UNC Lineberger Comprehensive Cancer Center
Data and Safety Monitoring Plan

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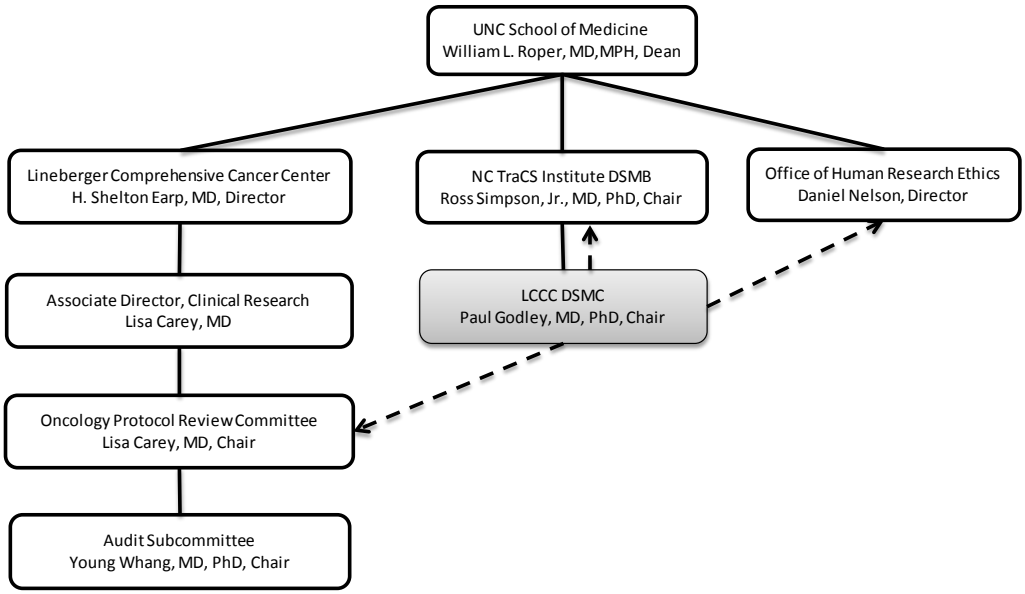
Lineberger Comprehensive Cancer Center supports selected and varied clinical research with a continuing strategic emphasis on clinical research, novel therapeutics, correlatives, and behavioral interventions. This research is conducted with a commitment to patient safety, research quality, and institutional integrity. This Data and Safety Monitoring Plan addresses the monitoring of patient safety and assessing study progress; the reporting of adverse events and unanticipated problems; and the accuracy and integrity of research data and protocol compliance.

Monitoring Progress of Trials and Safety of Participants

Overview and Organization

The Lineberger Comprehensive Cancer Center Data Safety and Monitoring Committee (LCCC DSMC, or DSMC) is the primary agent for assuring data and safety monitoring on UNC Lineberger Investigator-initiated trials. While the LCCC DSMC is responsible for review of these trials, the North Carolina Translational and Clinical Sciences (TraCS) Institute Data Safety Monitoring Board (DSMB) is responsible for reviewing data from clinical trials approved by the UNC Biomedical IRB. Accordingly, the minutes of the LCCC DSMC are reviewed by the NC TraCS DSMB. The LCCC DSMC has the authority to suspend research activities or investigators or to refer trials to the PRC or IRB for such actions. The DSMC meets monthly, with ad hoc review and additional meetings called when necessary. Five members present constitutes quorum.

As illustrated below, LCCC DSMC operates within the structure of the Cancer Center Protocol Review and Monitoring System, which also includes the UNC Lineberger Protocol Review Committee (PRC) and the PRC's Audit Subcommittee. The monitoring processes of these committees also operate within the institutional structure for ethical and regulatory oversight, the Office of Human Research Ethics (OHRE). OHRE supports and oversees the work of the Institutional Review Boards (IRBs).



The DSMC includes a chair, vice chair, and representation from biostatisticians and clinical researchers, including representation from East Carolina University (ECU). UNC Lineberger supports a collaborative relationship with ECU for the purposes of Protocol Review and Monitoring, including participation by ECU Investigators on the LCCC DSMC. The DSMC Chair appoints the DSMC members and Vice Chair, in consultation with the Cancer Center Director, the Associate Director for Clinical Research, and the Medical Director of the Clinical Protocol Office. The PRC Administrative Coordinator supports the activities of the DSMC. The table below shows DSMC Committee Membership as of 2011.

DSMC Committee Membership, 2011

Name	Title	Department
Paul Godley, MD, PhD, MPP (Chair)	Executive Associate Dean for Faculty Affairs and Faculty Development; Professor	Medicine: Hematology/Oncology
Kristy L. Richards, PhD, MD (Vice Chair)	Assistant Professor	Medicine: Hematology/Oncology
Joy Ostroff, RN, BSN, OCN	Director of Research Operations-Oncology Clinical Trials Network	Lineberger Comprehensive Cancer Center
Anastasia Ivanova, PhD	Associate Professor	Biostatistics
Dominic T. Moore, MS, MPH	Senior Biostatistician; Data Management Supervisor	Biostatistics; UNC Lineberger
E. Claire Dees, MD	Associate Professor; Chair, Developmental Therapeutics Working Group	Medicine: Hematology/Oncology
Young Whang, MD, PhD	Associate Professor	Medicine: Hematology/Oncology
Christine Walko, PharmD, BCOP	Clinical Assistant Professor	UNC Eshelman School of Pharmacy
Pamela Lepera, MD	Associate Professor	Leo W. Jenkins Cancer Center (ECU)

DSMC Conflict of Interest Policy

In compliance with the *Data and Safety Monitoring Guidelines* issued by the NCI and with the *University of North Carolina Conflict of Interest Policy*, trials that involve Data Safety and Monitoring Committee members as Principal Investigators, Co-Investigators, or staff may not be reviewed, nor voted on, by these Members. These Members may be present for general review discussion, to respond to queries

from the DSMC, and to provide feedback. Members are to recuse themselves from any voting relevant to DSMC review. In the event that the Chair is the Principal Investigator for the study, the Vice Chair will oversee deliberations and voting.

DSMC Meeting Conflict of Interest Procedures:

Sponsors of trials under review will be listed in the agenda. Members are responsible for declining review responsibilities for any trial for which they have a conflict. At the beginning of each DSMC Meeting, the DSMC Chair will read the definitions of conflicting interest (listed below). Members will be reminded to recuse themselves at the time of discussion of any protocol with which they have a conflict of interest. The reading of the definitions by the Chair and recusals will be noted in the meeting minutes.

Conflict of Interest Definitions:

A DSMC member is considered to have a conflicting interest if the DSMC member or anyone in the member's immediate family:

1. Serves as an investigator or has any involvement in the design, conduct, or reporting of the research
2. Has any ownership interest, stock options, or other financial interest related to the research unless it meets four tests:
    - <$10,000 when aggregated for immediate family
    - Publicly traded on a stock exchange
    - Value will not be affected by the outcome of the research
    - <5% interest in any one single entity
3. Receives any compensation related to the research unless it meets two tests:
    - <$10,000 in the past year when aggregated for immediate family
    - Amount will not be affected by the outcome of the research
4. Has a proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement
5. Has any board or executive relationship related to the research, regardless of compensation
6. Or any other reason for which a DSMC member believes that he/she cannot objectively review the research

Determination of Risk and Complexity

As part of the scientific review process, the PRC classifies studies by levels of complexity and risk to direct Data Safety Monitoring policies and audit requirements.

Protocols are classified into one of three risk categories: Minimal, Moderate, and High.

Risk Category	Types of Trials
Minimal	Nutritional, behavioral, psychosocial, diagnostic and other non-therapeutic studies
Moderate	• Phase I, II, or III therapeutic, palliative or prevention trials that are sponsored by national cooperative groups or NCI/NIH that already include independent appropriate/approved data and safety monitoring plans • Phase I, II, or III therapeutic, palliative or prevention trials sponsored by industry that include appropriate/approved data and safety monitoring plans • Investigator initiated Phase II, or III single institution studies that utilize FDA approved agents
High	• All investigator initiated clinical trials using investigational agents • All Phase I investigator initiated trials • All Phase II and III investigator initiated multi-center trials • All studies for which UNC holds the IND

The PRC reviews moderate and high risk clinical trials to determine complexity, using a seven-point scale. A point is added for each of the following:

- Conduct of pharmacokinetic studies (1 unit)
- Require use of a health provider for infusion or administration of protocol directed therapy and/or direct monitoring for toxicity following study drug administration (1 unit)
- Collection of biological samples for correlative science and/or observational studies (1 unit)
- Unusual route of administration and/or safety issues regarding administration (1 unit)
- An LCCC multi-center trial at 2-3 sites (1 unit)
- An LCCC multi-center trial with more than 3 sites (1 additional unit).
- Trials with none of these factors have a score of 0.

Trials that have greater complexity (≥ 4 points) require more frequent monitoring.

Monitoring and Oversight

For all trials, Principal Investigators are responsible for continuous monitoring of patient safety. Requirements for periodic data and safety monitoring are commensurate to the trial's risk and complexity, as described above. Periodic review by the DSMC, PRC, and OHRE provides oversight of the Principal Investigator's continuous monitoring. If risk or complexity is significant, the DSMC, PRC and/or OHRE may require additional reporting or alternative data and safety monitoring. Data safety and monitoring activities continue until all patients have completed treatment and until all patients have been followed to the point at which study-related adverse events would likely no longer be encountered.

Risk or Complexity Assignment	Frequency of Reporting
Minimal Risk	Annually based on OHRE anniversary date; DSMC may opt to exempt from future review
Moderate Risk	Annually based on the OHRE anniversary date; every six months for multi-center trials with a complexity rating of less than four
High Risk Phase I[1]*and Trials with Dose Escalation*	Monthly review of AEs contributing to DLT; full DSMC review every three months
High Risk Phase II	Every six months based on the OHRE anniversary date
High Risk Phase III	High-risk Phase III trials require an independent data and safety monitoring board (study DSMB). Lineberger Investigator-initiated Phase II trials will be referred to the NC TraCS DSMB. At the direction of the DSMB Chair, an alternative mechanism may be established to fulfill this function.
Complexity Rating ≥4	Quarterly review

Reporting Requirements

For each DSMC review, summary information regarding toxicity and accrual patterns, including information from all multicenter sites participating in the trial, is prepared and submitted by the Principal Investigator or designee.

Specific information submitted for review includes:

1. The number of patients entered, consented, consented but not treated, currently being treated, completed treatment and the number of patients who did not complete treatment
2. Grade 3 or greater reported Adverse Events to date
3. Serious Adverse Events and Unanticipated Problems since last report, with assurance of reporting to internal and external regulating bodies
4. Exceptions in eligibility or treatment and significant protocol deviations/violations
5. Significant literature reporting developments that may affect the safety of participants or the ethics of the study
6. Summaries of team meetings that have occurred since the last report
7. Results of interim analyses required by the protocol

Additional data is required based on the phase of the trial:

- For Phase I trials and other trials with dose escalation – Adherence to proposed dose escalation; Dose limiting toxicities. For monthly Phase I reporting – Adverse events contributing to dose limiting toxicities along with accrual data; minutes or summaries of team meetings
- For Phase I/II trials – Adherence to proposed dose escalation and transition to Phase II
- For Phase II and Phase III trials – Preliminary report of response and other endpoints listed in the primary and secondary objectives of the protocol

While Investigators are responsible for reporting safety data, the administration of the DSMC and LCCC as an institution support the reporting process. The DSMC Coordinator requests materials in advance of the meeting, providing blank review forms and spreadsheets, as well as any materials received at time

[1] Phase I/II trials are monitored as Phase I trials until MTD is reached and the trial moves to the Phase II setting.

of last review. OnCore™[2] will create a monthly DSMC Report from the Biostatistical and Clinical Data Management Core for review purposes. This report yields data on treatment related grade 3, 4, and 5 adverse events, serious adverse events, and dose-limiting toxicities viewable by patient and cohort or arm assignments. The DSMC Report is applicable in particular for monthly and quarterly reporting on high risk and Phase I trials.

If incomplete materials are received from the Principal Investigator, the DSMC Coordinator will contact the Principal Investigator to train and inform regarding information needed for review.

If materials requested by the DSMC are not received by the due date of the scheduled meeting, Investigators are allowed five days to respond with a plan to submit materials by the following meeting deadline (or 24 hours for more frequent, Phase I review). If no response is received, the trial will be temporarily suspended to accrual.

DSMC members receive review information approximately one week prior to the Committee meeting. Each study is assigned to a specific Committee member for presentation during the Committee meeting. The reviewer examines the trial information with a special focus on toxicity data, including an overview of grade 3 or greater adverse events, a summary of patient accrual including treatment status, and general safety information for each study to determine if any safety signal is found. The reviewer is responsible for the continuity of the study's progress from beginning to completion of patient treatment and data collection and should also assess potential futility in the review.

Participant confidentiality is assured in that no Protected Health Information (PHI) is included in any of the data provided. For Phase II and Phase III blinded trials, LCCC trials have a blinded and an unblinded statistician. These trials also have an "honest broker," someone unrelated to the trial who may view unblinded data as needed. Unless there is a safety signal, unblinded data are not examined. All members and support staff take HIPAA training annually.

The Committee may vote to take one of the following actions for each protocol reviewed:

- Full Approval: enrollment may continue; no outstanding questions regarding toxicity or accrual
- Conditional Approval: enrollment may continue conditional upon satisfactory response by the Principal Investigator to DSMC concerns regarding toxicities and/or accrual
- Suspension: enrollment immediately suspended pending Principal Investigator response to DSMC concerns regarding toxicity and/or accrual patterns
- Closure: study closed due to unacceptable toxicity and/or accrual patterns

All DSMC decisions are conveyed in writing to the Principal Investigator and designees and copied to the PRC and IRB. Principal Investigators may appeal DSMC decisions in writing to the chairman of the DSMC.

Temporary or permanent suspension of any NCI-sponsored clinical trial by the DSMC, UNC IRB, PRC, or NC TraCS DSMB will be reported by the LCCC Associate Director for Clinical Research to the NCI Project

[2] OnCore™ is a customizable, web-based clinical research platform. OnCore™ features custom reporting, the ability to create institution-specific or department-specific reports.

Manager for that trial. Any such actions made by the FDA, a commercial sponsor, or by the investigator him/herself, for an NCI-funded trial will likewise be reported to the appropriate NCI Program Director as requested in the NCI's *Data and Safety Monitoring Plans Review Criteria*.

Reporting Adverse Events

Documentation of Non-Serious Adverse Events (AEs)

For non-serious Adverse Events, documentation must begin from the first day of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

Collected information should be recorded in the Case Report Forms (CRF) for that patient. A description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug should be included. Documentation should occur at least quarterly.

Documentation of Serious Adverse Events (SAEs)

For any experience or condition that meets the definition of a serious adverse event (SAE), recording of the event must begin after signing of the informed consent and continue through the 30 day follow-up period after treatment is discontinued. For drug(s) with long half-lives, it may be appropriate to extend the 30 day follow-up period. These events must be recorded in the CRF for that patient within 24 hours of learning of its occurrence.

If the event is both serious AND unexpected, it must also be recorded on the MedWatch Form 3500A as per 21 CFR 312.32. For multi-site trials, if the event occurs at an Affiliate site, the MedWatch form will be faxed to the UNC Cancer Network (UNCCN) Study Coordinator along with supporting documentation defining the event and causality.

Reporting Serious and Unexpected AEs

FDA Reporting Requirements

UNC study personnel are responsible for informing the Principal Investigator of the SAE, and, if it is also unexpected, for forwarding all MedWatch 3500A forms to the FDA in accordance with 21 CFR 312.32 (for drugs under an IND) and 21 CFR 314.80 (for marketed drugs).

For multi-site trials, the UNCCN Study Coordinator will be responsible for informing each Affiliate Principal Investigator of all serious and unexpected SAEs or AEs.

IRB Reporting Requirements:

For single-site studies and multi-site trials conducted at UNC, the UNC IRB will be notified of all SAEs that qualify as an Unanticipated Problem (serious, unexpected, and related) as per the UNC IRB policies. In accordance with these policies, an aggregated list of all SAEs (including SAEs from affiliate sites relying on the UNC IRB) will be submitted to the UNC IRB annually at the time of study renewal. For all multi-site trials, affiliate sites using a local IRB of Record will submit adverse events per local IRB policy.

Trial Safety Monitoring

The Principal Investigator will provide continuous monitoring of patient safety with periodic reporting to the Data Safety Monitoring Committee (DSMC).

Meetings/teleconferences will be held at a frequency dependent on study accrual, and in consultation with the study Biostatistician. Phase I trials will meet weekly during active recruitment and treatment. These meetings will include the Investigators as well as Research Nurse Coordinators, Clinical Research Associates, Regulatory Associates, Data Managers, Biostatisticians, and any other relevant personnel the Principal Investigator may deem appropriate. At these meetings, the research team will discuss:

- Participant safety (AE reporting), dose escalation (if applicable), advancement from phase (if applicable), and stopping rules (as appropriate)
- Data validity, integrity, and completeness
- Enrollment and retention
- Protocol adherence

The team will produce summaries or minutes of these meetings and these will be among the materials provided for DSMC review. The summaries will be signed by the Principal Investigator or by a Co-Investigator in the absence of the Principal Investigator. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight of the Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data Safety Monitoring Board (DSMB).

Data Accuracy and Protocol Compliance

Auditing

Lineberger Comprehensive Cancer Center audits investigator initiated and NCI-funded clinical and prevention therapeutic trials to authenticate compliance and capture of accurate data through its Audit Subcommittee of the Oncology Protocol Review Committee (as illustrated in Organization and Overview section above). Included in audit are NCI-sponsored investigator initiated trials from outside institutions for which UNC is a participating site. These audits are coordinated by the PRC Administrative Coordinator and staffed by volunteers from UNC-Chapel Hill faculty, Fellows, and staff engaged in oncology clinical research. Standing audits are scheduled quarterly, with follow up or ad hoc auditing occurring as needed.

Audits take place once a trial has accrued its first patient, and then annually for all local-only investigator-initiated trials and bi-annually for multicenter investigator initiated trials. An independent audit volunteer reviews records for a randomly selected of 10% of the accrual since time of last audit (or study inception for first audits).

The Audit Subcommittee meets following the quarterly audit to review findings from the audit. Discrepancies found in audit are characterized as Major or Lesser. The Audit Subcommittee determines

if the audit findings are Acceptable or Unacceptable. Audit findings are addressed directly to the Principal Investigator, with a summary being issued to the Principal Investigator and the PRC. Principal Investigators may be required to present a Corrective Action Plan (CAP) in response to major discrepancies to be reviewed by the Audit Chair within 30 days of notification of the audit findings. The Audit Chair may choose to approve the Plan, or request additional information or clarification to ensure compliance. A rating of less than satisfactory may trigger audit of additional records, a full audit, or a repeat audit before the next scheduled audit.

Findings of substantial and/or serious protocol deviations may be identified through several mechanisms, including the audit function described above. Protocol deviations may also be identified via risk review by the DSMC, by PRC review at time of annual renewal or when substantive changes are made to the protocol. Ultimately, institutional response to protocol deviations, including those discovered by Audit Committee, PRC, and DSMC, are managed by OHRE via the IRB in accordance with federal law.

Multi-Center and LCCC-Only Monitoring

The LCCC Data Quality Plan for trials utilizing OnCore for clinical data collection outlines quality-control procedures for assuring data accuracy and completeness.

For multi-center trials, for each five patients accrued, one-fifth of patient charts are monitored for source verification, including OnCore eCRF validation. The LCCC Biostatistical Core provides a random selection of identified subjects. Monitoring reports are sent to the Principal Investigator with signature required. Follow up is required for deviations, queries and corrective action plans.

Requirements for Data Entry into OnCore

Data is expected to be entered into OnCore within two weeks after patient's study visit. Sites with data greater than 30 days behind in data entry may be placed on suspension for patient accrual and, if not resolved in a timely manner, may be withdrawn from study participation.