CP-CTNet REFGD07
Trial Conduct Guide for Lead Academic Organizations and Affiliated Organizations

Version 1.0
September, 2020

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REVISION HISTORY (most recent first)

Version	Effective Date	Summary of Changes
1.0	SEP-21-2020	Original version of document,

1. Concept, Protocol, Amendment, and System Variable Attribute Development and Submission and Approval

Agents to be studied will be announced twice yearly via the National Cancer Institute (NCI) Division of Cancer Prevention (DCP) solicitations for concepts for clinical trials. CP-CTNet sites are also expected to propose unsolicited concepts using agents or interventions available to their investigators. If a solicited or unsolicited concept is approved, the CP-CTNet Lead Academic Organization (LAO) is responsible for developing the protocol and protocol-related documents (e.g., informed consent form, Recruitment, Retention & Adherence Plan, any applicable recruitment materials, Pharmacokinetic and Biomarker Methods Development Report). The protocol is submitted to the NCI DCP Protocol Information Office (PIO) for NCI/DCP review and approval. The timeline from concept to activation is as follows:

- Concept Receipt to Concept Approval: 30 days
- Concept Approval to Protocol Receipt: 60 days
- Protocol Review and Approval (including CIRB approval): 210 days
- Protocol Approval to Activation (first participant on study): 90 days
- To accommodate for unknown delays, an extra 150 days has been added to the timeline to equal 540 days.

Should changes to the study become necessary, protocol amendments will be submitted to the DCP PIO.
The LAOs are responsible for developing the System Variable Attribute Report (SVAR) along with the protocol. The SVAR, an Excel file which represents the dictionary for each protocol-required electronic Case Report Form (eCRF), must be submitted with the second version of the protocol. The CP-CTNet SVAR Template, available on the Data Management Auditing and Coordinating Unit (DMACC) Portal Gateway, should be used as a starting point for all protocol-specific SVARs. The LAOs edit and add to this SVAR Template in order to capture all of the protocol-required data.

The protocol and protocol-related documents that the LAOs develop are emailed, along with the Protocol Submission Worksheet, to the PIO for review. Once these documents are reviewed by the designated CP-CTNet reviewers (DCP, DCP contractors, DMACC, etc.), the PIO emails any comments regarding the documents back to the LAO to address. Once all comments are addressed and any documents are updated as needed, the LAO emails the responses and updated documents back to the PIO for review. This process continues until the documents receive official DCP approval. To indicate official DCP approval, the LAOs receive an email from the PIO with a DCP approval letter attached. If documents are approved at different points in time, more than one DCP approval letter may be received.

References:

- The National Cancer Institute Cancer Prevention Clinical Trials Network Program Guidelines
- DCP CP-CTNet Chemoprevention Protocol Template
- SOP 02-03 Electronic Case Report Form Development
- CP-CTNet SVAR Template
- CP-CTNet Consolidated SVAR Review Document

2. Study Activation

After the PIO has issued the “Notice of Study Approval on Hold” letter and the CIRB has approved the protocol, the LAO conducts the Study Initiation Meeting (SIM). Sites then complete the regulatory document submission requirements as specified in SOP01-01 Regulatory Documents. When the first

site is activated, the LAO completes and submits a "Protocol Status Update Form" to the PIO to indicate that the study is active and open to accrual.

NCI requires qualifications verification for personnel conducting NCI-sponsored clinical research. As such, personnel are required to register and submit NCI-required documents via NCI's Registration and Credential Repository (RCR). There are 6 registration types:

- Investigator (IVR) - MD, DO, or international equivalent
- Non Physician Investigator (NPIVR) - advanced practice provider (e.g., NP or PA) or graduate level researcher (e.g., PhD)
- Associate Plus (AP) - clinical site staff (e.g., RN, CRA or Statistician) with data entry access to CTSU applications (e.g., RAVE, Stars)
- Associate (A) - other clinical site staff involved in the conduct of NCI-supported research
- Associate Basic (AB) - individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems

References:

- The National Cancer Institute Cancer Prevention Clinical Trials Network Program Guidelines
- SOP 01-01 Regulatory Documents

Regulatory Documents

DCP's list of required documents is provided below. Guidelines for completion of each document can be found in CP-CTNet SOP 01-01 Regulatory Documents.

- Form FDA 1572 - All Investigators
- Delegation of Tasks Log (DTL)
- Principal investigator (PI) Acknowledgement of Investigator's Brochure (IB) or Package Insert
- NCI Biosketch - All study staff
- Professional Licensure
- Financial Disclosure Form (FDF) - All study staff listed on DTL
- Good Clinical Practice (GCP) Training Certification- All study staff listed on DTL
- Office of Human Subject Protections (OHRP) Assurance
- Clinical Laboratory Improvement Amendments (CLIA) Certification
- College of American Pathologists (CAP) Certification
- Lab Normal Values (LNVs)
- Central Institutional Review Board (CIRB) or Independent Ethics Committee (IEC) Approval
- CIRB- or IEC-approved Informed Consent Document (ICD)
- CIRB- or IEC-approved Patient Recruitment Materials
- Certificates of Translation (if applicable)

Reference:

- SOP 01-01 Regulatory Documents

Completion of the Delegation of Tasks Log:

The DCP Regulatory Contractor will send a protocol-specific DTL to the LAO when a protocol receives initial approval by DCP's CIRB. Each LAO and AO will provide a protocol-specific DTL listing all study staff members who are registered as IVR, NPIVPR and AP. The DTL must be signed by each study staff member next to their designated task codes and the site PI. The PI's signature or initials acknowledging the staff member's role may not precede the staff member's signature date. LAOs will

provide the DTLs to DCP's Regulatory Contractor who will review and maintain the documents. The DCP Regulatory Contractor will provide the signed DTLs to DMACC.

Reference:

- SOP 01-01 Regulatory Documents

Study Initiation Meeting

The LAO Investigator, Site Coordinator and/or their designees are responsible for scheduling and conducting the study initiation meeting (SIM) for each study. The meeting is typically scheduled after DCP issues a "Notice of Study Approval on Hold" letter and the CIRB has approved the protocol. The SIM should be scheduled as close to the study activation date as possible. Key staff members from the LAO and each AO are responsible for attending the study initiation meeting before consenting or enrolling patients. DCP and DMACC staff may also attend the meeting. The SIM Report is available to review the topics that may be applicable to include on the agenda. The LAO is responsible for maintaining documentation related to the SIM. Complete details for the conduct of the SIM can be found in CP-CTNet SOP 01-02 Study Initiation Meeting.

References:

- SOP 01-02 Study Initiation Meeting
- Study Initiation Meeting Template

3. Site Activation

All required regulatory documentation and approvals must be obtained prior to any site activating a study. An active site is defined as an institution or clinical site that, after having completed regulatory and DCP requirements for study initiation, has been initiated/activated in the Stars registration/randomization system by DMACC, and is open to enroll/accrue patients. The requirements include regulatory approvals and documents, relevant sub-contract(s) in place, drug shipment authorization, ordering, and acknowledgment of receipt. Once the LAO informs DMACC and DCP that a site has met all requirements, DMACC will activate the site in Stars. DMACC will send a Confirmation of Activation email to inform LAOs, AOs, and DCP that the site has been activated.

DMACC has created a site activation checklist to be used as guidance for the LAOs to ensure the AOs have met all activation requirements.

References:

- SOP 01-03 Site Activation
- Site Activation Checklist for LAOs

4. Standard Operating Procedures

DMACC will distribute new and revised SOPs with a Sign-off Log. The SOPs will be posted to the CP-CTNet Public Website and DMACC Portal Gateway (cp-ctnet-dmacc.org), and will become effective within 5 business days of announcement. LAO and AO staff involved in trial conduct should read the SOPs and sign the log to confirm they have read them. Any new staff should also sign off on the SOPs.

The sign-off log should be maintained at each site and will be reviewed during audit visits. The LAOs and AOs should maintain all approved CP-CTNet SOPs on file at each site, or have a file note in the trial master file stating the SOPs are located on the CP-CTNet website.

Reference:

- SOP 02-05 Reviewing and Amending Standard Operating Procedures

5. CP-CTNet Public Website and DMACC Portal Gateway

The Website and Portal Gateway are designed to provide access to all systems, tools and resources for trial conduct within CP-CTNet. The Public Website provides information on the structure of CP-CTNet and DMACC, news and events, and program resources. The Portal Gateway is the restricted member area of the website, and contains the Dashboard, which provides access to the Medidata Rave electronic data capture system, the Stars registration/randomization system, and trial-specific documentation, educational/training materials and reports. The link to the website is: cp-ctnet-dmacc.org.

Reference:

- CP-CTNet REFGD08 Public Website/DMACC Portal Gateway Overview and User Registration Guide

6. Accrual Quality Improvement Program

The Accrual Quality Improvement Program (AQuIP) is a multi-component continuous quality improvement program that entails systematic protocol- and site-specific recruitment planning. It involves real-time reporting on recruitment activity and rates; monitoring and analysis of accrual data; data-driven accrual rate goals; and identification of improvement opportunities. The purpose of AQuIP is to promote efficient implementation of clinical trials through well-planned, carefully monitored participant accrual; uphold the 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; and ensure proper stewardship of public funds.

There are several resources available on the CP-CTNet Public Website and DMACC Portal Gateway (cp-ctnet-dmacc.org), including the Recruitment Retention and Adherence Plan Template, toolkit for recruitment resources, and library of training webinars, presentations, and documents. Accrual tracking and monitoring reports are also provided, to identify opportunities and interventions to address accrual issues.

Data related to AQuIP are entered primarily in Medidata Rave, with some data also entered in Stars. Data include:

- Pre-Screening data (e.g., pre-screen strategies and outcome, eligible for contact)
- Screening data (e.g., date of first contact, recruitment strategies, consent date and status, reasons consent not signed)
- Recruitment Journaling information – study- or site-wide events that may affect participant enrollment

References:

- SOP 02-04 Recruitment, Retention and Adherence
- Recruitment, Retention and Adherence Plan Template
- AQuIP Toolkit

7. Stars

Stars is the registration/randomization system developed by DMACC that is used to assign Participant Identification Numbers for Pre-Screening, Screening, and Registration/Randomization (enrollment). Once an ID is assigned, a confirmation file is emailed to the site staff performing the enrollment and any other designated staff. Data entered in Stars are automatically transferred to Rave within a few minutes of entry, so there is no duplication of data entry and all data are held in one central database.

References:

- Stars User Guide
- CP-CTNet Registration/Randomization and Medidata Rave Overview

8. Medidata Rave

Medidata Rave is the electronic data capture (EDC) system that sites use to enter protocol-specific eCRF data, as well as data related to AQuIP. Enrollments are automatically transferred from Stars to initialize the participant into Rave. At that time, visits and data collection screens are available to sites for data entry in Rave.

References:

- Daily QA in Rave
- CP-CTNet Registration/Randomization and Medidata Rave Overview

9. User Access to Stars and Rave

The LAOs determines the access to Stars and Rave for AO staff, and are able to proxy request the appropriate level of access based on the role(s) of each staff member (for example, privileges for data entry, enrollment, view-only). Access to Medidata Rave and Stars is granted on a study-specific basis for each system, so is available to request once a study is activated. Account requests can be made from the home page of the CP-CTNet Public Website or DMACC Gateway Portal (cp-ctnet-dmacc.org).

Once an account is approved for Rave, DMACC invites the user to the study/studies in which the site participates.

References:

- CP-CTNet REFGD08 Public Website/DMACC Portal Gateway Overview and User Registration Guide
- CP-CTNet Registration/Randomization and Medidata Rave Overview

10. Training for Stars and Rave

Prior to accessing Stars, site staff is required to read the Stars User Guide (available on the DMACC Portal Gateway (cp-ctnet-dmacc.org)), and electronically acknowledge they have done so. They will then receive a certificate of completion via email, to be retained in the Investigator Site File.

eLearnings, available directly in Rave, are required based on role (e.g., Study Coordinators/Data Managers, Investigators, Quality Control Coordinators (view-only)). If site staff have previously taken the required eLearnings, the system will show that the eLearnings have been completed, and staff will not be required to retake these trainings. Rave also has a suite of eLearnings available for a wide range of topics (e.g., query management, reports), should site staff be interested in further training. Certificates for completed eLearnings will be available directly in Rave.

Additional educational materials are available on the DMACC Portal Gateway (cp-ctnet-dmacc.org), such as study-specific eCRF completion guides, user guides, tip sheets, and video tutorials.

References:

- Stars User Guide
- Daily QA in Rave
- CP-CTNet Registration/Randomization and Medidata Rave Overview

11. Data Management

The CP-CTNet Master Data Management Plan (DMP) describes data management procedures to be followed to ensure the authenticity, integrity, and confidentiality of study data, and the protection of human subjects participating in CP-CTNet studies. This plan is in lieu of individual LAO DMPs and is to be followed by all LAOs and AOs. The DMP applies to all studies conducted within the CP-CTNet, to ensure consistency across sites and studies.

Data Entry

The LAOs and AOs are responsible for entering complete, reliable and accurate study data into Rave. There is an eCRF Completion Guide for each study in Rave, which provides guidance for forms completion. Data entry should be completed within 14 calendar days of the scheduled visit.

The LAO/AO PI is responsible for final sign-off of data in Rave at the end of study.

Reference:

- REFGD03 CP-CTNet Master Data Management Plan

Query Management

Edit checks are pre-programmed into Rave for certain data fields and automatic queries are displayed when nonconformant data (e.g., missing, out of range) are entered. Data fields without automatic edit checks are quality controlled by the Data Managers (DMs) at DMACC, and the DMs manually enter queries in Rave.

LAOs and AOs can access outstanding queries, and data submission/query response status at any time within Rave. Sites should regularly log into Rave to complete data and resolve queries. All queries must be resolved within 14 calendar days. Queries can be resolved by the site directly within Rave. To respond to a query, sites may either correct the data and provide a reason for the correction, or provide a reason directly within Rave why the data are accurate and do not need correction.

LAOs have view-only access to data from their AOs to facilitate their review of these data. If an LAO finds any data that requires further clarification, the LAO should email their questions to DMACC DMs, who review the questions and enter the appropriate queries into Rave.

Reference:

- REFGD03 CP-CTNet Master Data Management Plan

Serious Adverse Events

The enrolling site (LAO or AO) where the SAE occurred is responsible for reporting the SAE to the DCP Medical Monitor and DCP's Regulatory Contractor. If the SAE occurred at an AO, the AO must also report the event to the LAO. Contact the assigned DCP Medical Monitor (phone and email as listed in the protocol) and DCP's Regulatory Contractor, by phone (650-691-4400) or email (safety@ccsainc.com) within 24 hours of knowledge of an SAE. Email a copy of the completed DCP Serious Adverse Event Report Form to the DCP Medical Monitor (email as listed in the protocol) and to the DCP Regulatory Contractor (safety@ccsainc.com) within 48 hours of learning of the event. The information must be entered onto the form; the form should then be signed with a wet ink signature, scanned, and emailed. The DCP Medical Monitor and/or DCP Regulatory Contractor may request additional clarification or information.

References:

- SOP 02-01 Reporting Serious Adverse Events
- DCP Serious Adverse Report Forms Instructions for Completion

- DCP Serious Adverse Event Report Form

Protocol Deviations

The enrolling site is responsible to report protocol deviations on the CP-CTNet Protocol Deviation Notification Form. If the deviation occurred at an AO, the AO must report the event to the LAO. The LAO reviews and clarifies any discrepancies with the AO (if necessary). The LAO is responsible for submitting the LAO or AO completed deviation form to the DCP Medical Monitor and Nurse Consultant (emails as listed in the protocol) with a copy to DMACC. The DCP Medical Monitor and DCP Nurse Consultant will assign a deviation grade. DMACC distributes the completed form, including deviation grades and DCP comments to the LAO and/or AO, and DCP study staff.

The LAO is responsible for reporting deviations (including those that occur at an AO) that fall into the category of *serious or continuous noncompliance* or *unanticipated problem* to the CIRB via the IRB Manager (https://nci.my.irbmanager.com/), and notifying DCP study staff and DMACC.

References:

- SOP 02-02 Reporting Protocol Deviations
- CP-CTNet Protocol Deviation Notification Form

12. Biospecimen Procedures

As described in each protocol, the LAOs and AOs are responsible for collecting, processing, storing, and shipping 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.

Biospecimens designated for centralized storage and distribution must be confirmed as consented for future use ***prior*** to forwarding these specimens to FNLCR. An electronic item-level Material Transfer Manifest is to be submitted to FNLCR at diazmayoraln@mail.nih.gov and to DCP at NCIDCP-CTNetBiospecimens@mail.nih.gov prior to shipment of any biospecimens. 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 also be provided by FNLRC to ensure the proper packaging and transportation of biospecimens to the FNLCR repository.

References:

- 02-06 Biospecimen Submission Requirements
- Material Transfer Manifest

13. Auditing

The DMACC Clinical Trials Auditing Unit will conduct independent QA auditing of clinical trials data and processes at all CP-CTNet site LAOs and AOs.

LAOs will be audited at least one time annually and remotely as needed.

AOs will be audited remotely annually and as needed, or on-site if the AO has accrued >=10 participants in previous 12 months, or three years have elapsed since the AO's last on-site audit.

The Audit Team will create an Audit Report, including findings and any necessary corrective and preventative actions, and will provide the report to the site, and DCP within 15 business days of the

audit. 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 using the *Action-Item Site Response Form*. This response will indicate either resolution of the action item or include a corrective action plan with a projected resolution date. The reports are reviewed by the Director of Auditing and a DCP study representative. Once all items are resolved, the final Audit Report should be signed by the PI.

References:

- SOP 03-02 Site Preparations for Quality Assurance Audits
- Action Item Site Response Form

14. Site Closeout

DMACC will conduct a site closeout visit (on-site or remotely) for all active LAOs and AOs for each study after all study activities are complete, or at the discretion of DCP study staff. The visit will occur once all participants enrolled at the LAO/AO have completed study-related activities, all data have been entered into Medidata Rave, and outstanding data discrepancies have been resolved.

The Site Coordinator is responsible for coordinating the site closeout tasks in a timely manner. During the site closeout visit, DMACC will verify these items have been completed or will determine the completion status. For a complete list of tasks and responsibilities, refer to SOP 04-01 Preparations for Site Closeout.

DMACC prepares and submits via email, a Site Close-Out Visit Report, including a list of deficiencies and action items, if applicable, to the AO PI and Site Coordinator, and the LAO Site Coordinator, and DCP study team. The LAO/AO site staff must provide a response to DMACC regarding follow-up on findings and action items within 30 calendar days of receipt of the Site Close-Out Visit Report. DMACC notifies the site and the DCP study staff once the action item response is acceptable.

Reference:

- SOP 04-01 Preparations for Site Closeout

15. DMACC Communication Pathway

To enable DMACC to triage your questions efficiently, please include the following information in the subject heading when contacting DMACC via email:

- Site code
- Protocol Number
- Target Organ
- Question topic

16. DMACC Contact Information

Category	Email Support Group
Data Entry in Rave / Data Management / Protocol Questions	DataManagement_CP-CTNet@frontierscience.org
Audit	Audit_CP-CTNet@frontierscience.org
Registration / Randomization	Enrollment_CP-CTNet@frontierscience.org
Access to Systems (e.g., Portal Gateway, Medidata)	UserSupport_CP-CTNet@frontierscience.org
Education / Training	Training_CP-CTNet@frontierscience.org

Contact Management	ContactAdmin_CP-CTNet@frontierscience.org
Administrative	Admin_CP-CTNet@frontierscience.org

CP-CTNet Public Website and DMACC Portal Gateway: cp-ctnet-dmacc.org