LAURA AND ISAAC PERLMUTTER CANCER CENTER

Data and Safety Monitoring Plan

Benjamin Neel, MD, PhD, Director
Laura and Isaac Perlmutter Cancer Center
160 East 34th Street
New York, NY 10016

Version History

<table>
<thead>
<tr>
<th>Date</th>
<th>Version</th>
<th>Description</th>
<th>Author</th>
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<tr>
<td>November 18th, 2011</td>
<td>1.0</td>
<td>Initial</td>
<td>Lisa Gaynes, Administrative Director, Clinical Trials Office</td>
</tr>
<tr>
<td>August 15th, 2017</td>
<td>1.1</td>
<td>Revision</td>
<td>Erica Love, Administrative Director, Clinical Trials Office</td>
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<td>Nida Cassim, Associate Director, Clinical Trials Office</td>
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Introduction

This document describes the Data and Safety Monitoring Plan (DSMP) and description of the policies and procedures related to data safety and monitoring activities at the Perlmutter Cancer Center (PCC) which are applicable to all cancer clinical trials performed under the purview of the PCC. The PCC follows the National Cancer Institute (NCI) policy for Data and Safety Monitoring of Clinical Trials (https://deainfo.nci.nih.gov/grantspolicies/datasafety.pdf). The purpose of the PCC institutional DSMP is to ensure the protection of human subjects that participate in clinical trials at the PCC and to provide guidance to investigators developing data and safety monitoring plans for their individual trials. This plan describes:

- Policies and procedures in place to monitor progress of trials and safety of study participants.
- Policies and procedures for ensuring compliance regarding the reporting of Adverse Events (AEs).
- Policies and procedures for ensuring data accuracy and overall protocol compliance.
- Procedures for reporting unexpected events to the National Cancer Institute (NCI) Program Director.
- Structure of committees responsible for ensuring the protection of human subjects within the PCC.

The PCC Director and Associate Director for Clinical Research are ultimately responsible for and provide oversight of the cancer clinical trial related data and safety monitoring activities conducted at the PCC. PCC committees or groups with responsibilities for data and safety monitoring include the Protocol Review and Monitoring Committee (PRMC), the Data and Safety Monitoring Committee (DSMC), NYU Langone Health Institutional Reviews Board (IRB), the Clinical Trials Office (CTO), the Disease Management Groups (DMGs) and the Principal Investigator (PI). Other committees that ensure the protection of human participants in clinical research at the institutional level include DataCore and the Institutional Review Board (IRB).

Definitions

**Principal Investigator (PI):** The PI of each trial is responsible for every aspect of the design, conduct, final analysis and reporting of results for their clinical trials. All investigators are required to complete institutional training requirements, abide by federal policies and guidelines and abide by the commitments outlined in the FDA Form 1572. It is the primary responsibility of the investigator and research staff to monitor adverse events, trends in data and detect SAEs, which are then reported to the DSMC and IRB for review.

**Disease Management Groups (DMGs):** The Perlmutter Cancer Center Disease Management Groups (DMGs) are critical to the research mission of the Perlmutter Cancer Center. They create bridges between medical disciplines and between areas of research devoted to specific types of cancer. DMG members meet at least monthly to design and implement new clinical and translational research initiatives and investigator-initiated early phase trials, and also to prioritize clinical protocols. To learn more about our DMG’s visit https://med.nyu.edu/cancer/research/areas/dmg.
Clinical Trial: The PCC follows the Cancer Center Support Grant (CCSG) definition of clinical research:

**Patient-oriented research:** This type of research is conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual, tissue banking, and studies that do not require patient consent (e.g., retrospective chart reviews). Patient-oriented research includes:

- Studies of mechanisms of human disease
- Studies of therapies or interventions for disease
- Clinical trials, and
- Studies to develop new technology related to disease
- Epidemiological and behavioral studies: Studies among cancer patients and healthy populations that involve no intervention or alteration in the status of the participants, e.g. surveillance, risk assessment, outcome, environmental, and behavioral studies.
- Health services research: Protocol designed to evaluate the delivery, processes, management, organization, or financing of health care.

Clinical Protocol and Data Management

Clinical Trials Office

The Clinical Protocol and Data Management function at the PCC is named the Clinical Trials Office (CTO), and it provides the Laura and Isaac Perlmutter Cancer Center with a world-class infrastructure to support investigators in the efficient management and safe conduct of high-quality, high-impact cancer clinical research by providing central management and oversight functions for the coordination, facilitation, and reporting of cancer clinical research.

Data Integrity and Reporting

The PCC CTO utilizes a Clinical Research Management System (CRMS) module within Research Navigator to centrally store all cancer protocols, documents and, to store study and human subject level data required for summary reporting to the National Cancer Institute (NCI) and to the Clinical Trial Reporting Program (CTRP). A cancer center specific dashboard supported by the medical centers information technology department allows for real time monitoring of data needed for reporting purposes. In addition, the dashboard produces monthly metric based reports that are distributed to disease management group physician leaders and Cancer Center leadership.

The CTO provides administrative support to the following committees:

- Clinical Trials Office Oversight Committee (CTO-OC)
- Protocol Review and Monitoring Committee (PRMC)
- Data and Safety Monitoring Committee (DSMC)
- PCC Disease Management Groups (DMGs)
The direct assistance provided to the DSMC by the CTO includes the collection and maintenance of data on patients enrolled (including, but not limited to, accrual, toxicity, protocol deviations, adverse events and serious adverse events). In addition, the CTO Assists investigators in data review and safety monitoring report preparation for DSMC review and monitoring.

The CTO also provides clinical trials support to the PCC DMGs and investigators including:

- Study coordination and data management
- Regulatory affairs and administration oversight (assurance that all federal, state, and institutional regulations are followed. Assistance in preparation and submission of investigator-initiated trials (IITs), Cooperative Group, Externally Peer-Reviewed, and Industry-sponsored trials to the PRMC and NYU Langone Medical Center IRB).
- Safety Monitoring
- Internal Auditing (conducts internal audits and reports findings to the appropriate committees)
- Clinical Research Nursing
- Budget development and negotiation and contracting
- Medicare Coverage Analysis
- Information Technology (CTMS; Oracle Clinical; Velos, TrialMaster, RedCap)
- Education in the development and conduct of clinical trials

Clinical Trials Office Oversight Committee (CTO-OC)

Recognizing the significance of clinical research within a large academic medical center and its financial and organizational challenges, the Clinical Trials Office Oversight Committee (CTO-OC) regularly evaluates the progress toward internal and NCI defined benchmarks, performance of the various mechanisms to support the clinical research enterprise, and recommends necessary changes to optimize performance. Responsibilities of this committee include:

1. Review and approval of PCC policies and Standard Operating Procedures (SOPs) related to the conduct of clinical research.
2. Appointment of membership to the Protocol Review and Monitoring Committee (PRMC) and the Data and Safety Monitoring Committee (DSMC).
3. Review and approve resource requests to support clinical research initiatives and clinical trials across the PCC.

Membership

Members of the CTO-OC are key leaders of the PCC appointed by the Cancer Center Director. Their term is co-terminus with their leadership role. The committee meets bi-weekly. Ad hoc meetings are also held to address specific issues that require immediate attention and to ensure subject safety.

<table>
<thead>
<tr>
<th>Name and Qualifications</th>
<th>Title</th>
<th>Department</th>
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<tbody>
<tr>
<td>Benjamin Neel, MD, PhD</td>
<td>Director</td>
<td>Laura and Isaac Perlmutter Cancer Center</td>
</tr>
<tr>
<td>Anna Pavlick, DO</td>
<td>Medical Director, Clinical Trials Office</td>
<td>Laura and Isaac Perlmutter Cancer Center</td>
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Protocol Review and Monitoring Committee (PRMC)

The PCC PRMC conducts scientific review of all cancer-related clinical research (therapeutic and non-therapeutic) occurring at NYU Langone Health. The PRMC holds the authority to approve protocols that meet the scientific merit and scientific priorities of the PCC for activation, and to terminate protocols that do not demonstrate adequate scientific progress. All cancer-related studies that meet the definition of clinical research regardless of sponsorship type (institutional, industry, national, and externally peer reviewed) are required to be reviewed by the PRMC.

The intent of the PRMC review process is to enhance the quality of research by providing constructive communication to the investigator. Protocols are assigned to scientific reviewers with appropriate expertise in order to assess the significance and potential impact of a given study. In addition, investigators are required to submit a schema which outlines where the protocol under review is positioned in terms of priority within the DMG. The schema allows the PRMC reviewers to determine if there are competing protocols that may deter enrollment on the protocol under review. If a competing protocol is identified, the investigator must provide a written description of how the conflict will be handled. The CTO Protocol Development and Monitoring Unit (PDMU) provides administrative support to the PRMC.

Membership

Committee members are appointed by the CTO-OC. Membership includes representatives from medical oncology, hematology, radiation oncology, surgical oncology, pediatric oncology, pharmacology, biostatistics, basic science research, oncology nursing, supportive care, and clinical research administration. The PRMC meets on a bi-weekly basis. Administrative support of the PRMC is

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Institution</th>
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<tbody>
<tr>
<td><strong>Tim Strawderman, PhD</strong></td>
<td>Executive Director</td>
<td>Laura and Isaac Perlmutter Cancer Center</td>
</tr>
<tr>
<td><strong>Jeffrey Weer, MD, PhD</strong></td>
<td>Deputy Director</td>
<td>Laura and Isaac Perlmutter Cancer Center</td>
</tr>
<tr>
<td><strong>Erica Love, MA, MPH, CCRP</strong></td>
<td>Administrative Director, Clinical Trials Office</td>
<td>Laura and Isaac Perlmutter Cancer Center</td>
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<tr>
<td><strong>Michael Grossbard, MD</strong></td>
<td>Director, Hematologic Malignancies Clinical Program</td>
<td>Laura and Isaac Perlmutter Cancer Center</td>
</tr>
<tr>
<td><strong>Abraham Chachoua, MD</strong></td>
<td>Associate Director, Cancer Services</td>
<td>Laura and Isaac Perlmutter Cancer Center</td>
</tr>
<tr>
<td><strong>Nida Cassim, MPH</strong></td>
<td>Associate Director, Clinical Trials Office</td>
<td>Laura and Isaac Perlmutter Cancer Center</td>
</tr>
<tr>
<td><strong>Doug Levine, MD</strong></td>
<td>Director, Division of Gynecologic Oncology</td>
<td>Department of Obstetrics and Gynecology</td>
</tr>
<tr>
<td><strong>Samir Taneja, MD</strong></td>
<td>Vice Chair</td>
<td>Department of Urology</td>
</tr>
<tr>
<td><strong>Kwok-Kin Wong, MD, PhD</strong></td>
<td>Division Chief, Division of Hematology and Medical Oncology</td>
<td>Laura and Isaac Perlmutter Cancer Center</td>
</tr>
<tr>
<td><strong>Alec Kimmelman, MD, PhD</strong></td>
<td>Chair</td>
<td>Department of Radiation Oncology</td>
</tr>
<tr>
<td><strong>Russell Berman, MD</strong></td>
<td>Program Director</td>
<td>Department of Surgery</td>
</tr>
<tr>
<td><strong>Thomas Walsh, MBA</strong></td>
<td>Director for Business and Finance</td>
<td>Laura and Isaac Perlmutter Cancer Center</td>
</tr>
<tr>
<td><strong>Francisco Esteva, MD, PhD</strong></td>
<td>Associate Director of Clinical Research</td>
<td>Laura and Isaac Perlmutter Cancer Center</td>
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<tr>
<td><strong>Jennifer Wu, MD</strong></td>
<td>Director, Bellevue Cancer Center</td>
<td>Laura and Isaac Perlmutter Cancer Center</td>
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provided by the CTO. Minutes reflect the members present, substantive issues discussed, and voting results.

<table>
<thead>
<tr>
<th>PRMC Members</th>
<th>Committee A/B</th>
<th>Area of Expertise</th>
<th>Voting</th>
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<tbody>
<tr>
<td>Bhavana Pothuri, MD</td>
<td>A</td>
<td>Gynecologic Oncology</td>
<td>Y</td>
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<tr>
<td>Daniel Cho, MD</td>
<td>A</td>
<td>Phase I Drug Development Program</td>
<td>Y</td>
</tr>
<tr>
<td>David Kaminetzky, MD</td>
<td>A</td>
<td>Hematologic Malignancies</td>
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<tr>
<td>Douglas Kondziolka, MD</td>
<td>A</td>
<td>Neurosurgery</td>
<td>Y</td>
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<tr>
<td>Elliot Newman, MD</td>
<td>A</td>
<td>Gastrointestinal Cancer</td>
<td>Y</td>
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<tr>
<td>Freya Schnabel, MD</td>
<td>A</td>
<td>Breast Surgery/ Oncology</td>
<td>Y</td>
</tr>
<tr>
<td>Jennifer Wu, MD</td>
<td>A</td>
<td>Gastrointestinal Cancer</td>
<td>Y</td>
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<tr>
<td>Joshua S. Silverman, MD, PhD</td>
<td>A</td>
<td>Radiation Oncology</td>
<td>Y</td>
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<tr>
<td>Kent P. Friedman, MD</td>
<td>A</td>
<td>Department of Radiology</td>
<td>Y</td>
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<tr>
<td>Melissa Wilson, MD, PhD</td>
<td>A</td>
<td>Melanoma</td>
<td>Y</td>
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<tr>
<td>Peter B. Schiff, MD, PhD</td>
<td>A</td>
<td>Radiation Oncology</td>
<td>Y</td>
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<tr>
<td>Richard B. Hayes, PhD, MPH, DDS</td>
<td>A</td>
<td>Epidemiology</td>
<td>Y</td>
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<tr>
<td>Sharon L. Gardner, MD</td>
<td>A</td>
<td>Pediatric Oncology</td>
<td>Y</td>
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<tr>
<td>Yongzhao Shao, PhD</td>
<td>A</td>
<td>Division of Biostatistics</td>
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<tr>
<td>Arjun V. Balar, MD (Chair of A)</td>
<td>A/B</td>
<td>Genitourinary Cancers Program</td>
<td>Y</td>
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<tr>
<td>James L. Speyer, MD (Chair of B)</td>
<td>A/B</td>
<td>Breast Oncology</td>
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<tr>
<td>Yelena Novik, MD</td>
<td>A/B</td>
<td>Breast Oncology</td>
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<tr>
<td>Andrew S. Chi, MD, PhD</td>
<td>B</td>
<td>Neurologic Oncology</td>
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<tr>
<td>Kevin Du, MD</td>
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<tr>
<td>Sarah Mendez, PhD, RN</td>
<td>B</td>
<td>Nursing</td>
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<td>Douglas Levine, MD</td>
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<td>Obstetrics and Gynecology</td>
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<td>Jeffrey S. Weber, MD, PhD</td>
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<td>Judith Goldberg, Sc.D.</td>
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<td>Kanika Ballani, Pharm.D</td>
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<td>Kenneth S. Hu, MD</td>
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<td>Kepal Patel, MD</td>
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<td>Endocrine Oncology</td>
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<td>Leena Gandhi, MD, PhD</td>
<td>B</td>
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<td>Luca Paoluzzi, MD</td>
<td>B</td>
<td>Sarcoma</td>
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<td>Maxim Kreditor, MD</td>
<td>B</td>
<td>Hematologic Malignancies</td>
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<tr>
<td>Jiyoung Ahn, PhD</td>
<td>B</td>
<td>Population Health</td>
<td>Y</td>
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<tr>
<td>William L. Carroll, MD</td>
<td>B</td>
<td>Pediatric Oncology</td>
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<tr>
<td>Crystal Escano, RN, BSN</td>
<td>A/B</td>
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<td>Erica Love, MS, MPH, CCRP</td>
<td>A/B</td>
<td>Clinical Trials Office</td>
<td>N</td>
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<td>Fraustin Hsu</td>
<td>A/B</td>
<td>Clinical Trials Office</td>
<td>N</td>
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<tr>
<td>Joan Scagliola, MSN. RN</td>
<td>A/B</td>
<td>Nursing</td>
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<tr>
<td>Mary Charlotin, MS, MPH</td>
<td>A/B</td>
<td>Clinical Trials Office</td>
<td>N</td>
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<tr>
<td>Nida Cassim, MPH</td>
<td>A/B</td>
<td>Clinical Trials Office</td>
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Policies and Procedures

New protocols submitted to the PRMC are first reviewed by the PRMC Coordinator to confirm that all required components of a research protocol are included. The PRMC Coordinator meets with the PRMC Chairmen every two weeks to assign two peer reviewers (PR). There are two types of PRMC review, 1) administrative review and 2) full committee review. If a protocol falls outside the expertise of the current
PRMC membership or if members are not available, the Chair(s) will identify one or more members of the PCC to act as ad hoc reviewers. They submit a written review and may attend the PRMC as non-voting members, to participate in the discussion of the study.

Types of Review

**Administrative Review**

Administrative review is an expedited review mechanism and does not need to adhere to submission deadlines for fully convened meetings. Administrative reviews are performed by the PRMC Executive Committee, which is a sub-committee whose members are appointed by the PRMC Chair. This committee reviews the following:

- National Cooperative Group studies
- Externally Peer Reviewed studies
- Any peer-reviewed study supported by an NIH mechanism (e.g., R01s, U01s, U10s, P01s, and P50s, etc.).
- Observational studies that focus on cancer patients and healthy populations and involve no prospective intervention or alteration in the status of the participants and assess biomedical and/or health outcome(s) in pre-defined groups of participants. The participants in the study may receive diagnostic, therapeutic, or other interventions, but the investigator of the observational study is not responsible for assigning specific interventions to the participants of the study.
- Ancillary or Correlative studies that are stimulated by, but are not a required part of, a main clinical trial/study, and that utilize patient or other resources of the main trial/study to generate information relevant to it. Ancillary studies must be linked to an active clinical research study and should include only patients accrued to that clinical research study. Only studies that can be linked to individual patient or participant data must be reviewed.
- Laboratory-based studies using specimens to assess cancer risk, clinical outcomes, response to therapies, etc. Only studies that can be linked to individual patient or participant data are required to be reviewed.

Executive committee members have 5 business days from the time they receive a protocol to review each protocol. Reviewers who cannot meet this deadline must inform the PRMC Chair and PRMC Coordinator within 2 days of receipt, so that another committee member will have time to step in and meet the review deadline.

**Full Committee Review**

All Intervventional studies in which Individuals are assigned prospectively by an investigator based on a protocol to receive specific interventions require full committee review. The participants may receive diagnostic, treatment, behavioral, or other types of interventions. The assignment of the intervention may or may not be random. The participants are followed and biomedical and/or health outcomes are assessed.
Studies requiring full committee review require the PI or a sub-investigator to be in attendance on the day of the PRMC meeting to present a summary of their protocol. The PR and a representative from Biostats assigned to the protocol will also present a summary of their review. If the assigned PR is unavailable to attend the meeting, the Chair or Vice-Chair will present their review. Members of the committee will ask any questions or state any concerns they have for the PI or the PR. Once all concerns are addressed the PI will step out of the room and Chair will motion to vote on the protocols approval. Once a vote is made the PI will receive written notification of the PRMC approval within 24 hours via email as well as an updated status in Research Navigator. For each new study, the PI is required to submit the following:

- PRMC Application via research navigator
- Disease Management Group (DMG) approval to submit study to the PRMC
- Protocol document (addressing all items as furnished in the protocol template)
- An NYU research number assignment letter, or an NYU research number transmittal form completed to attain an NYU Research number
- A protocol schema, providing justification for opening the protocol and explanation of how it fits into the overall research program for the specific disease site (therapeutic studies), and how competing studies will be prioritized
- The number of available patients per year
- The number of patients expected to be accrued annually and over the life of the protocol
- Funding source or sponsor, and study type
- Proposed project dates
- A Risk/Benefit analysis
- Plans for data and safety monitoring

Committee Dispositions

There are four possible outcomes for each protocol:

**Approved**: When a study is approved, the PRMC Coordinator sends an approval letter to the PI, & the Regulatory Specialist. The PRMC status is also updated in Research Navigator. After receiving PRMC approval, the study team can proceed with obtaining IRB approval.

**Approved with conditional changes**: The committee approves the protocol with stipulations. Required modifications are made & subsequently approved by the PRMC Chair and/or the original reviewers. The PI is not required to attend a second committee meeting. The final determination is acknowledged under “Old Business” on the subsequent meeting agenda after the stipulations have been met.

**Deferred**: If a study requires major changes or the committee requests further information, the PRMC Coordinator will contact the PI with the revisions to be made. For IIT protocols, QAU approval is required. The protocol will be reviewed again at the next meeting after the changes are made. The PI or Co-PI are required to attend the next meeting for the second review.
Disapproved: The committee has concluded the trial does not have enough scientific merit, does not justify use of CTO resources, competes with other ongoing trials not expected to close within 3 months’ time or that the trial does not address the needs of the PCC cancer patient population.

Conflicts of Interest

Several specific actions are taken to avoid conflict of interest in the PRMC voting process:

- In the event that one of the PRMC co-chair(s) serves as the investigator or co-investigator for the study or amendment in question, the alternate co-chair will be responsible for establishing the level of risk, the need for a full committee review, and for assigning reviewers.
- All committee members involved as a PI or co-principal investigator of a study must abstain from voting.
- All committee members with a significant personal financial stake in the sponsor agency must abstain from voting.

Annual Progress Review and Accrual Monitoring

During initial review of the clinical trial, the PRMC evaluates accrual estimates to determine whether they are a reasonable estimate of potential study participants appropriate for the particular study, and a reasonable use of resources.

The PRMC then performs annual evaluation of studies prioritized for activation by the PRMC until enrollment is completed or the PRMC makes the decision to close the study. PIs of under accruing studies are updated with quarterly accrual progress reports showing the % accrual met to date and a reminder of the scheduled date of PRMC annual evaluation date on a quarterly basis. PI’s that are under their target accrual goal in the last quarter of the accrual year will be asked to submit a remediation plan at least 30 days prior to the annual evaluation date. The PRMC may accept the PI’s remediation plan and re-evaluate in 3 or 6 months or the PRMC may issue a disposition to close the study. The PRMC uses the following guidelines when conducting annual evaluations. These guidelines do not apply to orphan cancers.

- Studies that have enrolled less than 25% of target accrual within one full accrual year from activation will be closed by the PRMC at annual evaluation.
- Studies that have met 26%-50% of the accrual target at one full accrual year from activation may be asked to submit a remediation plan and the committee will vote on whether the study should be closed. If the committee votes to approve the remediation plan, the study will be re-reviewed in 3 months’ time.
- If the PI has not met 75% of the target accrual in that time, another remediation plan must be submitted and the committee will vote on whether to extend the trial for another 3 months or close the study. If PI fails to meet 75% of the target accrual after the second 3-month extension, the study will be closed by the PRMC.
- Studies that have enrolled more than 50% of subjects at 1 year will be given an additional 6 months to bring accrual up to 75%. If this goal is not met, the PI will be required to submit a remediation plan. The committee will vote on whether to extend the trial for another 3 months or close the study. If PI fails to meet 75% of the target accrual after the additional 3-month extension, the study will be closed by the PRMC.
Amendments

All sponsor initiated protocol amendments must be submitted to the PRMC for review and approval. The principal investigator must summarize and provide justification of the proposed revisions. Review of amendments will be sent to the same primary and secondary reviewers that initially reviewed the study. If the reviewers are unavailable, the chairs will designate another reviewer. If there are changes to the statistical section, Bio statistical review of the changes is required. Unless there are changes to risk level or significant changes to the study design, amendments are reviewed administratively and a response is sent to the PI within 5 business days. Amendments involving change in risk level or study design change will require a full committee review.

Data and Safety Monitoring Committee (DSMC)

Overview

The Data and Safety Monitoring Committee (DSMC) of the Laura and Isaac Perlmutter Cancer Center (PCC) at NYU Langone operates based on the NCI approved Charter. The DSMC is responsible for monitoring safety, conduct and compliance with protocol for cancer clinical trials that are not monitored by any other institution or agency.

The scope of DSMC reviews include Phase 0, Phase I, Phase II, Phase I/II studies, and Phase III studies that are:
- PCC Investigator Initiated protocols
- NCI Protocols – not monitored by NCI
- Multi-center clinical trials (Phase 0, Phase I, II & III with PCC as coordinating center) that fall within these categories.

Membership

The DSMC membership consists of clinical investigators/oncologists who are members of the PCC, biostatisticians from the PCC Biostatistics Shared Resource (BSR), DataCore personnel and Clinical Trials Office (CTO) support staff. The membership list below illustrates the voting and non-voting members of the DSMC.

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<thead>
<tr>
<th>DSMC Voting Members</th>
<th>Role</th>
<th>Discipline</th>
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<tbody>
<tr>
<td>Sylvia Adams, MD</td>
<td>Chair</td>
<td>Medical Oncology</td>
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<tr>
<td>Anne Zeleniuch-Jacquotte, M.D., M.S.</td>
<td>Co-Chair</td>
<td>Biostatistician</td>
</tr>
<tr>
<td>Mohammad Maher Abdul Hay, MD</td>
<td>Member</td>
<td>Medical Oncology</td>
</tr>
<tr>
<td>Benjamin Cooper, MD</td>
<td>Member</td>
<td>Radiation Oncology</td>
</tr>
<tr>
<td>Franco Muggia, MD</td>
<td>Member</td>
<td>Medical Oncology</td>
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Deirdre Cohen, MD  
Raoul Tibes, MD  
Samer Al-Homsi, MD  
Kenneth B. Hymes, MD  
Jean K. Lee, MD  
Judy Zhong, PhD  
Naamit Gerber, MD  
Zujun Li, MD  
Kaleb Yohay, MD  

Non-Voting Members  
Erica Love, MA, MPH, CCRP  
Nida Cassim, MPH  
Kanika Ballani, Pharm D  
Tsivia Hochman, M.S.  
Benjamin Levinson, Ph.D  
Anne Martocci  
Alexander Bragat  
Amit Gupta  
Fraustina Hsu  

Types of Trials Monitored

If a trial is already being reviewed by another data and safety monitoring committee (such as those formed by a national cooperative group, NCI, pharmaceutical sponsor, or study specific committee for a phase III trial) the PCC DSMC does not actively monitor the trial. More specifically, the scope of the PCC DSMC review includes Phase I, Phase II, and Phase I/II studies that are:

- NYU Investigator – Initiated protocols
- Any phase I and/or II multicenter clinical trials where the PCC serves as the data coordinating site.

Timing of Review

Phase I/II Dose Finding Trials: All phase I/II IITs are reviewed by the DSMC per the protocol defined data and safety monitoring plan (which has previously been approved by both the NYUCI PRMC and IRB) or
at least annually (from the date the first patient is enrolled). Internal monitoring occurs after the first three patients accrued have completed one cycle to ensure study integrity (protocol compliance and up to date data entry). Summary reports of these findings are submitted to the DSMC for review at the monthly meeting. Prior to a dose escalation, the investigator must submit a written rationale for escalation, including adverse events experienced in the current cohort, to the DSMC. In addition, the study must be reviewed by DSMC in order to move to the phase II portion of the trial if applicable at the end of phase I (after the last patient has completed treatment or has been removed from the trial for other reasons) when the recommended Phase II dose (RPTD) is identified.

Phase I Non-Dose Finding Trials: All Phase I non-dose finding trials (e.g., safety trials, immunogenicity trials) are monitored by DSMC per the protocol defined data and safety monitoring plan (which has been previously approved by both the NYUCI PRMC and IRB) or at least annually (from the date the first patient is enrolled) and at the conclusion of the study prior to study closure. Internal monitoring occurs after the first three patients accrued have completed one cycle to ensure study integrity (protocol compliance and up to date data entry). Summary reports of the monitoring findings are submitted to the DSMC for review at the monthly meeting.

Phase II Trials: All phase II trials are monitored by DSMC per the protocol data and safety monitoring plan (which has been previously approved by both the NYUCI PRMC and IRB) or at least annually (from the date the first patient is enrolled), at times of planned interim analyses (e.g., 2 Stage Simon Design), and at the completion of the study prior to study closure. Internal monitoring occurs after the first three patients accrued have completed one cycle to ensure study integrity (protocol compliance and up to date data entry). Summary reports of the monitoring findings are submitted to the DSMC for review at the monthly meeting. Additional interim reviews can be scheduled based on SAE reports, investigator identified issues, external information, etc.

**DSMC Review Process**

To facilitate DSMC reviews, a set of standard reports has been developed by the Biostatistics Shared Resource and implemented by the CTO. These reports are provided to the Committee at the time of review. All patient data are de-identified in these reports in compliance with HIPAA regulations.

The PI is present for the open portion of the DSMC review to present a summary of the status of the study. The most recent version of the protocol and amendments are made available for the review. A closed session is then held for committee members only and a recommendation is provided to the investigators. The DSMC may have questions for clarification by the study PI before a final recommendation is made. Possible recommendations resulting from the DSMC review are:

- **Full Approval:** study continues with no modifications required.
- **Conditional Approval:** modifications and/or clarifications are required prior to obtaining the DSMC’s full approval and enrollment may proceed as scheduled.
- **Suspension of Accrual:** enrollment is to be suspended immediately pending PI’s response to any DSMC concerns.
- **Closure:** study is to be closed.

Written responses by all PI’s are required for all questions within two weeks of the DSMC meeting. These responses are tracked and delinquent responses are identified to the Associate Director and Administrative Director of the PCC CTO for follow-up. DSMC summary recommendations are included in
the minutes of the DSMC review. DSMC reports, including the review and recommendations, are filed at the CTO in individual study files located on the protected CTO server.

Conflicts of Interest

The committee is composed of two co-chairs, if one is conflicted the other is will lead the discussion. If a financial or scientific conflict of interest arises for a chair or committee member (investigator, study team member) that committee member, or the chair, is excluded from the voting process. The individual with the COI is allowed to be present in the room for the open forum discussion, along with the principal investigator if it is a different person. However, during the closed-door session, the committee member with the COI is excused from the room and must abstain from all voting procedures related to the study outcome. Following the rules and procedures of the NYU Langone Medical Center IRB, the member’s absence from the room and voting, are documented in the DSMC minutes. The committee member is allowed to return to the room when all voting has completed and a final decision has been rendered and documented in the official minutes. A quorum consisting of a minimum of four voting members including one biostatistician, one clinician and one chair is required for the meeting to proceed. If multiple members of the committee have a COI, ad hoc members are recruited to meet the required minimum number for a quorum.

Guidance for protocol Specific Data and Safety Monitoring Plan (DSMP) by Level of Risk and Type of Trial

The DSMP for each trial is tailored to the nature, size and complexity of the research protocol and must also consider the expected level of risk of the research. Level of risk is determined by the PI with the assistance of the CTO Quality Assurance Unit (QAU) and is ultimately approved by the PRMC and DSMC. The PI and QAU will assign one of the risk levels outlined in Table 2 to be approved by the PRMC prior to study activation. Post study activation, the DSMC may identify an unexpected increase in the severity of toxicity and retains the authority to request a study amendment be processed to change the risk level of the study and possibly the protocols DSMP for added protections. In this case the protocol amendment would require re-review by both the PRMC, and the IRB.

A protocol specific DSMP is required for all studies that are:

- Considered greater than minimal risk
- Multi-site trials for which the PCC or any of its affiliates is the coordinating center
- Otherwise required to have a DSMP by the Food and Drug Administration (FDA) or National Institutes of Health (NIH)
- Determined by the NYU Langone Medical Center IRB to require a DSMP

Each trial is initially reviewed by the PRMC to ensure the following points are adequately addressed in the DSMP, should one be required:

- Procedures are in place to ensure the safety of subjects in accord with the level of risk
• An adequate bio-statistical design is present to ensure the data is captured correctly and adequately for statistical evaluation
• A realistic and adequate time span is allotted to meet target accrual based on the eligibility criteria and patient population
• Proper AE reporting instructions are included in the protocol
• For multi-site studies for which NYU is the lead or coordinating institution, an operational plan (addressing how dose escalations will be monitored across institutions, how adverse events will be reported in a timely manner to the PI and DSMC, how summary reports will be dispersed to sites and their IRB’s, etc.) ensuring proper oversight is required.

If the Investigator/Sponsor has not adequately addressed the above listed points, the trial is deferred for review until the proper modifications have been made, at which time the study is placed on enrollment hold and scheduled for re-review by the PRMC.

The monitoring level and frequency of DSMC review will correspond to the protocols given risk level determination. It is important to note that the phase of the study does not necessarily correlate to the risk determination, the phase of the study is taken into consideration, but is not the only determining factor. In addition to the study’s phase, its complexity, length, population, drug/device associated toxicity profile and study-specific safety measures are all taken into consideration when determining risk. Studies where an NYU investigator is the holder of the IND/IDE are considered high risk.

Table 1. Level of Monitoring for Interventional Therapeutic Trials

<table>
<thead>
<tr>
<th>Risk Determination</th>
<th>Data and Safety Monitoring Plan</th>
<th>Frequency of DSMC Review</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minimal Risk:</strong> No investigational intervention with a participant, such as observational studies to increase awareness or health promotion studies.</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Low Risk:</strong> The probability of participant harm or discomfort is minimal and/or is no greater than those encountered during routine assessments or examinations (i.e. standard of care procedures)</td>
<td>Quarterly interim monitoring visits</td>
<td>Annually</td>
</tr>
<tr>
<td><strong>Moderate Risk:</strong> Investigational interventions that anticipate severe toxicity in most participants and are not considered standard of care management. For example, multi-site Phase II-III therapeutic studies</td>
<td>Interim monitoring visits beginning within the first 6-8 weeks of first subject enrollment and every 6-8 weeks thereafter</td>
<td>Semi-Annually</td>
</tr>
<tr>
<td><strong>High Risk:</strong> Investigational interventions that anticipate life-threatening toxicity in a majority of participants and are not considered standard of care management. For example, Phase 1 dose-finding studies, gene therapy studies, and all studies for which an NYU investigator is the holder of the IND/IDE</td>
<td>Extensive monitoring by QA Specialist including real-time review of all eCRFs to ensure completeness and compliance with the protocol (100% source documentation verification). Additionally, a first subject audit is to be conducted within four weeks of enrollment. Results of routine monitoring are reported to PI and DSMC and when compliance matters are identified to the appropriate regulatory</td>
<td>Quarterly or as described in study-specific DSMP. For Phase 1 studies, outcome data are presented upon completion of each cohort</td>
</tr>
</tbody>
</table>
Data and Safety Monitoring for Non-NYU Initiated Trials

NCI Sponsored Cooperative Group Trials: Phase I, II and III cooperative group trials are monitored by established data and safety monitoring committees at the cooperative group level. The studies are not monitored by the NYU DSMC however they are monitored for progress by the PRMC. These studies are also included in the reviews conducted by the IAC. The IAC also conducts on site monitoring after the first two patients on each trial are enrolled and treated.

NCI or CTEP Sponsored Phase I and II Trials: Phase I and II NCI or CTEP sponsored trials are monitored by the NCI. Early phase I trials are monitored by the Clinical Trials Monitoring System (CTMS) contracted by Theradex, Inc. Later Phase I trials may be monitored quarterly via the Clinical Data Update System (CDUS). These trials are not monitored by the PCC DSMC but are monitored for progress by the PRMC. These studies are also included in the reviews conducted by the IAC.

All Phase Investigator Initiated Trials: Phase I and II Investigator Initiated trials must follow specific multi-level data and safety monitoring plans. Depending on the level of risk assigned by the PRMC, Phase I investigator initiated trials are monitored by the DSMC at least quarterly and Phase II are monitored at least semi-annually; however, usually more often as required per the protocol stopping rules or interim analyses. These trials are monitored for scientific soundness and progress by the PRMC initially and annually, and are monitored for safety and progress by the assigned PCC QA Specialist in accordance with their approved monitoring plan. In addition, these studies are included in reviews conducted by the IAC and are continually monitored for progress and safety at the DMG level.

Level of Monitoring for Non-Therapeutic, Interventional Studies

Studies that are non-therapeutic and interventional are reviewed initially and annually for scientific soundness and progress by the PRMC and NYU Langone Medical Center IRB. These studies are treated on a case by case basis and may be required to be annually reviewed by the DSMC should the risk be deemed to be more than minimal. These studies are also monitored at the DMG level. The assigned QA specialist will review and monitor the data on a quarterly basis to ensure overall data integrity and to ensure studies are progressing as planned.

Level of Monitoring for Non-Therapeutic, Non-Interventional Studies

Studies that are non-therapeutic and non-interventional (cancer control, quality of life, epidemiological, smoking cessation, risk assessment and archival tissue research studies) are reviewed initially for scientific soundness by the PRMC followed by an initial and annual review by the NYU Langone Health Institutional Review Board (IRB). Subsequently these studies are monitored annually for progress by the PRMC. These studies are also monitored weekly at the DMG level.

Monitoring Entity
The monitoring entity must be described in the DSMP submitted with the New Protocol Application. The monitoring entity is an identified individual or group assigned to conduct interim monitoring of data from research activities to assure the continuing safety of research participants, relevance of the study question, appropriateness of the study, and integrity of the accumulating data. Membership should include expertise in the relevant field of study, statistics and research design. The monitoring entity might be the Principal Investigator (PI), a Data Monitoring Board, or an equivalent body such as an industry-sponsored Data Monitoring Committee (DMC), an NIH sponsored cooperative group, a coordinating or statistical center, a monitoring committee formed by a sponsor other than NIH, or a Medical Monitor (an individual rather than a DMC). Depending on the needs of the study monitoring can be any of the following:

**Investigator:** The PI has ultimate responsibility to monitor their trial in real time. Continuous monitoring of events by the investigator, and prompt reporting of significant, unanticipated toxicity to the IRB, DSMC and, when applicable, the FDA, NIH or others, is mandatory. Regardless of DSMP’s by the sponsor or others, the PI is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care and for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

**Monitor/Monitoring Group:** A qualified and objective individual or group not directly involved with the design and conduct of the study (e.g., safety officer, designated Medical Monitor or Monitoring Group) could perform this function. These individuals may or may not be employees of the PCC or Medical Center or its affiliates or the study sponsor. However, conflict of interest is an important consideration when employees of the study sponsor have the primary responsibility for monitoring data from the standpoint of scientific integrity and participant safety. This type of plan is often appropriate to monitor data and safety for research studies that involve:

- endpoints that are not serious irreversible events;
- an intervention (for example, to relieve symptoms) that is not high risk and the effects of which would not generally be so compelling as to ethically warrant early termination for effectiveness;
- short term treatments where effects are evaluated over periods of a few days to a few months; and
- a smaller number of subjects where the study is completed quickly and the risk can be adequately assessed through simple comparisons.

In these studies, valuable secondary objectives such as characterization of the effect (i.e., magnitude, duration, time to response), assessment of the effect in population subsets, comparison of several doses/or comparison of the new product to an active control can be ethically pursued even when the conclusion regarding the primary efficacy outcome is clear. Early termination for effectiveness is rarely appropriate in such studies. First, the study may be essentially completed by the time any interim analysis to evaluate effectiveness could be undertaken. Second, the effectiveness of an intervention, for example, to relieve symptoms, would not generally be so compelling as to override the need to collect the full amount of safety data, or to collect other information of interest and importance that characterizes the effect.
Data and Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC): An independent Data and Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC) external to the trial organizers and investigators could perform this function. A DSMB/DMC is a formal committee that is established specifically to monitor data throughout the life of a study to determine if it is appropriate, from both the scientific and ethical standpoint, to continue the study as planned. In general, an independent DSMB/DMC is the most appropriate way to monitor data and safety for studies that involve:

- **Large numbers of subjects** where risk may better be accessed through statistical comparisons of treatment groups;
- **Blinded study treatment groups** where the validity and integrity of the study may be adversely affected by having an individual or group associated with the design and conduct of the study break the blind;
- **Multiple clinical sites** where there is a need for investigators to submit reports of adverse events to a central reporting entity, such as a coordinating center or statistical center, responsible for preparing timely summary reports of adverse events for distribution among the clinical sites, and to the IRBs;
- **High risk interventions** where death or severe disability is a major risk of research participation; and/or
- **Controlled trials with mortality or major morbidity as a primary or secondary endpoint** where increased morbidity or mortality may better be accessed through statistical comparisons of morbidity or mortality among treatment groups. DSMBs/DMCs are typically made up of individuals who have expertise in the field, experience in the conduct of clinical trials, and/or statistical knowledge, and who do not have any serious conflicts of interest, such as financial interests that could be substantially affected by the outcome of the trial, strong views on the relative merits of the interventions under study, or relationship with the sponsor or those in trial leadership positions that could be considered reasonably likely to affect their objectivity.

DSMBs/DMCs meet at least annually or more often depending on the nature of the trial being monitored. DSMBs/DMCs can monitor the timeliness of accrual (also assessed yearly by PRMC and more frequently by the Phase I/II Committee for appropriate studies), the quality of data collection and management (primary responsibility of the IAC), and the accumulating outcomes to assure the safety of participants and the scientific integrity of the study (in concert with IRB).

A DSMP is not required for research protocols that involve no more than minimal risk. No more than minimal risk is defined at the PCC as “The probability and magnitude of harm or discomfort anticipated by participating in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.” Trials that fall under this category must submit a summary of overall accrual to the PCC CTO annually for review by the PRMC. In addition, these trials are required to be submitted to the NYU Langone Medical Center IRB annually for continuing review.

Quality Assurance Unit and Internal Audit Committee (IAC)

The Internal Audit Committee (IAC) conducts quality assurance audits quarterly and is comprised of 1 chair (physician), nurses and CTO management staff, and conducts bi-annual audits on all PCC studies. Biostatistics randomly selects at least 10% of subjects enrolled in the past 6 months to be audited, at least one study per DMG, and designated reviewers will review each subject chart with regards to the following elements:

- Informed Consent process
- Screening and Eligibility
- Protocol compliance with regards to treatment, reporting of adverse events, and study procedures
- CRF Data Quality
- Regulatory Compliance

The 2017 NCI CTEP guidelines are used to classify deficiencies as critical, major or lesser. Based on these findings, the audit is categorized as Acceptable, Acceptable needs follow-up, or Unacceptable.
For-cause audits may be performed if concerns are raised regarding timeliness of data input, research staffing or study conduct. This may also occur per the recommendations of the Data Safety Monitoring Committee (DSMC) or per the request of the Clinical Trials Office Oversight Committee (CTO-OC).

The audit assessment is summarized and sent to each PI and research team being audited. If the findings are “Unacceptable” the IAC has the power to immediately suspend the trial from further enrollment until an acceptable corrective action plan is put in place by the PI. For findings that are “Acceptable, Needs Follow Up” the PI is required to submit a response with explanations and a corrective action plan within two weeks of receiving the audit assessment. If a response is not provided within the two-week time frame the PI will receive a warning letter stating the trial will be suspended from further enrollment if their response/corrective action plan is not received within 7 days. If a response is still not received after the 7-day time frame per the warning letter the IAC has the ability to suspend the trial from further enrollment. The Investigator, the IRB, CTO, and sponsoring entity are immediately notified of study suspension. In this instance, the CTO works with the Investigator and Research Team to address the deficiencies. All audit findings along with PI responses/corrective action plans are reviewed collectively by senior leadership at CTO-OC. The IAC works with the DMG to ensure any “reportable” findings (any protocol violations/deviations/adverse events that are harmful (to the patient), related (in any way to participation on the trial) and unexpected), as defined by NYU Langone Medical Center IRB are promptly reported to the NYU Langone Medical Center IRB. Unacceptable findings are reported to DSMC at the next scheduled review. Studies are automatically scheduled for re-auditing if the initial audit yields and unacceptable or Acceptable, Needs Follow Up finding after 3 additional patients have been enrolled to assess whether the corrective action plans were implemented and successful.

**Adverse Event (AE) Reporting Compliance**

**Adverse Event Reporting and Monitoring by Trial Sponsorship Type**

Investigators are required to report all adverse events occurring during the course of a clinical trial to the appropriate regulatory body or bodies. If the event is unanticipated, expedited reporting is mandated. The steps taken within the PCC to ensure proper reporting of adverse events are described below by type of trial. Additionally, further detail regarding the internal monitoring and review of these events are outlined. Both the IRB and the DSMC have the authority to suspend further enrollment until any concerns related to the event are addressed. In addition, the IRB has the authority to close the study immediately if they determine there has been an unacceptable level of risk to the subjects. A flow diagram is attached to visually supplement the following written description of our process for reporting and monitoring serious adverse events (Appendix III).

**Investigator Initiated Trials:**

**NYULMC IRB:** The IRB reviews Reportable Events in an expedited manner as they occur during the course of a clinical trial. A Reportable Event is defined by the IRB as any adverse event that is related or possibly related, unanticipated and the event places subjects at a greater harm than previously known and/or requires changes to the conduct of the study. When the investigator becomes aware of an event the study team is notified. If the event meets the criteria as being reportable to the IRB or meets the criterion of being serious per the protocol, details of the event (grade, expectedness, attribution etc.) are entered into the protocol-specific database and the PCC Medical Events Form is completed and scanned into EPIC. The safety officer is triggered to review these events to determine with the investigator whether the event needs to be submitted to the IRB. If the event is considered reportable a report is generated and submitted to the IRB within 24 hours of the staff’s awareness of the event. The IRB also reviews a cumulative report of all reportable events per trial at the annual continuing review. The IRB may decide to stop further accrual or require follow up from the investigator if they deem the level or frequency of toxicity to be unanticipated.
**Per Protocol:** Any event considered serious or reportable per the protocol is submitted to the proper regulatory body per the protocol. For trials involving commercially available agents only (no IND involved) serious adverse events are reported through Food and Drug Administration Medwatch (http://www.fda.gov/medwatch/index.htm).

**DSMC:** All adverse events are monitored per the protocol’s data and safety monitoring plan and/or at time points predetermined by the type of protocol (outlined in Data and Safety Monitoring Committee (DSMC) section) or at least annually. Reports that include every event regardless of grade, expectedness and attribution as well as reports that are specific to grade 3 and 4, and reports that are specific to those events considered serious or reportable are generated for DSMC review. SAEs are reported via email to the safety officer, who then forwards the SAE report to the study’s designated primary reviewer and DSMC Chairs for review. One of three determinations will be made by either the reviewer or the DSMC chairs:

- Send queries for clarification to PI regarding treatment attribution and/or resolution of SAE or completeness of other information. The reviewer may request a cumulative review of all SAEs on the study to date.
- SAE report is considered to be adequate.
- Request for full DSMC committee review of protocol, based on SAE reports, at the next scheduled meeting.

**Industry Trials:**

**NYULMC IRB:** The IRB reviews Reportable Events in an expedited manner as they occur during the course of a clinical trial. A Reportable Event is defined by the IRB as any adverse event that is related or possibly related, unanticipated and the event places subjects at a greater harm than previously known and/or requires changes to the conduct of the study. When the investigator becomes aware of an event, the study team is notified. If the event meets the criteria as being reportable to the IRB or meets the criterion of being serious per the protocol, details of the event (grade, expectedness, attribution, etc.) are recorded on either a sponsor-specific SAE form or the PCC Medical Events Form and scanned into EPIC. The assigned Regulatory Specialist works with the investigator and/or Research Nurse to review these events to determine whether the event needs to be submitted to the IRB. If the event is considered reportable a report is generated and submitted to the IRB within 24 hours of the staff’s awareness of the event via the Research Navigator System. The IRB also reviews a cumulative report of all reportable events per trial at the annual continuing review. The IRB may decide to stop further accrual or require follow up from the investigator if they deem the level or frequency of toxicity to be unanticipated.

**Per Protocol:** Any event considered serious or reportable per the protocol is submitted to the proper regulatory body per the protocol. This may include reporting via MedWatch reports, or reporting directly to the sponsor or CRO should one be involved.

**DSMC:** Industry trials are generally monitored by an outside data and safety monitoring committee and thus are not reviewed by the PCC DSMC. These AE’s and SAE’s are reviewed at a frequency pre-determined by the industry’s data and safety monitoring committee.

**Cooperative Group and NCI Trials:**

Adverse Event (AE) reporting is conducted in accordance with the NCI Guidelines for Investigator’s on Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP Investigational Drug’s (INDs) and Investigational Devices (IDEs). (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf).

At the PCC, a Medical Events Form is utilized to capture events and details of events needed to assess whether expedited reporting is required in real time in order to meet NCI adverse event reporting guidelines.
NYULMC IRB: The IRB reviews Reportable Events in an expedited manner as they occur during the course of a clinical trial. A Reportable Event is defined by the IRB as any adverse event that is related or possibly related, unanticipated and the event places subjects at a greater harm than previously known and/or requires changes to the conduct of the study. When the investigator becomes aware of an event the study team is notified. If the event meets the criteria as being reportable to the IRB or meets the criterion of being serious per the protocol, details of the event (grade, expectedness, attribution etc.) are captured on the PCC Medical Events Form and scanned into EPIC and submitted to the IRB via the Research Navigator System. For NCI trials, expectedness is determined by use of the CAEPERS that is included in the protocol. The assigned regulatory specialist is triggered to review these events to determine with the investigator whether the event needs to be submitted to the IRB. If the event is considered reportable a report is generated and submitted to the IRB within 24 hours of the staff’s awareness of the event. The IRB also reviews a cumulative report of all reportable events per trial at the annual continuing review. The IRB may decide to stop further accrual or require follow up from the investigator if they deem the level or frequency of toxicity to be unanticipated.

Per Protocol: Any event considered serious of reportable per the protocol is submitted to the proper regulatory body per the protocol. This may include reporting via AdEERS (Adverse Event Expedited Reporting System) on trials for which the NCI is also the IND sponsor.

DSMC: The PCC conducts a range of NCI sponsored cooperative group trials (listed below) all of which are monitored and mandated by longstanding established data and safety monitoring committees at the cooperative group level. Early Phase I NCI or CTEP sponsored trials are monitored quarterly by CDUS. These cooperative group studies are not monitored by the PCC DSMC.

- Cancer and Leukemia Group B (CALGB)
- Gynecologic Oncology Group (GOG)
- Radiation Therapy Oncology Group (RTOG)
- Southwest Oncology Group (SWOG)
- Children’s Oncology Group (COG)
- Eastern Cooperative Oncology Group (ECOG)
- National Surgical Adjuvant Breast and Bowel Project (NSABP)
- NCI National Clinical Trials Network (NCTN)
- NCI Experimental Therapeutics Clinical Trials Network (ETCTN)

Quality Control Functions to ensure compliance with AE and SAE Reporting

Research Nurses or Clinical Coordinators are educated on proper and timely reporting of AE’s and SAE’s during their training months. They are required to complete adverse event tracking forms and progress notes at every contact with the research patient. This data is scanned in the patient’s electronic medical record which is obtained by the data manager/research coordinator for reporting within two weeks of the patients visit for data entry. In the case of an event that is considered serious or qualifies for expedited reporting, the Research Nurse/Clinical Coordinator is required to complete an internal SAE form and forward to the Research Coordinator/Data Manager within 24 hours of becoming aware of the event. The Data Manager/Research Coordinator must then report the event as required by protocol the same day.

To ensure proper AE and SAE reporting, continuous monitoring occurs at the DMG level weekly in which the research nurse/clinical coordinator meets with the data manager/research coordinator and investigators to review research cases. IITs are monitored by the assigned QA specialist every 6-8 weeks or more frequently if written in the studies DSMP after the first subject enrollment. Industry sponsored trials are monitored by a representative sent from the sponsor or Clinical Research Organization (CRO) every 4-6 weeks to ensure all AE and SAE’s have been reported.
Collecting and Reporting AE’s and SAE’s occurring on Multicenter Studies for which NYU is the Lead Institution:

When NYU is the lead institution or coordinating institution of a multicenter study a plan for obtaining all documentation must be established and presented to each institution at each Site Initiation Visit. Sites are required to submit all de-identified medical records related to the patient’s participation in the research study along with completed NYU Adverse Event Tracking forms and Tumor Measurement Forms when applicable within two weeks of the patients visit. Outside sites are required to report SAE’s or adverse events that require expedited reporting to NYU via the PCC External Sites Medical Events Form in addition to the other protocol required reporting and reporting required within their own institution. The SAE is then processed within NYU accordingly. All data received from outside sites is entered into the database utilized by NYU and are reported at least semi-annually to the DSMC. If sites do not submit data properly or within the predetermined two-week time span, the PCC CTO may instruct the site to hold any further enrollment until data is received. Upon DSMC review, results are communicated to each institutions PI and assigned regulatory coordinator. In addition, DSMC review results are reported to NYU IRB at each annual review. All IND safety reports that are received at NYU are also forwarded to each sites PI and regulatory coordinator instructing them to review each document and report to their institutional IRB’s.

Conflict of Interest (COI)

Management of study investigators that have conflicts of interest

The conflict of interest process begins through three separate, self-reporting mechanisms. First, any individual participating, or conducting, any research activities at the New York University are required to file an Annual Financial Disclosure with the Conflict of Interest Management Unit (COIMU), under the NYU Office of Compliance. Second, as part of the Institutional Review Board application for each submission, an investigator is queried about current or potential conflicts of interest. Further, at the initiation of each study, all study team members are required to complete an Investigator Financial Disclosure form, which are then maintained by the Conflict of Interest Management Unit. Study team members, as defined by the IRB, are key research personnel who:

• Design, conduct or direct the research
• Apply for grants or awards to perform research
• Serve as a principal investigator, co-investigator or sub-investigator
• Enroll subjects
• Obtain consent from human subjects
• Make decisions related to eligibility of human subjects
• Analyze, report, present or publish research data

The process of evaluating COI begins with the IRB. No new proposal or continuation is considered complete, or allowed to be reviewed by the IRB, unless the Annual Disclosure Form and Investigator Financial Disclosure Form are completed and accompanying the submission. At the time of a proposal or continuation submission, any self-disclosed conflicts of interest are reviewed and sent to the Conflict of Interest Management Unit, which is a university-wide division, under the NYU Office of Compliance. The study is placed on hold at the IRB level until a determination is rendered by the COIMU.

Once the COI is submitted to the COIMU, a review of the conflict is conducted based on the nature of conflict. A supplemental form, requesting more extensive details of the conflict, is provided by the investigator to the COIMU.

If a COI is financial in nature and under $10,000 the COIMU will make a determination, in writing and submit to the IRB. If the COI is over $10,000, involves intellectual property with potential gains, not limited to, licensing and commercial use, it will be sent to the NYULMC Research Conflict of Interest Committee. This committee meets
monthly to review all COI above the $10,000 threshold. The committee reviews the COI, makes a determination—management of the conflict or elimination of the investigator or sponsored project. This determination is submitted in writing to the IRB. Determination letters from the committee are also sent to the investigator with the COI and the principal investigator of the project.

If the investigator is permitted to participate in the project, after review, they are subject to a conflict of interest management plan that maintains research integrity and serves the best interests of subjects enrolled in the study. The COI management plan may include disclosure in the informed consent form as well as disclosure in publications or presentations developed as a result of the research. The plan, which must be agreed upon by the investigator with the COI and the principal investigator of the project, are subject to review of the IRB. Violations of this policy are subject to disciplinary actions, including termination of employment or association with the medical center. This policy may be viewed at http://webdoc.nyumc.org/nyumc/files/cmu/u5/cy_on_COI_in_Research_and_Sponsored_Programs.pdf.
Appendix I: Adverse Event Reporting and Monitoring Flow Diagram
Appendix II: Committee Structure and Relationships: Clinical Research Oversight for the Safety of Clinical Research Participants

NYU Langone Health Institutional Review Board (IRB)
- Promote and protect the welfare of human subjects
- Initial ethical review
- Continuing ethical review
- Review of AEs and other Unexpected Events

Clinical Trials Office Oversight Committee (CTO-OC)
- Evaluates progress toward institutional, center and NO defined clinical research related benchmarks
- Reviews and approves SOPs
- Reviews quarterly IAC results and DSMMC and PRMC activity
- Reviews and approves incremental resource requests

 Protocol Review and Monitoring Committee (PRMC)
- Initial scientific review
- Initial bio-statistical review
- Assessment of ability to meet target accruals goals relative to PCC catchment area
- Protocol amendment review
- Prioritization for activation
- Resource request review
  - IITs
  - Risk level review
- Protocol DSMFR review

Protocol Development and Monitoring Unit (PDMU)
- Assist investigators with protocol development
- Administrative support of the PRMC

Clinical Trials Office (CTO)
- Regulatory Affairs Unit
  - Provides regulatory support to investigators and DMOs
    - IRB, IRIS, FDA submissions
- Business Operations Unit
  - Provides Medicare Coverage Analysis and budget development and negotiation support to investigators
  - Ensures overall billing compliance
- Data Coordination Unit
  - Provides data management support to investigators and DMOs
  - Provides real-time data entry and supports external routine monitoring
- Clinical Coordination Unit
  - Provides recruitment support to investigators and DMOs
  - Help with informed consent eligibility, protocol adherence, etc.

Data and Safety Monitoring Committee (DSMMC)
- Initial risk level review
- Initial protocol specific DSMP review
- Routine safety review
- Review of QAU and IAC results
- Study level safety assessments
- Dose escalation assessments
- AE and Unexpected Event review

Internal Audit Committee (IAC)
- BI-annual auditing for compliance:
  - Regulatory, treatment administration, protocol adherence, data integrity, response, informed consent, eligibility
  - Evaluation and communication of results

CTO Quality Assurance Unit (QAU)
- Assist investigators with protocol development
- Routine monitoring for data integrity and compliance
- CTO staff training and education
- Administrative support of the DSMMC
- CTRP reporting
- Control registrar (eligibility review)
- Multisite trial operations

Disease Management Group (DMG)
- Initial protocol review
- Feasibility assessment
  - Applicability to catchment area
  - Research eligibility assessment
  - Logistic feasibility
  - Group level prioritization
- IITs
  - Protocol risk level assessment
  - DSMFR review