a minimum, one of the listed personnel must be the Shipping Designee at the drug shipment site.

4.2. The above staff sign off initially and for every M-SOP version regardless of if the modification affects their task(s) or not.

4.3. Each LAO, accruing LAO, and AO must ensure that all current and new relevant staff have documented evidence of training on the most recent version of the M-SOP by either:

- Collecting signatures from the relevant staff on the *CP-CTNet M-SOP Acknowledgement Sign-Off Log*, or
- Using their own process which must be outlined in a site-specific SOP.

4.4. LAOs, accruing LAOs, and AOs must be able to provide documented evidence of staff training and their site-specific SOP (if applicable) upon request, as this documentation is reviewed during DMACC QA audits.

4.5. LAOs, accruing LAOs, and AOs may determine how to collect documented evidence of staff training within their site.

- LAOs may provide guidance to their accruing LAOs and AOs about how to collect documented evidence of staff training on the M-SOP within their site. However, LAOs should not dictate for a given study how accruing LAOs and AOs should obtain sign-offs on the M-SOP. This allows each accruing LAO and AO to have a consistent way of obtaining sign-offs on the M-SOP across studies.

6. AMENDING SOPS DUE TO LOCAL INSTITUTIONAL POLICY

1. CP-CTNet SOPs are to be adopted by the LAOs, accruing LAOs, and AOs as written unless they are in direct conflict with local institutional policy. If this is the case, the LAO may amend the applicable SOPs only after obtaining written approval from DCP.
2. If LAO, accruing LAO, and/or AO PIs or Coordinators need to amend individual SOPs to comply with local institutional policy, the LAO:

2.1. Collects all LAO, accruing LAO, and AO amendment requests and electronically submits them as a package to DMACC (Documentation_CP-CTNet@frontierscience.org). DCP and DMACC review the package.

- The submission package includes:
  - A cover letter requesting the changes to the SOPs, including rationale for the requested changes.
  - The ‘clean’ copy of the revised SOPs with the ‘Site Version Date’ in the footer.
  - The ‘tracked changes’ copy of the revised SOPs with the ‘Site Version Date’ in the footer.

2.2. Communicates DCP’s decision regarding the amended SOPs to all applicable LAO, accruing LAO, and AO staff.

2.3. Adds the ‘Effective Site Version Date’ and ‘This SOP has been amended in compliance with local institutional policy.’ to the footer of the amended SOPs once approved by DCP.

2.4. Distributes the DCP-approved amended SOPs to all applicable LAO, accruing LAO, and AO staff for their use.

2.5. LAOs, accruing LAOs, and AOs should maintain all approved SOPs that are revised based on local institutional policy on file at each site.

2.6. Individual SOPs that have been amended to meet local institutional policy are not included in the M-SOP or posted on the CP-CTNet DMACC public website.

7. ADDITIONAL INFORMATION

1. Please send questions and comments to Documentation_CP-CTNet@frontierscience.org.

8. REFERENCES

Note: All CP-CTNet SOPs are included in the *CP-CTNet Manual of Standard Operating Procedures (M-SOP)*, which is available on the CP-CTNet DMACC public website.

Resource	ID	Location
CP-CTNet DMACC Public Website	Website	cp-ctnet-dmacc.org
CP-CTNet M-SOP Acknowledgement Sign-Off Log	Log	Program Resources
DCP Delegation of Tasks Log	Form	prevention.cancer.gov

9. APPENDICES

1. None.

Title: Biospecimen Submission Requirements

Document ID:	CP-CTNet SOP 02-06
Version:	4.0
Version Date:	January 26, 2024

REVISION HISTORY (most recent first)

Version	Effective Date	Summary of Changes
4.0	JAN-26-2024	Updated to reflect the new version of the *CP-CTNet Material Transfer Manifest*. Made minor updates throughout the document.
3.0	FEB-21-2023	Added section 3 Definitions, updated FNLCR contact information.
2.0	SEP-10-2020	Added that shipments to FNLCR are confirmed upon receipt.
1.0	AUG-17-2020	Original version of document.

1. INTRODUCTION AND PURPOSE

As described in each protocol, the Lead Academic Organizations (LAOs) and accruing LAOs and Affiliated Organizations (AOs) are responsible for collecting, processing, storing, and shipping Cancer Prevention Clinical Trials Network (CP-CTNet) study biospecimens to the appropriate laboratories for biomarker and/or other analyses. Any remaining biospecimens after analyses and other study-related activities are completed are required to be shared with the research community. These biospecimens may be submitted to the Frederick National Laboratory for Cancer Research (FNLCR) for storage and distribution to the community for investigational use.

2. SCOPE

This document details the responsibilities of the LAOs regarding biospecimen data collection and shipment to FNLCR. These responsibilities may be delegated to the accruing LAOs and AOs as described in the protocol.

3. DEFINITIONS

Term	Definition
AO	Affiliated Organization
BSI	Biological Specimen Inventory
CP-CTNet	Cancer Prevention Clinical Trials Network
DCP	Division of Cancer Prevention
DMACC	Data Management, Auditing, and Coordinating Center
FDA	Food and Drug Administration
FNLCR	Frederick National Laboratory for Cancer Research
LAO	Lead Academic Organization
M-SOP	Manual of Standard Operating Procedures
NCI	National Cancer Institute
SAE	Serious Adverse Event
SOP	Standard Operating Procedure

4. PROCEDURES

1. Requirements for study-specific biospecimen management, including collection, storage, banking, and shipping, are defined in section 12 of each study protocol.
2. Storage and distribution of biospecimens required at the end of a study may be managed by FNLCR.
    - 2.1. Biospecimens designated for centralized storage and distribution must be confirmed as consented for future use ***prior*** to forwarding these specimens to FNLCR. Any biospecimens that are lacking this consent should ***not*** be shipped to FNLCR and should be managed per institutional requirements.
    - 2.2. An electronic item-level *CP-CTNet Material Transfer Manifest* is to be submitted prior to shipment of any biospecimens to FNLCR. DMACC will assist the LAOs in preparing the Manifest.
    - 2.3. The ***minimum data items required*** for each biospecimen submitted are listed below. Additional data may be required and/or requested depending on the specialized needs of

the study, protocol requirements, and/or material group of the biospecimen(s) being submitted.

- BSI ID
- Study ID
- Material Type
- Current Label
- Label Status
- Volume
- Volume Estimate
- Volume Unit

2.4. The shipper or designated representative provides a signature and date within the Manifest to verify that all biospecimens listed on the Manifest have been reviewed as consented for future use.

3. The Manifest should be submitted to FNLCR at NCI-FrederickCSPBPTLStaff@mail.nih.gov and to DCP at NCIDCP-CTNetBiospecimens@mail.nih.gov at least 48 hours prior to shipping the listed biospecimens.

3.1. When the LAO, accruing LAO, or AO is ready to ship the biospecimens, they will contact FNLCR. A webinar will be held by FNLCR with the institution responsible for shipment, to discuss the specifics of the study's biospecimen collection, review supply and shipment instructions, and develop a timeline for related tasks and activities. Supplies and related materials will be provided by FNLRC to ensure the proper packaging and transportation of biospecimens to the FNLCR repository.

4. Supplies are provided by FNLCR for frozen, chilled, and room temperature shipments, as required. The supplies will include packaging, instructions, points of contact, shipping address, and prepaid courier documents.

4.1. Biospecimens should be shipped with a copy of the Manifest and a packing slip in each package. The shipping address for these materials is noted on the Manifest and in section 5 below. Details regarding completion of the Manifest and packing slip will be reviewed during the pre-shipment webinar with the responsible institution.

4.2. All shipments to FNLCR are confirmed when they arrive (box, condition, temp, # of boxes, # of vials).

5. The FNLCR Head of Bioprocessing and Trial Logistics is responsible for general oversight of this process, laboratory administration, shipping supplies, and biospecimen database inquiries:

BioProcessing Laboratory
Attn: Norma Diaz/Consortia
4600 Wedgewood Blvd
Suite K
Frederick MD 21703
(301) 228-4200
NCI-FrederickCSPBPTLStaff@mail.nih.gov

5. ADDITIONAL INFORMATION

Please send questions and comments regarding this SOP to cp-ctnet.labdatamanagers@frontierscience.org.

6. REFERENCES

Note: All CP-CTNet SOPs are included in the *CP-CTNet Manual of Standard Operating Procedures (M-SOP)*, which is available on the CP-CTNet DMACC public website.

Resource	ID	Location
CP-CTNet Material Transfer Manifest	Form	Program Resources

7. APPENDICES

- None

Title: Unblinding Participants

Document ID:	CP-CTNet SOP 02-07
Version:	2.0
Version Date:	January 26, 2024

REVISION HISTORY (most recent first)

Version	Effective Date	Summary of Changes
2.0	JAN-26-2024	Replaced references to sites with accruing LAOs and AOs and made minor editorial updates throughout document.
1.0	FEB-21-2023	Original version of document.

1. INTRODUCTION AND PURPOSE

This document provides guidelines for unblinding participants enrolled in Cancer Prevention Clinical Trials Network (CP-CTNet) studies that involve randomization with blinded treatment assignment.

2. SCOPE

This document details the responsibilities related to unblinding participants for staff at Lead Academic Organizations (LAOs), accruing LAOs, Affiliated Organizations (AOs), the Division of Cancer Prevention (DCP), and the Data Management, Auditing, and Coordinating Center (DMACC).

3. DEFINITIONS

Term	Definition
AO	Affiliated Organization
CIRB	Central Institutional Review Board
CMDMRU	Co-Manager of the Data Management and Reporting Unit
CP-CTNet	Cancer Prevention Clinical Trials Network
DCP	Division of Cancer Prevention
DM	Data Manager
DMACC	Data Management, Auditing, and Coordinating Center
DSMB	Data Safety Monitoring Board
IRB	Institutional Review Board
LAO	Lead Academic Organization
M-SOP	Manual of Standard Operating Procedures
MM	Medical Monitor
NC	Nurse Consultant
PI	Principal Investigator
PID	Participant Identifier
SL	Scientific Lead

4. CATEGORIES AND REASONS FOR UNBLINDING

1.1. Full study unblinding takes place when all data forms have been keyed into the database for all participants, data cleaning has been completed including resolution of any outstanding data queries, and the study team has declared the study dataset to be complete. On a date predetermined by the study team, treatment assignments are provided to all participating accruing LAOs and AOs for each participant enrolled in the study.

1.2. Emergency unblinding of individual participants by the Accruing LAO or AO Pharmacist of Record, as requested by the Accruing LAO or AO Study Investigator, takes place when the information is needed for the immediate medical management of a participant. Guidelines for emergency unblinding can be found in section 8.9 of each study protocol.

5. PROCEDURES

1.1. **Full Study Unblinding**

- During the preparation of the study closeout timeline, the study team (DCP MM, DCP NC, DCP SL, LAO staff, and DMACC staff) should confirm the plan for unblinding the participants. Before unblinding the participants can take place:

  - The unblinding date should be determined in advance by the study team along with the timetable for study closeout.
  - The DMACC DM should send a draft unblinding memo to the study team for review and for the addition of any study-specific language the study team wishes to include.
  - All data forms need to be keyed; all data needs to be cleaned; and the study team needs to declare the study dataset to be complete.

- The DMACC CMDMRU prepares unblinding lists for each accruing LAO and AO.
- On the date the study team has specified, the DMACC CMDMRU securely emails each Accruing LAO or AO Study Investigator the unblinding memo and the unblinding list for the participants from their accruing LAO or AO. The DMACC CMDMRU should copy the DCP MM, NC, and SL on this email.
- Each Accruing LAO or AO Study Investigator or designee informs their participants of their study treatment. Any participant-facing material(s) that the accruing LAO or AO decides to use to inform their participants of their study treatment must be approved by the CIRB.

1.2. Emergency Unblinding of Individual Participants

- In the rare circumstance where an Accruing LAO or AO Study Investigator or designee determines that there is an immediate medical need to know the study treatment of an individual participant (per section 8.9 of each study protocol), the Accruing LAO or AO Study Investigator or designee contacts the Accruing LAO or AO Pharmacist of Record to obtain the assigned treatment.
- Within 24 hours, the Accruing LAO or AO Study Investigator or designee must then document the reason for emergency unblinding and send the protocol number, PID, and reason for unblinding to the CIRB and their local IRB as well as the Protocol PI, DCP MM, DCP NC, DCP SL, LAO Statistician, DMACC Statistician, DMACC DM, and DSMB (if applicable).
- There must be written documentation of the communication from the Accruing LAO or AO Study Investigator or designee to the Accruing LAO or AO Pharmacist of Record and from the Accruing LAO or AO Pharmacist of Record back to the Accruing LAO or AO Study Investigator or designee, preferably at the time of the initial request/response, but if that is not feasible, then at least within 24 hours.

6. ADDITIONAL INFORMATION

Please send questions and comments to DataManagement_CP-CTNet@frontierscience.org.

7. REFERENCES

Note: All CP-CTNet SOPs are included in the *CP-CTNet Manual of Standard Operating Procedures (M-SOP)*, which is available on the CP-CTNet DMACC public website.

Resource	ID	Location
DCP CP-CTNet Chemoprevention Protocol Template	Template	Program Resources

8. APPENDICES

- None

Title: Site (LAO/AO) Preparations for Quality Assurance Audits

Document ID:	CP-CTNet SOP 03-02
Version:	3.0
Version Date:	February 21, 2023

REVISION HISTORY (most recent first)

Version	Effective Date	Summary of Changes
3.0	FEB-21-2023	Major updates to all sections.
2.0	SEP-30-2021	Added scheduling timelines as well as changed 10% of participants or a minimum of 7 (it previously said 25%), added information about the risk assessment tool.
1.0	AUG-17-2020	Original version of document.

1. INTRODUCTION AND PURPOSE

The National Cancer Institute (NCI)/Division of Cancer Prevention (DCP) requires Quality Assurance (QA) audits of clinical trials data and processes at each Lead Academic Organization (LAO) and Affiliated Organization (AO). Audits are conducted by the Cancer Prevention Clinical Trials Network (CP-CTNet) Data Management, Auditing, and Coordinating Center (DMACC).

Auditing is an independent quality assurance function for systematic evaluation of trial processes and documents to determine whether trial-related activities are conducted, and data are recorded, analyzed, and accurately reported according to the protocol, the sponsor's Standard Operating Procedures (SOPs), relevant Good Clinical Practice (GCP) guidelines, applicable regulatory requirements, federal regulations, and National Institutes of Health (NIH)/NCI/DCP policies. Audits are performed by DMACC on a routine and ad hoc basis, and are a snapshot in time of the CP-CTNet sites' compliance with program requirements.

The specific purpose of the auditing program is as follows:

- Document the accuracy of data submitted to Medidata Rave, the Stars registration/randomization system, and DCP
- Verify investigator compliance with protocol and regulatory requirements
- Verify adherence to CP-CTNet policies and procedures
- Provide site staff with resources for a more thorough understanding of regulatory requirements, GCP, data collection and data management practices, as necessary

Auditing also provides the opportunity for LAOs, AOs, DCP, and DMACC to work together to identify areas for systemic and policy-level improvements in order to increase both efficiency and compliance, to better ensure the protection of human subjects, and to enhance the quality and integrity of CP-CTNet clinical trials. Additionally, audits provide sites the opportunity to address any questions or concerns about CP-CTNet processes or related issues.

The major objectives of the audit program are to ensure compliance with the protocol and all federal and regulatory requirements, to verify accurate recording and reporting of study data that could affect the interpretation of primary study endpoints, and to ensure participant safety. The four main components reviewed during an audit are:

- Essential documents
- Policy, procedure, and site operations
- Pharmacy and drug accountability
- Participant study charts

Routine Quality Assurance Audits:

1. Accruing sites (AOs and LAOs) are eligible for audit once they have enrolled a minimum of three (3) participants to a CP-CTNet protocol. If a site has not enrolled more than two (2) participants within 12 months of opening to accrual, the audit team will consult with DCP and the LAO to determine when to conduct the first audit. If a site Investigator has accrued to more than one protocol, all of the Investigator's CP-CTNet protocols may be reviewed during the audit visit, even if not all protocols have enrolled the minimum three (3) participants.

The audit team makes every effort to conduct the first QA audit at an AO on-site and to perform an on-site audit with each accruing study team at least once every three (3) years. Interim audits at AOs are performed remotely.

2. LAOs are audited on-site annually unless institutional policies prohibit on-site audits, in which case the audit is performed remotely. Annual audits review LAO oversight of AOs with active studies. Any protocols that the LAO is an accruing site for (i.e., an accruing LAO) that have enrolled a minimum of three (3) participants are also reviewed at this time.

For-cause Audits:
A "for cause" audit may be conducted at any time upon request from DCP or the CP-CTNet Steering Committee. Most "for cause" audits are conducted on-site. A "for cause" audit may be triggered by:

- Concerns that the study is not being conducted in accordance with the protocol or standard regulations regarding the conduct of clinical research.
- Concerns about participant safety.
- Questions about data quality, integrity, misconduct, or fraud.
- Concerns about compliance with policy and procedures.

2. SCOPE

This document details the responsibilities of the LAO and AO Site Coordinators and Principal Investigators (PIs) regarding the conduct of a QA audit.

3. DEFINITIONS

Term	Definition
AE	Adverse Event
AO	Affiliated Organization
AQuIP	Accrual Quality Improvement Program
CIRB	Central Institutional Review Board
CP-CTNet	Cancer Prevention Clinical Trials Network
DCP	Division of Cancer Prevention
DMACC	Data Management, Auditing, and Coordinating Center
DSMC	Data Safety and Monitoring Committee
DSMP	Data and Safety Monitoring Plan
EMR	Electronic Medical Record
GCP	Good Clinical Practice
ICD	Informed Consent Document
IRB	Institutional Review Board
LAO	Lead Academic Organization
M-SOP	Manual of Standard Operating Procedures
MM	Medical Monitor
NC	Nurse Consultant
NCI	National Cancer Institute
PD	Protocol Deviation
PI	Principal Investigator

Term	Definition
QA	Quality Assurance
SAE	Serious Adverse Event
SDV	Source Data Verification
SL	Scientific Lead
SOP	Standard Operating Procedure
SVAR	System Variable Attribute Report

4. SCOPE OF A DMACC QUALITY ASSURANCE AUDIT

1. The scope of the DMACC QA audit includes but is not limited to:
    1.1. Investigator Site File of Essential Documents:
        - Well organized, current, and complete in accordance with SOP 01-01 *Essential Documents Submission for Sponsor's Record*.

    1.2. Site Operations, Policy and Procedure review:
        - Assurance of participant confidentiality
        - Documentation of training and qualifications of staff (general and protocol specific)
        - Documentation of regular communication:
            - Between LAOs and AOs
            - LAO dissemination of DCP, DMACC, CIRB, and DCP Regulatory Contractor communications to AOs as appropriate
            - LAO communication of AO generated questions, concerns, issues to DCP, DMACC, CIRB, and DCP Regulatory Contractor as appropriate
        - Protocol compliance:
            - 100% adherence to eligibility criteria
            - Deviations from the protocol are identified and reported in compliance with SOP 02-02 *Reporting Protocol Deviations*.
            - Serious or continuous noncompliance and unanticipated problems are reported to the CIRB, local IRB, and DSMC in compliance with the policies and procedures specified by each entity.
        - Participant recruitment, retention, adherence (RRA) and reporting is in compliance with SOP 02-04 *Participant Recruitment, Retention, Adherence, and Reporting Requirements*.
            - The RRA Plan developed for the protocol (provided by the LAO) is being followed.
            - Documentation of accrual efforts (pre-screening and screening) in Stars is complete and current.
            - Accrual rates are on target.
            - The AQuIP recruitment journal in Medidata Rave (Rave) is current and complete and documents events, situations, conditions, or efforts that may have an impact (either positive or negative) on accrual at the site.

- The clinical evaluations and procedures described in the protocol are complete for each participant and are performed in accordance with the methods and within the timeframe specified for each.
- Study visits and interim contacts are complete and performed within the specified timeframe.
- Collection of clinical labs and biospecimens for endpoints analysis is complete.
    - Biospecimens are collected, labeled, inventoried, processed, stored, and submitted for endpoint analysis (or analyzed on-site) as specified by the protocol.
- Off-agent and off-study criteria are adhered to.
- Criteria for dose modification of study agent are followed.
- AEs are assessed and reported accurately, completely, and in a timely fashion.
- Serious adverse events are correctly identified and reported within 24 hours of knowledge of the event.

1.3. Pharmacy/Drug Accountability:

- Storage is secure and environmental conditions (such as temperature) are monitored and maintained within the parameters specified in the study protocol.
    - Any excursions from the protocol-specified storage conditions are documented.
- Study agent accountability records are maintained, are current, available for review, and include:
    - Study agent order receipts.
    - An accurate physical inventory of dispensed, un-dispensed and returned study agent.
    - A record of per participant study agent dispensing and returns documenting:
        - Institution Name
        - Protocol name and number
        - Agent name, dose form, and strength
        - Participant initials, study ID number and, when applicable, randomization number
        - Date and quantity dispensed to participant
        - Date and quantity returned by participant
        - Manufacturer, lot number and expiration date, if applicable
        - Balance Forward/Balance
        - Recorder’s initials
    - An accurate account of final study agent disposition (either returned to the supplier or destroyed on-site as specified in the study protocol)
    - Measures are in place to ensure study agent is dispensed only upon receipt of a prescription or written orders from an authorized prescriber and dispensed only to a registered study participant.

1.4. Participant Case Review:

- Informed consent.
- Inclusion/Exclusion Criteria

- Investigational agent compliance (administration, dose modification, etc.)
- AE/SAE reporting
- General data management quality (e.g., timely, complete, and accurate Rave data entry and query response)
- Participant-specific AQuIP data (strategies, reasons not enrolled, etc.)
- Protocol deviation identification and reporting
- Concomitant medication documentation and reporting
- Specimen collection, processing, storage, shipment
- Secure record storage
- A minimum of three (3) participant charts per protocol/per site will be selected for case review. The cases selected for review will include the first two (2) participants enrolled at the site and any participants that experienced an SAE. The remaining cases will be randomly selected from the participants enrolled at the site at the time the audit visit is scheduled.
- The first two (2) participants enrolled per protocol, per site will have 100% source document verification of study data. Source data verification for the remaining participant cases selected for review will be targeted. The level of targeted source data verification is determined by the risk level assigned to the protocol by the DCP reviewers during the initial protocol review.

5. SCHEDULING

Prior to contacting an AO regarding scheduling an audit, the LAO will be notified so that they can notify the AO and reiterate the purpose of the audit and inform them that the DMACC Clinical Trials Auditing Unit will be contacting them soon. In the CP-CTNet, auditing is not limited to for-cause or to high accruing sites. All AOs can expect to be audited once they have accrued the minimum of three (3) participants.

A “Request to Schedule Audit” email will be sent six (6) weeks in advance to the Organization Investigator(s) listed on the protocol. One or more additional key study staff members, who the LAO identifies as being study staff likely to be responsible for coordinating the audit at the site, will be copied on the email. The “Request to Schedule” includes:

1. Desired date range for conducting the audit
2. Anticipated length of time to complete the audit
3. Request for a brief pre-audit meeting with the PI and key study staff on the first day of the audit
4. Request to schedule a pharmacy visit (if applicable)
5. Request for a 30-minute “summary of findings” meeting with the PI and key study staff at the end of the final day of the audit. The DCP MM, SL, and NC for the protocol as well as LAO staff members are invited to participate by phone/video.

An “Audit Confirmation” email and agenda is sent to the site once a date for the audit is agreed upon. The agenda will include the list of participant cases selected for review during the audit.

6. SITE COORDINATOR RESPONSIBILITIES FOR LAO AND AO

1. Collaborate with the auditor(s) to identify a mutually agreeable date for the on-site or remote audit to allow maximum participation by site staff.

2. Acknowledge receipt of the confirmation email, confirming the date and objectives of the audit.
3. Communicate audit logistics and objectives to site and pharmacy staff.
4. If on-site, ensure that adequate workspace will be available for the auditor(s) during the visit.
5. Ensure all relevant materials are available for review. This should include:
    5.1. All essential documents (including communication files)
    5.2. A signed ICD for each individual registered to the study (enrolled and screen failures)
    5.3. Complete source documents (or copies) for participants selected for case review, including eligibility checklists, medical records, laboratory data, worksheets, questionnaires etc.
        - If an EMR system is used, the auditor(s) may be granted access to the system or the records may be printed for review by the auditor(s). A staff member should be available to assist with the system if necessary.
    5.4. When sending sources documents for review during a remote audit, ensure all participant identifiers are removed per your local policies.
    5.5. SAE documentation and PDs (refer to SOP 02-01 *Reporting Serious Adverse Events* and SOP 02-02 *Reporting Protocol Deviations* for requirements).
    5.6. Logs and documentation for enrollment, screening, and monitoring/auditing visits

    Note: For remote/virtual audits, the auditor will contact the site coordinator in advance to arrange for access to the documentation, and/or relevant electronic systems.
6. Ensure all entries in Rave (the database of record) are current, complete, and accurate and any data queries received to date are addressed.
7. Communicate any institution-specific policies to the auditors in advance of the audit (visitor policies, Covid-19 policies, vaccine requirements, etc.).

7. RESPONSIBILITIES FOR LAO ONLY

Provide documentation to support performance of the following:

1. Tracking the receipt of regulatory documents from accruing LAO/AO(s) and submission of those documents to the DCP Regulatory Contractor.
2. Method(s) of communicating information to accruing LAO/AO(s). Examples include meeting minutes, email documentation or an active website link.
3. Tracking staffing changes, accrual and retention patterns, PDs, SAEs, data entry, research specimen tracking, and query resolution at accruing LAO/AO(s).
4. Accruing LAO/AO(s) are trained on the most current CP-CTNet SOPs.
5. Accruing LAO/AO staff are trained on the current protocol.
6. SDV of participant charts for accruing LAO/AOs as indicated in SOP 03-03 *LAO Oversight Activities*.
7. For studies deemed to be high risk per the *Protocol Risk Assessment* tool by the DCP protocol review team, 100% review and confirmation of eligibility **prior** to randomization/enrollment for all sites seeking to enroll a study candidate on a protocol deemed “high risk” by the DCP study team. The risk level assigned to a protocol is documented on the Consensus Review of the first submission of a protocol to DCP for review.

Provide the following documents:

1. SVAR Worksheets for each CIRB-approved version of the protocol.

2. All versions of the LAOs DCP-approved DSMPs including the time frame during which each was in effect.

8. DOCUMENTATION REQUIREMENTS

1. The Audit Team creates an Audit Report in the Audit System housed on the CP-CTNet DMACC Portal Gateway. The report contains a list of action items that must be addressed by the site.
2. The report is opened to the Director of the DMACC Clinical Trials Auditing Unit for review/approval within 15 business days of the audit.
3. Access is then granted to the DCP study team for review.
    3.1. The DCP study team has eight (8) business days to review and comment on the report.
4. Upon completion of DCP review (or after eight (8) business days - whichever is sooner), access to the report is granted to the site.
5. The LAO or AO Site Coordinator will respond to all action items identified during a QA audit within thirty (30) calendar days of receipt of the report to respond to the audit findings using the *Action-Item Site Response Form*.
    5.1. This response will indicate either resolution of the action item or include a corrective action plan with a projected resolution date.
    5.2. For items with a projected resolution date, the CP-CTNet auditor will follow-up on those items every thirty (30) days until all items are resolved.
    5.3. The reports are reviewed by the DMACC Director of the Clinical Trials Auditing Unit and a DCP study representative.
    5.4. Once all items are resolved, the final Audit Report is signed by the Organization Investigator.
6. If the site does not respond within the thirty calendar day timeframe, an auditor will contact the site to help remedy any issues delaying the response.
    6.1. If the site does not respond or resolve the issue within seven calendar days, the auditor will document the site's noncompliance in an email to the site, with DCP representatives copied, and will record this as a major violation in the Audit Report.

9. ACTION-ITEM RESPONSE FORM

1. To avoid any potential pitfalls during preparation of the Site Action-Item Response Form, the following should be considered:
    1.1. Document every step of corrective and preventative action implementation (documentation of root cause analysis, development of new procedures, any training, etc.).
    1.2. Specify the timeframe for completion of the corrective and preventive actions.
2. Adherence to and implementation of the agreed upon corrective and preventive action is critical and may be the scope of a future audit.
3. Sites are requested to review the Audit Reports and record agreement or disagreement with each audit finding. If you do not agree, a reason and if applicable, additional supporting documentation should be provided to the auditor.
    3.1. For example, if the findings cited no evidence of hematologic values or radiotherapy treatment in the patient's chart, but values exist or radiation was given, it is necessary to send copies of the reports, which confirm the values or treatment. Any supporting documentation provided to the auditor must be anonymized prior to sending.

4. The auditor will follow up with the site to obtain necessary confirmatory documentation. If the PI confirms the documentation is not available, the PI or designee should flag the data as unconfirmed in Rave. If these data are related to eligibility criteria, inability to provide appropriate documentation may render the participant ineligible.
5. If the audit of individual participant source documents indicates data have been entered incorrectly in Rave, and the PI agrees with this assessment, the site will make the appropriate changes to the database based on the Audit Report.
6. Sites should retain all audit reports and correspondence available for future audits (e.g., in Regulatory Binder or protocol Trial Master File).
7. All Audit Reports and Site Action-Item Response Forms will be distributed to:
   7.1. LAO PI and Site Coordinator.
   7.2. AO PI and Site Coordinator (as applicable).
   7.3. Per protocol DCP MM.
   7.4. Per protocol DCP SL.
   7.5. DCP NC.
8. Any Audit Reports that identify major deficiencies within the site will also be accessible to:
   8.1. DCP Program Director.
   8.2. DCP Program Official.

   Note: The Audit Team will also notify the DCP Regulatory Contractor of any unreported or misreported SAEs.

10. ADDITIONAL INFORMATION

Please send questions and comments to the DMACC at Audit_CP-CTNet@frontierscience.org

11. REFERENCES

Note: All CP-CTNet SOPs are included in the *CP-CTNet Manual of Standard Operating Procedures (M-SOP)*, which is available on the CP-CTNet DMACC public website.

Document	ID	Location
Essential Documents Submission for Sponsor's Record	SOP 01-01	Program Resources
LAO Oversight Activities	SOP 03-03	Program Resources
Participant Recruitment, Retention, Adherence, and Reporting Requirements	SOP 02-04	Program Resources
Protocol Risk Assessment to Determine the Level of Targeted Source Data Verification During a CP-CTNet Audit	DMACC REFGD09	Program Resources
Recruitment, Retention and Adherence Plan	Form	Program Resources
Reporting Protocol Deviations	SOP 02-02	Program Resources
Reporting Serious Adverse Events	SOP 02-01	Program Resources

12. APPENDICES

1. None

Title: Lead Academic Organization Oversight Activities

Document ID:	CP-CTNet SOP 03-03
Version:	5.0
Version Date:	January 26, 2024

REVISION HISTORY (most recent first)

Version	Effective Date	Summary of Changes
5.0	JAN-26-2024	Updated to highlight the difference between Lead vs. Collaborating LAOs on CNTs and to highlight that UPs and SCNCs should be discussed with DCP prior to CIRB submission.
4.0	JUL-13-2023	Updated to highlight that LAO staff should review and sign off on the M-SOP. The links to documents hosted on the DCP website were updated to ensure that documents download as expected.
3.0	FEB-21-2023	Added section 3, Definitions, and removed reference to REFGD07.
2.0	JUN-13-2022	Extensive rewrite of the SOP to provide specific guidance on the roles and responsibilities associated with LAO oversight of accruing LAOs and AOs.
1.0	AUG-17-2020	Original version of document.

1. INTRODUCTION AND PURPOSE

A Cancer Prevention Clinical Trials Network (CP-CTNet) Lead Academic Organization (LAO) manages and assumes responsibility for its network protocols on behalf of the Division of Cancer Prevention (DCP). The LAO Principal Investigator (PI) is responsible for the routine quality control monitoring of the conduct of network protocols at their accruing LAO and Affiliated Organizations (AOs). Any time an LAO is accruing at its own site, the accruing LAO is treated the same as an AO and is subject to the same selection criteria and oversight. The same holds true for a CP-CTNet Cross-Network Trial (CNT) in which an LAO is participating as an accruing site.

Note: The DCP protocol numbering convention for CP-CTNet CNTs is INT, which stands for "inter-network trial" (e.g., INT21-05-01).

It is the responsibility of the LAO to provide the infrastructure necessary to oversee and support study activities performed by its accruing LAO and AOs to ensure that they are conducted, recorded, and reported in compliance with the current approved protocol version, REFGD03 *CP-CTNet Master Data Management Plan*, the Data and Safety Monitoring Plan (DSMP), CP-CTNet Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) as described in *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)*, and any additional applicable regulations (e.g., in-country requirements for AOs that reside outside of the United States (US), etc.). The LAO PI may delegate specific tasks associated with this oversight to qualified personnel; however, the LAO PI retains overall oversight responsibility for accruing LAOs and AOs.

As per *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)*, clinical trial quality assurance consists of "all those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with GCP and the applicable regulatory requirement(s)", while quality control includes "the operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled." In CP-CTNet, quality control monitoring is performed remotely (e.g., LAO staff are not expected to travel to their accruing LAOs and AOs to conduct study monitoring visits), and in complement with data management and quality assurance auditing conducted by the Data Management, Auditing, and Coordinating Center (DMACC). The DCP Study Team and DCP Regulatory Contractor also support the LAO with certain aspects of its routine quality control monitoring.

2. SCOPE

This document details the specific responsibilities of LAO PIs and/or designees in relation to the oversight of study activities for their respective accruing LAOs or AOs.

3. DEFINITIONS

Term	Definition
AE	Adverse Event
AO	Affiliated Organization
AQuIP	Accrual Quality Improvement Program
CIRB	Central Institutional Review Board
CNT	Cross-Network Trial
Collaborating LAO	An LAO that is involved in a CNT that has oversight responsibilities for its own accruing LAOs and AOs.
CP-CTNet	Cancer Prevention Clinical Trials Network

Term	Definition
DCP	Division of Cancer Prevention
DMACC	Data Management, Auditing, and Coordinating Center
DSMP	Data and Safety Monitoring Plan
DTL	Delegation of Tasks Log
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
ICH	International Council for Harmonization
INT	Inter-Network Trial or INT is the DCP protocol numbering convention for CP-CTNet trials (e.g., INT21-05-01).
IRB	Institutional Review Board
LAO	Lead Academic Organization
Lead LAO	An LAO that takes primary responsibility for the administrative aspects of the CNT and has oversight responsibilities for its own accruing LAOs and AOs.
M-SOP	Manual of Standard Operating Procedures
NCI	National Cancer Institute
PD	Protocol Deviation
PI	Principal Investigator
PIO	Protocol Information Office
RCR	Registration and Credential Repository
SAE	Serious Adverse Event
SCNC	Serious or Continuing Non-Compliance
SDV	Source Data Verification
SIM	Study Initiation Meeting
SOP	Standard Operating Procedure
UP	Unanticipated Problem

4. LAO ROLES AND RESPONSIBILITIES

LAO oversight of its accruing LAO and AOs begins with careful site selection, assistance with the collection of the essential documents required to open a study at an accruing LAO or AO, conducting a SIM, and additional targeted training of accruing LAO or AO study staff. It continues with frequent communication to ensure that the study is progressing in accordance with the planned timeline and accrual goals. During the active phase of the study (e.g., pre-screening/recruitment, screening, enrollment, study intervention, and follow-up), the LAO provides routine quality control monitoring that focuses on the protection of the rights and well-being of the study participants, compliance with the protocol, GCP, and regulatory guidance, complete, accurate, and timely entry of study data, PD and AE reporting, investigational product management, and research specimen management. LAO oversight ends with study closeout at each site.

Note: For CNTs, multiple LAOs participate and have different roles and responsibilities based on if they are a Lead LAO or a Collaborating LAO. The Lead LAO takes primary responsibility for the administrative aspects of the CNT and has oversight responsibilities for its own accruing LAO and AOs. Each Collaborating LAO involved in the CNT has oversight responsibilities for its own accruing LAO and AOs, but not for the cross-network administrative aspects of the CNT. See REFGD06 *Cross-Network Trials Guidelines* for more information.

1. **Site Selection**: The addition of an accruing LAO or AO to an LAO's roster is subject to approval by the DCP CP-CTNet Director. The *Guidelines for Modifications to a Lead Academic Organization Roster* reference document describes the process for submitting a request for approval of an accruing LAO or AO. When vetting an accruing LAO or AO for addition to the roster, the LAO should consider whether:

    1.1. The accruing LAO or AO Investigator has adequate qualifications and resources to conduct the study safely and properly.

    1.2. The accruing LAO or AO has adequate staffing for protocol implementation throughout the duration of the study.

    1.3. The accruing LAO or AO staff has the ability and expertise to:

    - Create, submit, track, organize, and store the regulatory documents for the study.
    - Identify, recruit, pre-screen, consent, screen, and enroll eligible study candidates, and document these efforts using the Stars registration/randomization system at each stage of the enrollment process.
    - Meet the accrual goals for their site within the specified timeframe.
    - Conduct study visits as outlined in the protocol schedule of events and complete any additional participant contacts within the required window.
    - Conduct protocol-required assessments and procedures with study participants within the required window.
    - Complete protocol-required assays (if applicable).
    - Maintain accurate, complete, and up-to-date source data, documents, and other study records.
    - Provide the LAO with access to participant source documents and other documents for the purposes of remote monitoring oversight.
    - Assess, document, track, and report AEs as specified in the protocol.
        - See *DCP Baseline and Adverse Event (AE) Reporting Guidelines* for more information.
    - Identify and report deviations from the protocol.
        - See SOP 02-02 *Reporting Protocol Deviations* for more information.
    - Enter study and AQuIP data into Medidata Rave completely, accurately, and within the required timeframes. Medidata Rave is the clinical trials data management system used for all CP-CTNet studies.
        - See SOP 02-04 *Participant Recruitment, Retention, Adherence, and Reporting Requirements* for more information.
    - Respond to data queries within the required timeframes.
    - Handle and dispense study agent in full compliance with the protocol, GCP, and institutional, state, and in-country regulations.

- Track the receipt, use, return, and final disposition of study agent(s) as specified by the protocol, and in compliance with GCP and institutional, state, and in-country regulations regarding the use and handling of prescription medications.
- Collect, process, store, track, and submit any protocol-required specimens using a virtual specimen repository or other equivalent specimen tracking system.
- Perform and report the results of any tests and/or assays if required by protocol.

1.4. The accruing LAO or AO has adequate facilities to:

- Conduct study visits, as outlined in the protocol schedule of events, in a safe, clean, private, and professional space supplied with any equipment and materials required to perform study visits and protocol-required assessments and procedures.
- Access and enter data into Medidata Rave through a secure interface.
- Securely store regulatory documents, participant study source documents, and other study records and limit access to those materials to study personnel and individuals with oversight responsibilities.
- Store the study agent(s) in accordance with the recommended conditions and monitor those conditions throughout the course of the study.
- Store the study agent(s) securely and limit access to authorized staff and those responsible for oversight.
- Store the study agent(s) separately from any commercially available supply of the same agent.
- Process and store study specimens in accordance with the protocol and ship (when required) in accordance with regulations covering the transportation of biohazardous materials.
- Complete any protocol-required tests and/or assays.

2. **Study Initiation and Targeted Training of Accruing LAO and AO Study Staff**:

2.1. The LAO is responsible for conducting a SIM in compliance with SOP 01-02 *Study Initiation Meeting*. This includes recording the SIM and sharing the SIM recording with key accruing LAO and AO staff who were unable to attend the meeting, new key staff at existing accruing LAOs and AOs that join the protocol after the meeting was completed, and key staff at new accruing LAOs and AOs.

- DMACC participates in the preparation process for each SIM by working with the LAO Coordinator to develop a study-specific training topic list, and provides training during the SIM based on the DMACC responsibilities outlined in the *CP-CTNet Study Initiation Meeting Report Template*. The LAO should coordinate with DMACC (via DMACC_SIM_CP-CTNet@frontierscience.org) before scheduling the SIM to ensure that DMACC trainers are available to present at the SIM.

2.2. DMACC provides supplemental training on various CP-CTNet procedures and systems. The LAO is responsible for ensuring that all accruing LAO and AO staff are aware of, and have completed, any required or recommended trainings. See REFGD12 *Training Registration Guide* for information about registering for CP-CTNet training sessions.

2.3. The LAO is responsible for ensuring that accruing LAO and AO staff members have been appropriately trained on the protocol and study procedures. Training must be documented.

Note: Recorded attendance during the SIM constitutes as initial training on the protocol and study procedures.

2.4. The LAO is responsible for ensuring that re-training is provided if performance or compliance issues are identified at an accruing LAO or AO. Upon request, DMACC can assist the LAO by developing trainings on topics identified as being an issue.

3. **Communication**: The LAO acts as the main line of communication between the accruing LAOs and AOs and DCP, DMACC, and the DCP Regulatory Contractor.

3.1. The LAO PI and/or designee(s) is responsible for:

- Communicating information regarding changes to procedures, the availability of new and revised policies on the CP-CTNet DMACC Public Website and Portal Gateway, and announcements from DMACC and DCP to accruing LAOs and AOs in a timely and systematic manner.
    - See SOP 02-05 *Creating, Reviewing, and Amending Standard Operating Procedures* for more information.

  Note: All LAO staff are responsible for reviewing and signing off on the M-SOP to ensure that they are familiar with all network policies and can provide appropriate oversight of their accruing LAOs and AOs in accordance with these policies.

- Distributing all relevant information about the protocol and study operations to accruing LAO and AO staff, including CIRB protocol approval notifications and the associated approved materials and documents, continuing review approvals, pending protocol amendments, CIRB protocol amendment approval notifications and the associated materials and documents, and any additional details about pending and final decisions.

- Conducting regularly scheduled conference calls with accruing LAOs and AOs and the DCP Study Team to review AQuIP data and recruitment and/or retention strategies, discuss study progress including relevant AEs, track staffing resource or facility changes at the accruing LAOs and AOs, and identify and address areas of concern. Documentation of these calls should include the preparation of an agenda of topics prior to the call and the distribution of meeting minutes after the call.

- Developing electronic mail distribution lists (e.g., listserv, contact list) for immediate dissemination of important information from DCP, DMACC, and DCP contractors.

- Requesting that accruing LAO or AO staff send questions about protocol implementation and other protocol-specific issues to the LAO Coordinator so that they may reply or search for solutions in a consistent manner across sites.

- Developing an appropriate file structure for saving electronic communications to accruing LAOs and AOs to ensure that they can be readily retrieved (e.g., a communications folder). This includes the communications listed above and documentation related to agreements or significant discussions regarding study administration, PDs, study conduct, and AE reporting. Specific documentation may include emails, agendas, and meeting minutes. The communications that should be saved in the LAO's essential documents file are described below in section 4.

4. **Essential Documents**:

4.1. The LAO is responsible for ensuring that the accruing LAO or AO understands and is compliant with the collection, completion, and submission of regulatory documents required for CP-CTNet studies as described in SOP 01-01 *Essential Documents Submission for Sponsor's Record*.

4.2. The DCP Regulatory Contractor is responsible for maintaining the Trial Master File of essential documents required for each CP-CTNet study. They conduct a thorough review of the regulatory documents submitted for this file. However, to avoid delays, the LAO is asked to do a quick review of documents received from the accruing LAO or AO to ensure that the correct version of the document has been used, all fields have been completed, and the document is signed and dated, prior to forwarding those documents to the DCP Regulatory Contractor.

4.3. The LAO should assist the accruing LAO or AO with understanding the Cancer Therapy Evaluation Program (CTEP) Identity and Access Management System (IAM) and provide guidance, as needed, with the use of the NCI Registration and Credential Repository (RCR). However, the LAO is not responsible for collecting, reviewing, or tracking any of the documents collected through the RCR system (e.g., the Statement of Investigator (Form FDA 1572), Financial Disclosure Form, NCI Biosketch, GCP Training Certification and Professional Licensure).

- If the LAO would like to help a site expedite the completion of those documents, or if the drug shipment authorization is being held up by missing documents, the DCP Regulatory Contractor will provide a list of the outstanding documents to the LAO.

4.4. The LAO is not responsible for maintaining a "shadow file" of regulatory documents, however, a system for documenting the receipt of non-RCR regulatory documents from the accruing LAO or AO and transmission of those documents to the DCP Regulatory Contractor should be in place to ensure complete and timely collection and submission of those documents.

4.5. The LAO is responsible for ensuring that the accruing LAO or AO is maintaining an essential documents file and that the file is organized, current, complete, and available for quality assurance auditing by DMACC and/or inspection by regulatory authorities. This file may be electronic or paper based.

Note: The RCR serves as the official repository for the Financial Disclosure Form, NCI Biosketch, GCP training certificate, and professional licensure. Copies of these documents do not need to be maintained in the accruing LAO's or AO's essential documents file.

4.6. The LAO should provide guidance to the accruing LAO or AO to help comply with local institutional requirements regarding the local IRB ceding to the CIRB, study activation/closeout, filing of amendments, submission of UPs and SCNCs to the CIRB, and reporting of SAEs.

Note: UPs and SCNCs should be discussed with the DCP Study Team prior to CIRB submission.

- See SOP 02-01 *Reporting Serious Adverse Events* and SOP 02-02 *Reporting Protocol Deviations* for more information.

4.7. The LAO is responsible for reporting staffing changes at the LAO- and AO-level to the DCP Regulatory Contractor and DMACC (Admin_CP-CTNet@frontierscience.org) as per

REFGD13 *CP-CTNet Responsibilities for Personnel Changes*, and ensuring these changes are documented on the site's DTL.

- The DCP Regulatory Contractor ensures that new staff have completed their required documents in the RCR and stops tracking documents in the RCR for staff that are no longer associated with the study.
- DMACC updates the CP-CTNet Contact List as changes are reported.

Note: A PI change at the LAO- or AO-level must be reported to PIO with an accompanying amendment to reflect this change.

5. **Documentation Requirements**:

5.1. The LAO is responsible for documenting its oversight activities and maintaining copies of protocol-specific communications in its essential documents file. These documents should be readily accessible, and may be requested by DCP, the DCP Regulatory Contractor, and/or DMACC at any time during the conduct of the study. Types of documentation include:

- Reports regarding protocol implementation and operations, and other major issues or changes.
- Documents that describe progress, barriers, and outcomes in 'Notes to File' as necessary.
- Communications from DCP, DMACC, the DCP Regulatory Contractor, and the accruing LAO or AO.
- Documents to support the tracking of the receipt of regulatory documents from the accruing LAO or AO and the forwarding of those documents to the DCP Regulatory Contractor.
    - For more information, see SOP 01-01 *Essential Documents Submission for Sponsor's Record*.
- Documents to support methods of communicating information to the accruing LAO or AO as listed in section 3 (e.g., meeting minutes, email documentation, or an active website link).
- Documents to support methods of tracking staffing changes, accrual and retention patterns, PDs, SAEs, data entry, research specimen tracking, and query resolution at the accruing LAO or AO.
    - For more information, see SOP 03-02 *Site Preparations for Quality Assurance Audits*.

6. **Informed Consent Document Review and Confirmation of Eligibility**:

6.1. The LAO is responsible for the review of 100% of the signed Informed Consent Documents obtained for all individuals screened for study participation. At a minimum, the following elements should be addressed as part of the LAO review:

- Informed consent was obtained prior to the conduct of any study-specific procedures.
- The correct version was used.
- The individual who obtained the informed consent was delegated that authority.

- The document was correctly signed and dated by all parties (including co-signers or witnesses if required).

6.2. To help ensure participant safety, all eligibility checklists will require a two-person review and sign off at the accruing LAO or AO **prior** to entry of the checklist data into Stars. One of these two parties must be a registered Investigator or Non-Physician Investigator for the protocol in the NCI RCR and be delegated the *Eligibility Assessments* task on the DTL. The names of the two parties will be typed into Stars. The signed eligibility checklist (wet signature or electronic) is kept at the enrolling site and serves as source documentation of the confirmation of eligibility.

6.3. For studies deemed to be high risk by the DCP protocol review team per the Protocol Audit Risk Assessment Tool, 100% review and confirmation of eligibility of all participants will be required by the LAO **prior** to enrollment of each eligible participant at the accruing LAO or AO. The protocol audit risk level is documented on the Consensus/Concurrence Review form and reviewed during the SIM, as per the *CP-CTNet Study Initiation Meeting Report Template*.

6.4. For studies deemed to be low or moderate risk by the DCP protocol review team per the Protocol Audit Risk Assessment Tool , review and confirmation of eligibility of the first two participants enrolled at each accruing LAO or AO, at minimum, will be required by the LAO. The review and confirmation of eligibility may take place following enrollment/ randomization. Review and confirmation of eligibility beyond the first two participants enrolled at each accruing LAO or AO is at the discretion of the LAO based upon the performance of the accruing LAO or AO, complexity of the eligibility criteria for the given protocol, and/or any other factors the LAO believes warrant continuing review and confirmation of eligibility.

7. **Quality Control Monitoring and Management of Study Data**: The Stars registration/ randomization system is used by accruing LAOs and AOs to pre-screen, screen, and enroll participants onto CP-CTNet studies and to generate associated *Pre-Screen*, *Screening*, and *Participant IDs* (see USRMAN01 *CP-CTNet Stars User Guide* for more information). Medidata Rave is used by sites to enter study data, record study pre-screening and screening efforts, and record site-level AQuIP recruitment journaling situations or events that may impact study recruitment efforts. The LAOs and DMACC Data Managers work together to ensure the quality and integrity of study data. This section outlines the LAO's roles and responsibilities for the quality control monitoring and management of study data and provides information about how DMACC Data Managers support these efforts.

7.1. eCRFs: DMACC Data Managers take the lead in the creation of eCRFs for each CP-CTNet study. The LAO is responsible for reviewing the eCRF data fields and ensuring that all data elements are included as per protocol requirements.

7.2. Study Accrual: The LAO is responsible for the oversight of accruing LAO and AO study recruitment efforts, including:

- Ensuring that accruing LAO and AO recruitment efforts are accurately and completely documented in Stars and Medidata Rave.
    - This includes identifying the protocol-specific pre-screen eligibility criteria that define the study target population and ensuring that accruing LAOs and AOs enter data on all individuals who meet that criteria and are reviewed for potential study

participation, regardless of whether they agree to participate or are found to be eligible for the study.

- Tracking participant enrollment in relation to accruing LAO- or AO-specific accrual targets.
- Checking the CP-CTNet AQuIP Recruitment Journal in Medidata Rave to ensure that accruing LAOs and AOs are accurately and completely documenting any site-specific factors that affect or could potentially affect accrual at their site.
- Reviewing recruitment and/or retention strategies with the accruing LAO or AO (as appropriate) to meet accrual targets.

7.3. DMACC Data Monitoring: A DMACC Data Manager is assigned to each CP-CTNet study. Data Managers monitor the data entered into Medidata Rave on an ongoing basis. DMACC data monitoring includes:

- Pre-programmed edit checks for specific data fields which trigger an automated query when a required data field is left blank or non-conformant data are entered (e.g., a word entered in a numeric data field, an inappropriate number of letters or digits entered, or a value entered that falls outside of a specified range).
- Ensuring that data entry in Medidata Rave is complete, accurate, and timely by checking eCRFs for completeness, cross-checking eCRFs for consistency and accuracy, and cross-checking data entry against protocol-specified study contact and procedure windows.
- Manual entry of queries when data entry is incomplete or appears inconsistent with network data entry policies and procedures, protocol requirements, or with data entered on other eCRFs.
- Informing LAOs when outstanding data issues are identified and requesting that they follow up with the accruing LAO or AO. DMACC sends monthly query reports to LAOs for each of their studies, which include any outstanding queries or data issues. These reports serve as a reminder that queries and data issues should be addressed by the accruing LAO or AO within 14 calendar days.

7.4. While DMACC monitors the aspects of data entry described above, the LAO maintains the overall responsibility for participant safety and the integrity of study data, which includes:

- Reviewing monthly query reports from DMACC and assuring that the accruing LAO or AO addresses those queries correctly and within the required time frame.
- Running and reviewing additional Medidata Rave reports to ensure that the accruing LAO or AO is performing as expected. Information about the Medidata Rave reports available to assist with accruing LAO and AO oversight is available in QKREFGD01 *Medidata Rave Reports* and USRMAN03 *Rave Reports Resource Guide for the CP-CTNet Project*.
- SDV: DMACC Data Managers do not have access to participant source records, therefore, it is the responsibility of the LAO to perform 100% SDV on a minimum of the first two participants enrolled per protocol at each accruing LAO or AO to ensure that data entry is accurate, complete, and verifiable and study processes and procedures are being conducted in accordance with the protocol. The focus and amount of SDV on subsequent participants should be determined by the LAO based on the accruing

LAO's or AO's performance, the LAO's DCP-approved DSMP, and any protocol-specific data or safety concerns.

- The accruing LAO or AO should be instructed to upload or share source documents in a manner that is 21 CFR Part 11-compliant for review by the LAO.
- The LAO staff responsible for performing SDV are granted the *LAO Staff* role in Medidata Rave and can enter manual SDV-related queries for their accruing LAOs and AOs directly in Medidata Rave for the duration of each study. This allows for consistency in the presentation of queries to the accruing LAOs and AOs and a unified audit trail of queries and responses.
- To avoid conflicting or overlapping queries, manual query entry by the LAO should be limited to variances from source data. Any other type of data entry error or discrepancy detected during SDV should be brought to the attention of the DMACC Data Manager assigned to the study who will generate the appropriate query. See REFGD01 *CP-CTNet Source Documentation Guide* and REFGD03 *CP-CTNet Master Data Management Plan* for more information.

Note: LAOs should document and save any communications with accruing LAOs and AOs that are not entered directly into Medidata Rave.

- Ensuring timely reporting of AEs and treatment-related morbidity information, including the reporting of SAEs. The LAO is responsible for the safety of all study participants and should routinely monitor the AE data entered into Medidata Rave and ensure that the protocol PI and DCP Study Team are notified of any concerning trends, unexpected events, or SAEs.
  - Accruing LAOs and AOs should be routinely asked about AEs during regularly scheduled study calls and encouraged to contact the LAO immediately with any questions or concerns about AEs and reminded of the steps to take should a participant experience an SAE. The LAO should assist the accruing LAO or AO with the reporting of SAEs.
  - See *DCP Baseline and Adverse Event (AE) Reporting Guidelines* and SOP 02-01 *Reporting Serious Adverse Events* for more information.
- Ensuring that PDs are reported according to SOP 02-02 *Reporting Protocol Deviations*.
- Ensuring that the data/assessments/specimen collection required for study endpoints are present.
- Ensuring that research specimen management is consistent and adequate at the accruing LAO or AO and includes the use of a research specimen tracking system or tracking log.
  - A research specimen tracking log includes basic elements applicable to the protocol, such as the type of research specimen, specimen number, date and time of collection and shipping, and storage location.
- Developing a corrective action plan when issues are identified.
- Informing DMACC of any data issues that are identified during routine quality control monitoring activities. The LAO retains the overall responsibility for its accruing LAO's and AOs' data entry performance.

- LAOs may email the DMACC data management group email address (DataManagement_CP-CTNet@frontierscience.org) as data issues are identified. To enable DMACC to triage questions efficiently, the following information should be included in the email subject heading: protocol number and question topic.

8. **Study Agent**: The LAO is responsible for ensuring that the accruing LAO or AO is handling the study agent in accordance with the protocol, GCP, any state and/or in-country regulations, and the network guidelines listed below.

   8.1. The accruing LAO or AO should:

   - Document the receipt of study agent from the supplier.
   - Store study agent securely, limit access to authorized personnel, monitor storage conditions to ensure they remain within protocol-specified ranges for temperature and/or humidity, and store study agent separately from any commercially available supply of the same agent.
   - Ensure supply of study agent is sufficient by maintaining an inventory.
   - Ensure study agent is dispensed only to eligible study participants and in the amount and dose specified in the protocol.
   - Document the dispensing of study agent to a participant and the amount of unused study agent returned by the participant. An accruing LAO or AO should use its institution's drug accountability logs or system to document drug distribution, return, inventory, etc.
   - Instruct participants in the proper use, handling, storage, and return of their study agent.
   - Document the final disposition of unused study agent in accordance with the protocol. If institutional policy or state and/or in-country regulations preclude final disposition in the manner described in the protocol, the accruing LAO or AO should document the variance in a 'Note to File' saved with its essential documents file and the LAO should notify the repository and DCP Study Team.

   8.2. This oversight may be accomplished remotely by requesting copies of relevant SOPs from the accruing LAO or AO pharmacy, requesting reports of temperature excursions, interview with the pharmacist, or review of study agent dispensing logs for those participants selected for SDV.

5. ADDITIONAL INFORMATION

DMACC is a resource for both LAO and AO staff. Please contact the DMACC email support groups below for questions or guidance:

Category	Email Support Group
Data Entry in Medidata Rave / Data Management / Protocol	DataManagement_CP-CTNet@frontierscience.org
Audit	Audit_CP-CTNet@frontierscience.org
Registration / Randomization	Enrollment_CP-CTNet@frontierscience.org

Category	Email Support Group
Access to Systems (e.g., Portal Gateway, Stars, Medidata Rave, Audit System)	UserSupport_CP-CTNet@frontierscience.org
Contact Management	ContactAdmin_CP-CTNet@frontierscience.org
Documentation	Documentation_CP-CTNet@frontierscience.org
Education and Training	Training_CP-CTNet@frontierscience.org
Administrative	Admin_CP-CTNet@frontierscience.org

6. REFERENCES

Note: All CP-CTNet SOPs are included in the *CP-CTNet Manual of Standard Operating Procedures (M-SOP)*, which is available on the CP-CTNet DMACC public website.

Document	ID	Location
CP-CTNet DMACC Protocol Risk Assessment Form	Form	Program Resources
CP-CTNet Master Data Management Plan	REFGD03	Program Resources
CP-CTNet Responsibilities for Personnel Changes	REFGD13	Program Resources
CP-CTNet Source Documentation Guide	REFGD01	Program Resources
CP-CTNet Stars User Guide	USRMAN01	Program Resources
CP-CTNet Study Initiation Meeting Report Template	Template	Program Resources
Creating, Reviewing, and Amending Standard Operating Procedures	SOP 02-05	Program Resources
Cross-Network Trials Guidelines	REFGD06	Program Resources
CTEP Identity and Access Management	Application	CTEPcore.nci.nih.gov
DCP Baseline and Adverse Event (AE) Reporting Guidelines	Reference	Program Resources
DCP Delegation Task Log Master Task List	Reference	Program Resources
Essential Documents Submission for Sponsor's Record	SOP 01-01	Program Resources
Good Clinical Practice: Integrated Addendum to ICH E6(R1)	E6(R2)	FDA.gov
Guidelines for Modifications to a Lead Academic Organization Roster	Reference	Program Resources
Medidata Rave Reports	QKREFGD01	Program Resources
NCI Registration and Credential Repository	Application	CTEPcore.nci.nih.gov
Participant Recruitment, Retention, Adherence, and Reporting Requirements	SOP 02-04	Program Resources

Document	ID	Location
Protocol Risk Assessment to Determine the Level of Targeted Source Data Verification During a CP-CTNet Audit	DMACC REFGD09	Program Resources
Rave Reports Resource Guide for the CP-CTNet Project	USRMAN03	Program Resources
Reporting Protocol Deviations	SOP 02-02	Program Resources
Reporting Serious Adverse Events	SOP 02-01	Program Resources
Site Preparations for Quality Assurance Audits	SOP 03-02	Program Resources
Study Initiation Meeting	SOP 01-02	Program Resources
Training Registration Guide	REFGD012	Program Resources

7. APPENDICES

- None.

Title: Instructions for Accruing LAO and AO Closeout

Document ID: CP-CTNet SOP 04-01

Version: 2.0

Version Date: January 26, 2024

REVISION HISTORY (most recent first)

Version	Effective Date	Summary of Changes
2.0	JAN-26-2024	Complete rewrite of document to delineate the accruing LAO and AO responsibilities versus the LAO responsibilities in relation to closeout and to clarify closeout for cross-network trials. Added section 3 Definitions and a table to section 7 References.
1.0	AUG-17-2020	Original version of document.

1. INTRODUCTION AND PURPOSE

Accruing Lead Academic Organizations (LAOs) and Affiliated Organizations (AOs) are responsible for meeting all study obligations as part of their closeout. The accruing LAO and AO closeout process ensures that all study-related activities have been accurately reconciled, documented, and reported. This process takes approximately three months from the initial decision to initiate closeout, but may take longer if there are unforeseen delays.

As part of its monitoring responsibilities, the LAO ensures that closeout activities for all accruing AOs and its accruing LAO (as applicable) are completed for each study after all study activities are complete, or at the discretion of the Division of Cancer Prevention (DCP). For cross-network trials (CNTs), each participating LAO is responsible for the closeout activities of each of its AOs and its accruing LAO (as applicable). The accruing LAO or AO closeout activities may be done onsite or remotely at the discretion of the LAO in consultation with the DCP Medical Monitor (MM).

Note: The DCP protocol numbering convention for CP-CTNet CNTs is INT, which stands for "inter-network trial" (e.g., INT21-05-01).

In accordance with SOP 04-02 *Overall Study Completion for LAOs* (in draft), the Data Management, Auditing, and Coordinating Center (DMACC) Auditors audit the study closeout process that occurs at the LAO. Once all accruing AOs and the accruing LAO (as applicable) have been closed out, DMACC then audits the LAO oversight of the accruing LAO and AO closeout process. This can be done as part of the LAO oversight audit and may include a high-level process of reviewing the accruing LAO (as applicable) and AO closure Standard Operating Procedures (SOPs), closeout reports, checklists, etc.

2. SCOPE

This document details the responsibilities of LAOs and accruing LAOs and AOs regarding the conduct of closeout activities and outlines the information and materials that accruing LAOs and AOs are expected to prepare and provide to the LAOs for closeout.

3. DEFINITIONS

Term	Definition
Accruing LAO	A department within the Lead Academic Organization that contributes accrual to the study. Acts as an AO in the study.
AO	Affiliated Organization
CIRB	Central Institutional Review Board
CNT	Cross-Network Trial
CP-CTNet	Cancer Prevention Clinical Trials Network
DCP	Division of Cancer Prevention
DM	Data Manager
DMACC	Data Management, Auditing, and Coordinating Center
FDA	Food and Drug Administration
INT	Inter-Network Trial or INT is the DCP protocol numbering convention for CP-CTNet trials (e.g., INT21-05-01).
IRB	Institutional Review Board
LAO	Lead Academic Organization. This organization is responsible for managing all aspects of the study, including study oversight for their accruing LAO and AOs.

Term	Definition
MM	Medical Monitor
NCI	National Cancer Institute
PI	Principal Investigator
SOP	Standard Operating Procedure

4. ROLES AND RESPONSIBILITIES

1. Before accruing LAO or AO closeout:

    1.1. The LAO is responsible for initiating and overseeing the accruing LAO or AO closeout process after:

    - All participants enrolled at the accruing LAO or AO have completed study-related activities; and
    - All data for the accruing LAO or AO are entered into Medidata Rave and all outstanding data discrepancies are resolved. This is confirmed by the DMACC DMs via an email to the LAO once all data for the accruing LAO or AO is cleaned. If the LAO has any questions about this process, they may contact the DMACC Data Management and Reporting Unit at DataManagement_CP-CTNet@frontierscience.org.
        - The LAO then completes a final review and makes the final determination that all data for the accruing LAO or AO are entered into Medidata Rave and all outstanding data discrepancies are resolved.

    1.2. The accruing LAO or AO, DCP, or the LAO may elect to close the accruing LAO or AO early if the accruing LAO or AO fails to accrue participants or is faced with other issues that may necessitate closure (e.g., PI leaving the accruing LAO or AO with no replacement, change in staffing status, budget constraints, etc.).

    - DCP, the LAO, or the accruing LAO or AO may initiate the closeout process. Once the process is initiated, the LAO informs DCP of the pending closure and works with the accruing LAO or AO to perform the closeout activities.
    - If the accruing LAO or AO has received study agent, study agent return or disposal must be handled as outlined in the protocol, pharmacy manual, and/or other study documents.

    1.3. If a proposed accruing LAO or AO has not been activated, accruing LAO or AO closeout activities are not required.

    - The LAO sends a letter to the accruing LAO or AO (with a copy to DCP study staff, DMACC, and the DCP Regulatory Contractor) stating that the accruing LAO or AO was not activated; therefore, accruing LAO or AO closeout activities are not required.

      Note: If the accruing LAO or AO is removed from the study, the protocol cover page must be updated, and a protocol amendment must be submitted to the CIRB.

    1.4. Regulatory documents collected by the LAO for the closing accruing LAO or AO are managed as directed by the LAO and/or as required by institutional policy.

    - The DCP Regulatory Contractor manages essential documents submitted to them by the accruing LAO or AO for the closing accruing LAO or AO.

2. During accruing LAO or AO closeout:

2.1. **Accruing LAO and AO Responsibilities:** Complete all applicable local closure activities included in the *CP-CTNet Accruing LAO and AO Closeout Checklist*. The accruing LAO or AO Coordinator should perform all local site closure activities and work with the LAO Coordinator as needed.

2.2. **LAO Responsibilities:** The LAO Coordinator is responsible for verifying that the accruing LAO or AO completed all applicable local closure activities included in the *CP-CTNet Accruing LAO and AO Closeout Checklist* in a timely manner. For CNTs, each participating LAO is responsible for the closeout activities of each of its AOs and its accruing LAO (as applicable). Once all accruing AOs and the accruing LAO (as applicable) have been closed out, DMACC then audits the LAO oversight of the accruing LAO and AO closeout process. This can be done as part of the LAO oversight audit and may include a high-level process of reviewing the accruing LAO (as applicable) and AO closure SOPs, closeout reports, checklists, etc. Additional LAO responsibilities include:

- If the study met its accrual goal or is closing to accrual for any other reason, notify the DMACC Data Management team (DataManagement_CP-CTNet@frontierscience.org) that all accruing LAOs and AOs for the study should be closed to accrual in Stars, the registration/randomization system for CP-CTNet.
    - If a specific accruing LAO or AO is closing to accrual but the study remains open to accrual, notify the DMACC Data Management team (DataManagement_CP-CTNet@frontierscience.org) that the specific accruing LAO or AO for the study should be closed to accrual in Stars.
- Notify the DCP Regulatory Contractor of accruing LAO or AO closure and confirm that there are no outstanding essential documents prior to the accruing LAO or AO closing the study with the local IRB, Ethics Committee, and/or CIRB.
- Prior to accruing LAO or AO closure, the LAO should contact the DMACC Auditors and DCP to see if any auditing activities are required (e.g., participant chart review, regulatory/essential documents check, pharmacy review, etc.).
- Maintain records of communication with each accruing LAO or AO to verify that appropriate support and oversight was provided to the accruing LAO or AO during the closeout process (as needed).
- Ensure that the *CP-CTNet Accruing LAO and AO Closeout Checklist* is completed and signed by the accruing LAO or AO Coordinator, accruing LAO or AO PI, and LAO staff.

5. DOCUMENTATION REQUIREMENTS

Each accruing LAO and AO is responsible for maintaining all study records in a secure manner, including source documents, laboratory data, pharmacy documents, regulatory documents, and study communications. See REFGD03 *CP-CTNet Master Data Management Plan* for more information.

1. Study records must be accessible for inspection by authorized NCI/DCP representatives, DMACC Auditors, the local IRB, the CIRB, FDA personnel, and/or any drug company supporting the study.
2. If the study is conducted outside of the United States or United States territories, additional requirements may apply that are specific to the country of the AO participating in the study.
3. The study records must be maintained and accessible as specified in the protocol.

6. ADDITIONAL INFORMATION

Please send questions and comments to Documentation_CP-CTNet@frontierscience.org.

7. REFERENCES

Note: All CP-CTNet SOPs are included in the *CP-CTNet Manual of Standard Operating Procedures (M-SOP)*, which is available on the CP-CTNet DMACC public website.

Resource	ID	Location
CP-CTNet Accruing LAO and AO Closeout Checklist	Checklist	Program Resources
CP-CTNet Master Data Management Plan	REFGD03	Program Resources
Essential Documents Submission for Sponsor's Record	SOP 01-01	Program Resources
Overall Study Completion for LAOs	SOP 04-02	In Draft

8. APPENDICES

1. None