CHARTER
Data and Safety Monitoring Board
Cancer Prevention Clinical Trials Network Cross-Network Trials

1. INTRODUCTION

The Cancer Prevention Clinical Trials Network (CP-CTNet) comprises five Lead Academic Organization (LAOs), each with10-15 Affiliated Organizations (AOs), and Data Management, Auditing, and Coordinating Center (DMACC) and is supported by the Division of Cancer Prevention (DCP), National Cancer Institute (NCI), National Institutes of Health. It performs early phase clinical trials to assess the safety, tolerability, and cancer preventive potential of agents and interventions of varying classes, many of which target molecules or processes known to be important during carcinogenesis.

The Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to the National Cancer Institute to monitor participant safety, data quality and evaluate the progress of cross-network trials. Cross-network trials are those trials conducted jointly by multiple LAOs and AOs with a designated LAO serving as a sponsor, and the DMACC will provide the statistical support for cross-network trials.

This charter defines the roles and responsibilities of the DSMB for the CP-CTNet Cross-Network Trials. The DSMB will serve in accordance with the guidelines set forth in this charter. Typically, DSMB members review and agree to the charter at the initial meeting. If changes to the charter are necessary, the DSMB reviews and affirms their agreement with the changes. Their concurrence will be noted in the DSMB meeting summary.

2. RESPONSIBILITIES

Generally, the first responsibility of the DSMB will be to review the final protocol of the cross-network clinical trials and approve the data and safety monitoring plan. After initial review, and at periodic intervals during the course of the trials, the DSMB responsibilities are to:

- Provide input to assist the investigator(s) in protecting the safety of the trial participants;
- Provide input to the investigator(s) on major changes to the research protocol, informed consent documents and plans for data and safety monitoring;
- Provide input to the investigator(s) on the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the trial sites, and other factors that may affect trial outcomes;
- Review areas of concern regarding the performance of individual sites and provide feedback to the investigator(s) on actions to be considered regarding sites that perform unsatisfactorily;
- Consider factors external to the trial when relevant information becomes available, such as scientific or chemopreventive developments that may have an impact on the safety of the participants or the ethics of the trial;
- Provide input to the investigator(s) on modification of the trial protocol or possible early termination of the trial because of attainment of trial objectives, safety concerns, low

likelihood of showing a benefit of the intervention, or inadequate performance such as enrollment and retention problems;
- If appropriate, review the interim analysis of efficacy in accordance with stopping rules which are clearly defined in the protocol and have the concurrence of the DSMB;
- Provide input to the investigator(s) on the potential impact of ancillary studies on the integrity of the parent trial.

3. MEMBERSHIP

The members will be appointed by the DCP/NCI. Members of the DSMB shall have no financial, scientific, or other conflict of interest with the trials under review. The DSMB is a multidisciplinary group consisting of 5 members, including one biostatistician. Collaborators or associates of the CP-CTNet investigators in the trials are not eligible to serve on the DSMB. Written documentation attesting to absence of conflict of interest is required at least annually. The DCP/NCI will appoint a DSMB Chairperson. S/he is responsible for overseeing the meetings and developing the agenda in consultation with the DSMB Executive Secretary assisted by the DSMB Coordinator at the CP-CTNet DMACC. The DCP/NCI reserves the right to add members should there be need for additional expertise. Additional experts may be consulted as ad-hoc members by the DSMB if needed. Members will serve a term of five years. Members will be required to give adequate notice if they are unable to serve the full term so there is appropriate time to find a replacement.

4. DSMB MEETINGS

The DSMB will typically meet once or twice a year, or as deemed necessary. A quorum of all DSMB members is required in order to convene a meeting of the DSMB. Meetings shall be closed to the public because discussions may address confidential participant data. Meetings are attended, when appropriate, by the principal investigator and members of his/her staff, as well as the trial statistician. Meetings may be convened via teleconference or in person. An ad hoc meeting of the DSMB may be called at any time by the DSMB chairperson should questions of participant safety arise.

5. MEETING FORMAT

An appropriate format for DSMB meetings consists of an open, closed, and executive session. This format may be modified as needed.

5.1 Open Session

Members of the DSMB, DSMB Executive Secretary, and the unmasked statistician and DSMB Coordinator, both from DMACC, the principal investigator(s), trial coordinators and the trial biostatistician, and relevant CP-CTNet Program staff may attend the open session. Issues discussed will include the conduct and progress of the trial, including participant recruitment, data quality, general adherence and toxicity issues, compliance with protocol, and any other logistical matters that may affect either the conduct or outcome of the trial. Proposed protocol amendments will also be presented in this session. Participant-specific data and data by intervention group may not be presented in the open session.

5.2 Closed Session

The closed session will be attended only by DSMB members, the Executive Secretary, the DSMB Coordinator and the unmasked trial biostatistician. The discussion at the closed session is completely confidential. All materials from the closed session will be destroyed at the end of the meeting. Analyses of outcome data are reviewed by masked intervention groups, including baseline characteristics, primary and secondary outcomes, adverse events, adherence and dropouts, and examination of any relevant subgroups. The DSMB may request additional analyses. The DSMB may request unmasking of the data for either safety or efficacy concerns.

5.3 Executive Session

The executive session will be attended only by DSMB members, the Executive Secretary, and the DSMB Coordinator, who will discuss the information presented during the open and closed sessions and provide recommendation on the continuation, modification or termination of the trial, or other changes to the conduct of the trial. The DSMB can be unmasked at any time if desired.

The DSMB will make one of the below recommendations:

☐ **APPROVE STUDY CONTINUATION**
The study can continue without change.

☐ **APPROVE STUDY CONTINUATION WITH MODIFICATIONS**
The study or study plan should be modified. Modifications may include, but are not limited to, changes in inclusion/exclusion criteria, frequency of visits or safety monitoring, alterations in study procedures, adjustments in sample size, changes in duration of observation and follow up.

☐ **SUSPEND STUDY**
The study should be suspended, allowing subject visits to occur as scheduled to monitor subject safety, but not allowing new subjects to be enrolled until CP-CTNet DSMB concerns have been appropriately addressed.

☐ **DISCONTINUE STUDY or TREATMENT ARM**
The protocol should be discontinued, or one treatment arm of the protocol should be discontinued, (with provision for orderly discontinuation) due to:

a. Serious concerns about subject safety
b. Serious concerns about the safety of interventions
c. Benefits do not outweigh the risks to subjects
d. Protocol outcomes do not justify risk
e. New developments impact subject safety/ethics
f. Unreasonable degree of difficulty of procedures
g. Other – Please specify

Termination may be suggested by the DSMB at any time. Reasons for early termination include:

- Serious adverse effects in entire intervention group or in a dominating subgroup;
- Greater than expected beneficial effects;
- A statistically significant difference by the end of the trial is improbable;
- Logistical or data quality problems so severe that correction is not feasible.

Sound rationale for the recommendation of continuation, modification or termination of the trial should be presented.

6. REPORTS TO THE DSMB

Reports will be prepared by the unmasked statistician at DMACC. The reports will be distributed to the DSMB at least five days prior to a scheduled meeting. These reports shall be provided in the DMACC's secure web portal gateway or via another secure platform. DSMB reports for randomized clinical trials in which the investigators are masked generally consist of two parts: an open report and a closed report.

Open Reports: Open reports generally include administrative reports by site that describe participants screened, enrolled, completed, and discontinued, as well as baseline characteristics of the trial participants. Other general information on trial status may also be presented. Listings of adverse events and serious adverse events as well as any other information requested by the DSMB may also be in the open report, but none of the data should be presented in an unblinded manner. The DSMB may direct additions and other modifications to the reports on a continuing basis.

Closed Report: Closed reports generally present the same information as presented in the open reports but by masked treatment group, e.g. A vs B. The reports may also contain data on trial outcomes, including safety data, and depending on the trial, efficacy data. If a trial has an interim analysis, it is also discussed in the closed report.

7. DOCUMENTATION OF DSMB MEETINGS

Formal DSMB meeting minutes are prepared by the Executive Secretary with the assistance of the DSMB Coordinator for each DSMB meeting, distributed in a timely manner after each meeting, and reviewed and approved at the subsequent meeting. The Executive Secretary is responsible for preparation and transmission of the formal DSMB minutes to the DSMB Chair and the CP-CTNet Director within 14 calendar days of each meeting or call. Minutes will document whether there is conflict of interest on the part of DSMB members and will summarize the key points of the discussion and debate, requests for additional information, response of the investigators to previous recommendations, and the recommendations from the current meeting. The DSMB Chair will review and approve them on behalf of the DSMB. Once the CP-CTNet Director has reviewed and approved the minutes, they are considered final.

After each DSMB meeting, a memo will be sent to the primary study investigator(s) including a summary of the ongoing safety of the study participants and any recommendations made by the DSMB.

- If the DSMB does not identify any safety or other protocol-related concerns, the memo will state that:
  - a review of outcome data, adverse events, and information relating to study performance (e.g., data timeliness, completeness, and quality) across all centers took place on a given date
  - the observed frequency of adverse events did not exceed what was expected and indicated in the informed consent;
  - a review of recent literature relevant to the research took place, and;
  - the DSMB recommended that the study continue without modification of the protocol or informed consent
- If the DSMB does identify concerns, NCI staff will distribute, as soon as feasible, preferably within 7 calendar days of the DSMB meeting, the memo as outlined above, outlining the

concerns and the basis for any recommendations that the DSMB has made in response to the concerns. Adverse event reporting will be consistent with NCI policy.

Once approval from the DCP/NCI is obtained, the memo will be distributed to the individual cross-network trial PIs, the cross-network trial biostatisticians, and the lead LAO coordinators by the DSMB Coordinator at DMACC. It is the responsibility of the PI/designated LAO coordinator to distribute the memo to the NCI CIRB, all co-investigators and applicable local IRBs.

8. CONFIDENTIALITY AND OBJECTIVITY

All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality. Closed meeting documents should be removed from the DSMB member's computer following each meeting.

In order to maintain their objectivity, DSMB members are expected not to discuss the trials with the investigators except during DSMB open meetings.