

**Herbert Irving Comprehensive Cancer Center
Columbia University Medical Center**

DATA AND SAFETY MONITORING PLAN

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Summary

The Herbert Irving Comprehensive Cancer Center (HICCC) considers the safety of participants in clinical trials to be an extremely high priority.

For purposes of this plan, a clinical trial is defined operationally as a prospective study involving human subjects designed to answer specific questions about the effects of a particular biomedical or behavioral intervention, which may include drugs, treatments, devices, behavioral or nutritional strategies. Participants in these trials may be patients with cancer or people without a diagnosis of cancer, but at risk for cancer.

Various individuals and committees are responsible for ensuring that monitoring of different types of trials is timely and effective. The HICCC Director and the Associate Director hold the overall responsibility for data and safety monitoring. Others with data and safety monitoring responsibilities include the HICCC Protocol Review and Monitoring Committee (PRMC), the Data and Safety Monitoring Committee (DSMC), the Principal Investigator(s) (PI) of NIH grants and contracts supporting clinical trials, and the PIs of individual clinical trials.

The method and degree of monitoring will vary depending upon the phase of the study and the degree of risk encountered by subjects.

The HICCC Data and Safety Monitoring Plan has been designed to ensure that all clinical trials implemented at our center are of high quality, are routinely monitored, and that our reporting techniques fulfill sponsor, institutional, and governmental requirements.

DATA AND SAFETY MONITORING PLAN

Introduction

The Herbert Irving Comprehensive Cancer Center (HICCC) considers the safety of participants in clinical trials to be among our highest priorities. In accordance with NIH policy, every interventional trial conducted at the HICCC must include a plan for data and safety monitoring, including descriptions of data to be collected and adverse event reporting procedures. The HICCC Data and Safety Monitoring Committee (DSMC) is responsible for, and dedicated to, data and safety monitoring of ongoing clinical trials. The DSMC is separate and distinct from the HICCC Protocol Review and Monitoring Committee (PRMC), which oversees scientific quality and resource utilization for cancer clinical trials.

The HICCC DSMC originally received NIH approval in 2002. The DSMC monitors the safety and conduct of existing therapeutic trials, focusing on local investigator-initiated clinical trials. Additional studies may be considered for oversight by the HICCC DSMC at the discretion of the PRMC, the IRB, or the Principal Investigator (PI). The DSMC can initiate internal monitoring of a specific clinical trial to be conducted by the Clinical Protocol Data Management (CPDM) Compliance Core, and the DSMC reviews and acts on all audits undertaken by the CUMC IRB Compliance Oversight Team (COT).

The responsibilities of the DSMC are to ensure that the monitoring of different types of trials is timely and effective. The HICCC Associate Director oversees the operations of the DSMC. Clinical research at HICCC ranges across all investigative phases and is supported by a broad range of sponsors. Thus, it is essential that the DSMC operate according to the DSM Plan and independently from PRMC, CPDM and other entities.

As of February 2016, there were 331 interventional protocols which were active for accrual or closed to enrollment, including 58 Phase I trials, 42 Phase I/II, 78 Phase II trials, 7 Phase II/III, 113 Phase III studies, 1 Phase III/IV trial, 2 Phase IV trial, 23 Pilot/Feasibility trials, 1 Extension trial, 1 expanded access and 5 interventional trials for which a phase is not applicable. Of the 331 interventional trials that were active at CUMC, 259 were open to accrual. There were 99 National Clinical Trials Network (NCTN, formerly Cooperative Group) trials, 51 investigator-initiated institutional studies, 153 industry-sponsored trials, and 28 externally peer-reviewed protocols at the HICCC. Every effort is made to prioritize investigator-initiated trials.

The HICCC DSMC has the primary responsibility of monitoring all investigator-initiated interventional protocols. As of February 2016, there were 39 active investigator-initiated interventional protocols, including 13 Pilot trials, 6 Phase I trials, 7 Phase I/II trials, 10 Phase II studies, 1 Feasibility, 1 Pilot/Feasibility and two interventional trials for which a phase is not applicable.

The method and degree of monitoring done by the DSMC will vary depending on the phase of the study and the degree of risk encountered by subjects. The HICCC Data and Safety Monitoring Plan (DSMP) has been developed to coordinate and provide

oversight for data and safety monitoring for all interventional trials consistent with the National Institutes of Health Policy for Data and Safety Monitoring dated June 10, 1998 (<http://grants.nih.gov/grants/guide/notice-files/not98-084.html>) with further guidance issued on June 5, 2000 (<http://grants.nih.gov/grants/guide/notice-files/not-od-00-038.html>)

Study investigators and clinical trials staff submit reports of unanticipated problems (UPs) involving risks to subjects or others to the Columbia University Medical Center (CUMC) Institutional Review Board (IRB) or other IRBs of record (WIRB, NCI, CIRB, NCI Pediatric IRB) and the HICCC DSMC for review and recommendation

The Columbia IRB Reporting Unanticipated Problems Involving Risk to the IRB policy may be found at: <http://www.columbia.edu/cu/irb/policies/index.html>

The conduct of the HICCC clinical research is in full accordance with CUMC IRB policy, which may be found at:

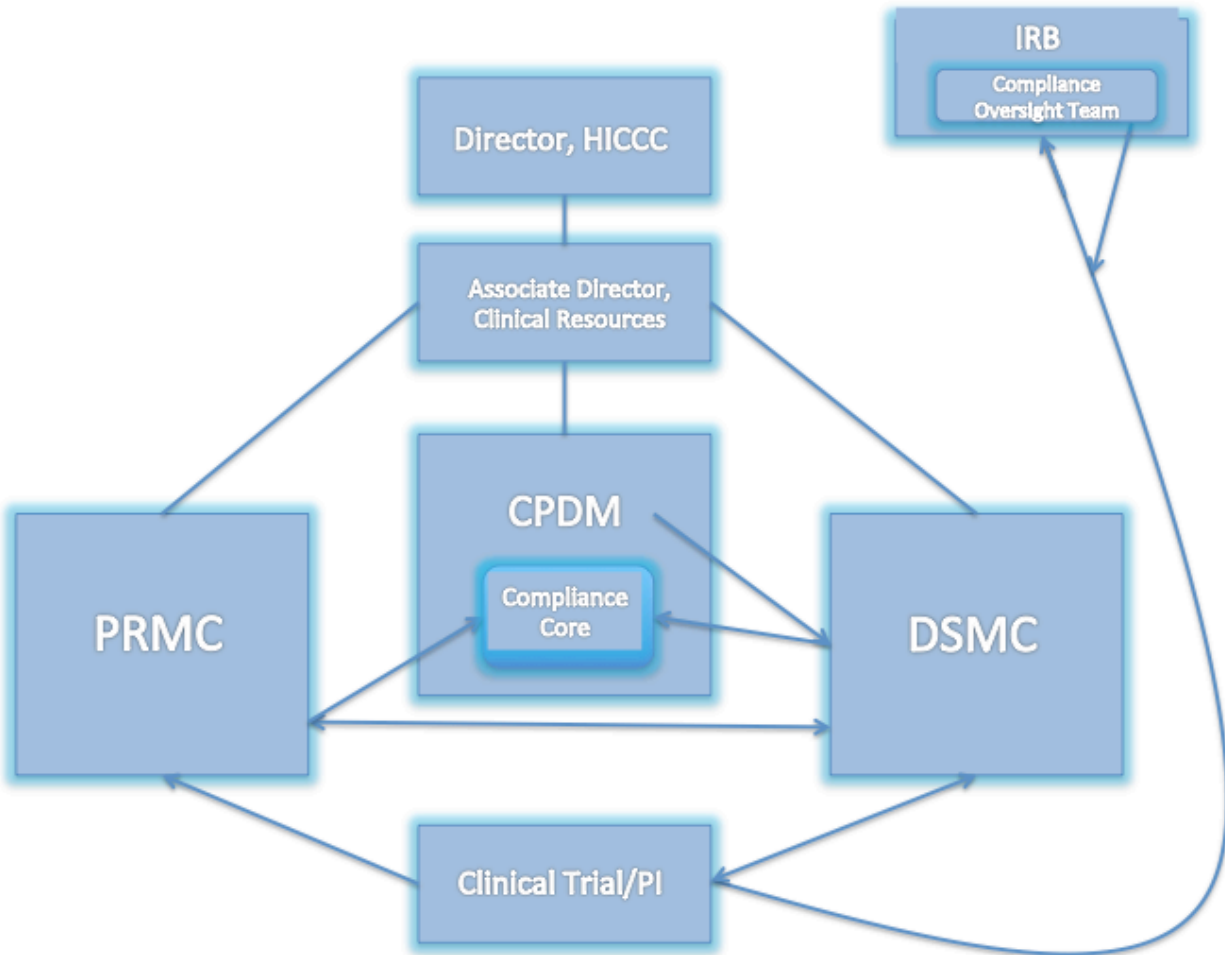
<http://www.columbia.edu/cu/irb/documents/SOPVersion4.2November22012.pdf>

HICCC Data and Safety Monitoring: Organization and Responsibilities

The principal investigator of each study is ultimately responsible for every aspect of the design and conduct of the relevant protocol. The study PI is obligated to ensure that:

- All studies must have a structured adverse event determination, monitoring and reporting system, including procedures for referring and/or treating subjects experiencing unanticipated problems (UP). Investigator-initiated protocols should state that the HICCC DSMC will review UP reports and other issues that are submitted related to participant safety
- Protocols must include the proposed human subjects consent form and describe procedures for protection of human subjects
- All blinded studies should describe a randomization scheme, and if needed, specific criteria and procedures for unblinding
- The schedule for reporting adverse events to the DSMC, the IRB and/or the NIH/FDA must be described. In multi-site studies, the study PI is responsible for notifying sub-sites of problems identified by the DSMC and sending the DSMC reports to individual sub-site PIs, who in turn are required to submit these reports to their local IRBs.

In specific cases where an outside agency is the sponsor of the test agent, i.e., holder of the Investigational New Drug (IND) application or Investigational Device Exemption (IDE), PIs must submit individual UP reports to the funding agency (as sponsor) in accordance with agency and FDA regulations.



Types of Clinical Trials and Monitoring Requirements

The HICCC DSMC Plan has been designed to ensure that all clinical trials implemented at our center are monitored, and that reporting procedures fulfill sponsor, institutional, and governmental requirements. The following levels of monitoring apply to therapeutic trials as well as prevention and behavior modification trials.

Types of Trials

The phase and the degree of risk for the individual trial direct the manner and frequency of monitoring. This section will describe the type of trial and monitoring techniques used in each phase of clinical trial. Listed under each study phase are procedures to follow for studies conducted under the various types of sponsors: NIH/NCI, industry, and investigator-initiated/institutional studies.

NIH/NCI Sponsored Trials/National Cancer Institute National Clinical Trial Network (NCTN) Protocols

The HICCC conducts clinical trials of the Southwest Oncology Group (SWOG), Children's Oncology Group (COG), National Surgical Adjuvant Breast/Colorectal

Program (NSABP), Alliance for Clinical Trials in Oncology, Eastern Cooperative Oncology Group (ECOG), Gynecological Oncology Group (GOG), and Radiation Therapy Oncology Group (RTOG) and their successor cooperative groups such as NRG Oncology.

Local monitoring of UPs and annual safety reports are required per CUMC IRB policy and will occur regardless of the NCTN agency bearing the overall responsibility for data and safety monitoring. The HICCC DSMC may review the UPs and these annual reports and if necessary, will recommend suspension of local participation if patient safety is at risk.

Industry Sponsored Trials

Local monitoring of UPs and annual industry sponsor safety reports are required per CUMC IRB policy and will occur regardless of the outside sponsor bearing overall responsibility for data and safety monitoring. The HICCC DSMC may review the UPs and these annual reports and if necessary, will recommend suspension of local participation if patient safety is at risk.

External Peer Reviewed Trials and Investigator-Initiated Institutional Studies

All pilot, feasibility, Phase I, Phase II, and Phase III externally peer-reviewed and institutional trials initiated by a CUMC investigator are required to use the HICCC DSMC for oversight and monitoring. The DSMC will determine the frequency of monitoring relative to the level of risk. Per CUMC IRB policy UPs must be submitted within specified guidelines for review by the DSMC and the IRB. At the time of renewal the latest DSMC study safety report must be submitted.

The HICCC DSMC will track UPs, SAEs and the toxicity profile of CUMC and sub-site participants and when necessary will recommend suspension or termination of the overall trial or at sub-sites if patient safety is at risk.

Protocol Review and Monitoring Committee (PRMC)

Clinical protocol review is conducted by the Protocol Review and Monitoring Committee (PRMC). The Protocol Review and Monitoring Committee (PRMC) reviews the scientific merit, scientific priorities, and progress of all clinical protocols involving cancer patients at the HICCC. In addition to the scientific review, the PRMC is also responsible for accrual monitoring. The PRMC meets biweekly in coordination with IRB Subpanel 4 (the Oncology Review Subpanel) to review newly submitted interventional protocols. The PRMC has three functions: 1. Review protocol concepts and finalized versions protocols for scientific merit and prioritization to ensure efficient use of HICCC resources; 2. Monitor accrual and scientific progress with the responsibility of deciding upon protocol continuation and the authority to close trials for insufficient progress; and 3. When appropriate, to review and act on reports from the DSMC that have relevance for the scientific integrity of clinical research.

Initial Review

The PRMC conducts full reviews of all new protocols involving cancer treatment or risk intervention. In particular, investigator-initiated institutional studies, industry-sponsored trials, and externally peer-reviewed protocols are subject to full committee review.

NCTN studies and other NCI vetted trials are subject to review regarding feasibility and are administratively approved by the PRMC Chair. The specific elements of the protocol that are addressed by reviewers include, but are not limited to, the merit of the research question, and the innovation of the study design, feasibility, proper allocation of institutional resources, if the appropriate number of patients are available locally, and whether the statistical plan is adequate to test the study hypothesis. The PRMC also ensures that trials do not overlap in eligibility criteria, which may lead to competition for the same pool of patients.

The submission to both the PRMC and the IRB are done simultaneously via RASCAL, the proprietary Columbia University information system for research regulatory management and compliance.

Continuing Review

For all studies, the lead principal investigator is required to submit a continuing review application (CRA or progress report) to the IRB and PRMC 60 to 90 days before the annual expiration date of the IRB protocol. This progress report need to include: 1) the number of subjects enrolled on the trial, 2) the number of subjects treated, 3) a summary of all Unanticipated Problems (UPs) in accordance with the CU IRB UP policy (using current CTCAE grading, including UPs requiring immediate reporting), 4) and significant literature developments that may affect the safety of participants or the ethics of the study.

The PRMC will review continuing renewal applications for all studies before they can be reviewed by the IRB. The PRMC Manager will decide whether or not the study can be administratively facilitated using expedited review criteria. As with new protocols, expedited review for continuing studies is conducted for non-therapeutic protocols involving specimen collection, use of discarded materials, or most observational or epidemiological studies, as well as for therapeutic protocols that are closed to enrollment. Any amendments and/or modifications to the protocol, informed consent, and personnel submitted as part of the renewal application will be simultaneously reviewed. The PRMC will make the judgment as to whether or not the study should continue unchanged, if it requires modification, or if it should be closed based on unacceptable risk to patients or inadequate accrual.

Continuing review generally focuses on any changes in study design, the existence of new data that would significantly affect the original design, overall study accrual, accrual of women and minorities, outcome to date, and safety data for each study. Protocols must be accruing patients at (or close to) the projected rate or the investigator is asked to submit a plan to increase accrual and/or a justification for incomplete accrual. At the time of continuing review, studies with insufficient accrual for which no credible plan is developed for timely accrual or studies that have already achieved accrual goals, are closed to local CUMC enrollment or terminated if no subjects are in long-term follow-up. In addition, the PRMC has a policy that is supportive of rare disease trials based on NCI cancer incidence and prioritizes rare disease trials sponsored by the NCI.

Once the PRMC has approved the renewal, the IRB will review and make their recommendations for continuation, revision, or closure.

PRMC membership

Name	Degree	Title	Field of Expertise and Program Affiliation
Antonio Tito Fojo (Chair)	MD, PhD	Professor of Medicine	Medical Oncology
Mark Frattini (Co-Chair)	MD, PhD	Associate Clinical Professor of Medicine and Experimental Therapeutics	Hematology/Oncology
Jennifer Amengual	MD	Assistant Professor of Medicine	Hematology/Oncology
Diane George	MD	Assistant Professor of Clinical Pediatrics	Pediatric Oncology
Hanina Hibshoosh	MD	Professor of Clinical Pathology	Pathology, Histopathology and Tissue Shared Resource
Moshe Kelsen	MBA	Executive Director	CPDM
Suzanne Lentzsch	MD, PhD	Assistant Professor of Clinical Medicine	Hematology/Oncology
Alyssa Macchiaroli	BSN, RN	Clinical Research Nurse	CPDM
Paula McKinley	PhD	Assistant Professor of Clinical Behavioral Medicine	Psychiatry
Jennifer Oberg	EdD	Director of Research, Developmental Therapeutics Program	Pediatric Oncology
Paul Oberstein	MD	Assistant Professor of Medicine	Medical Oncology
Ran Reshef	MD	Assistant Professor of Medicine	Hematology/Oncology
Naiyer Rizvi	MD	Assistant Professor of Medicine	Medical Oncology
Arindam RoyChoudhury	PhD	Assistant Professor of Biostatistics	Biostatistics
Gary Schwartz	MD	Chief of the Division of Hematology and Oncology	Medical Oncology
Wei Yann Tsai	PhD	Professor of Biostatistics	Biostatistics
Sven Wenske	MD	Assistant Professor of Urology	Urology
Jason Wright	MD	Assistant Professor of Obstetrics and Gynecology	Gynecological Oncology

PRMC Responsibilities for Data and Safety Monitoring

Following protocol activation, the PRMC will:

- As necessary, review HICCC and other sponsor DSMC reports
- Facilitate implementation of HICCC, DSMC recommendations by the HICCC PI and study staff
- As necessary, request that the DSMC provide advice to the study PI on safety issues, data management, quality, analysis, recruitment, retention, and protocol adherence issues that arise over the course of the study and continuation or termination of the study
- Acknowledge reports of serious data discrepancies found by the DSMC, CPDM, or other sources. This acknowledgment should be in writing and include a plan describing the steps that are to be taken next and should be sent to the Principal Investigator, the Chair of the DSMC, the HICCC Director of Clinical Resources, and HICCC CPDM Leadership.
- Ensure preparation and dissemination of a clinical alert in the event of a clinically significant finding. This dissemination should also include informing the IRB and the subjects of this clinical alert and providing them and their health provider with comprehensive information about what may affect the subjects' well-being.
- Reserve the option, at any point in the trial, to obtain an independent audit of a sample of primary subject records for comparison with the trial's regular audit reports.

HICCC Clinical Protocol and Data Management (CPDM) Office

The Herbert Irving Comprehensive Cancer Center (HICCC) Clinical Protocol and Data Management (CPDM) Office centrally administers the implementation and conduct of interventional oncology clinical trials. Clinical research activities are managed under this single reporting structure ensuring uniformity and consistency. The CPDM assist investigators and academic/research staff in implementing oncology clinical trials and provides administrative resources and infrastructure to initiate and sustain investigator initiated, federally funded (NCI consortia), externally peer-reviewed, and industry sponsored clinical research with the highest integrity.

Investigators negotiate sponsored budgets and contracts in cooperation with the CUMC Clinical Trials Office (CTO) and Sponsored Projects Administration (SPA). The CTO also provides investigators and CPDM Administration with monthly financial reports, summarizing the financial details for their sponsored projects.

The HICCC Clinical Informatics Shared Resource (CISR) assists the CPDM with National Cancer Institute (NCI) Clinical Trials Report Program (CTRP) data submissions, including batch uploads. CISR also assists CPDM in providing support for Velos eResearch (clinical trial management software), including new hire and on-going training, investigator-initiated case report form design, interface development, security and oversight, and NCI reporting.

The centralized CPDM allows for efficient and organized staff development and training, timely activation of clinical research protocols, optimal screening and recruitment of patients, data collection and submission, and quality control and compliance oversight. In addition to the Medical Director, the CPDM employs approximately 50 staff.

CPDM Compliance Core Quality Monitoring

The Clinical Protocol Data Management (CPDM) of the HICCC has a Compliance Core tasked with ongoing monitoring of investigator-initiated interventional trials being conducted at HICCC. In addition, through the Compliance Core, the CPDM oversees central subject registration. Central subject registration reduces the likelihood of accruing ineligible participants by verifying that timely, accurate, and complete source documentation is provided during the informed consent process. The central registrars ensure the real time entry of accrual information into Velos.

Externally sponsored protocols (including industry, NCTN, non-CUMC externally peer-reviewed or non-CUMC investigator initiated) that are frequently monitored or audited by the sponsor are not routinely reviewed to avoid duplicative work; however, a summary of deficiencies is requested from the sponsor following each audit visit. The Compliance Core may also monitor such trials if the PRMC, DSMC and CPDM leadership feel that sponsor monitoring is insufficient.

Monitoring of Investigator-Initiated Trials

The CPDM Compliance Core will assign a compliance coordinator as a lead monitor for each investigator-initiated interventional trial at HICCC, regardless of the level of risk. Monitoring is done to verify that trial conduct follows the approved protocol and all federal, state, and local regulations, and that the study data is accurate and complete. For each investigator-initiated trial, the compliance coordinator will follow a Study Specific Monitoring Plan, utilizing the FDA endorsed Risk Based Monitoring (RBM) approach. Critical data points and identified areas of compliance will be reviewed.

Initial monitoring will take place after the first few subjects are enrolled and ongoing monitoring will be performed based on a Study Specific Monitoring Plan. The DSMC, PRMC, CPDM leadership, or the PI may request more frequent monitoring. On an ongoing basis, the compliance coordinator will review previous monitoring letters to verify that previous issues and findings have been resolved and identify any newly identified findings during their visits.

Monitors will verify that informed consent is properly obtained, eligibility is met (if not already vetted by the CPDM Central Registration Office), and study procedures are conducted according to the study protocol. Monitors will verify that the data reported in the case report forms accurately reflect the source documents, that all toxicities have been reported to date, and that all AEs have been reported according to IRB and DSMC requirements.

Findings will be categorized into groups such as protocol compliance, informed consent process, AEs, records and reports, etc. Findings will be rated by significance into one of three categories:

1. **Critical Findings:** High risk of having a major impact on the analysis of the trial, the data integrity, or result in substantial risk of regulatory authority action toward the PI or HICCC

2. Major Findings: Do not compromise trial conduct or data, but represent a departure from the protocol or a stated International Conference of Harmonization GCP guideline, regulation, or New York Presbyterian Hospital and CUMC SOPs. A finding with an actual or potential effect on patient safety, data integrity, or study outcome
3. Minor Findings: represent a violation of the protocol, stated GCP guideline, regulation, or New York Presbyterian Hospital and CUMC SOPs, but is a finding with minimal or no impact on patient safety, data integrity, or study outcome.

After each visit, monitoring follow-up letters will be disseminated to the PI, research team, and DSMC management. If the trial involves an IND in which a CUMC Faculty member is the Sponsor-Investigator, the CU Clinical Trials Office IND Assistance management will also be included. The final monitoring report will be reviewed by DSMC to determine if additional information and clarification is needed. If applicable, the committee's action and recommendations will be sent to the PI. The same process will apply to sub-sites participating in CUMC lead multi-center trials. The Compliance Core will conduct remote or on site monitoring of the affiliates.

The Compliance Core will defer monitoring activities to those departments that wish to utilize their own internal QA monitors so long as the reports are forwarded to the DSMC using the same reporting process as outlined above. If the reports received are deemed unacceptable, the DSMC will have the CPDM Compliance Core assume monitoring oversight.

Data and Safety Monitoring Committee (DSMC)

The HICCC Data and Safety Monitoring Committee (DSMC) in accordance with NIH policy and following Columbia University Medical Center (CUMC) IRB policy, is responsible for, and dedicated to, data and safety monitoring of ongoing clinical trials. The DSMC was established to monitor the safety and conduct of existing CUMC oncology trials, focusing on local investigator-initiated interventional trials. The committee will assume responsibility for other interventional trials when it is deemed appropriate by the Protocol Review and Monitoring Committee (PRMC), IRB or at the request of the PI. The DSMC differs from the PRMC and is a separate and distinct entity with a focus on study participant safety and careful review of observed toxicities.

The DSMC consists of nine voting members who are appointed by the HICCC Director and Associate Director. Members include four medical oncologists, a pediatric oncologist, a surgical oncologist, the director of clinical research nursing, a biostatistician, and a clinical research coordinator. The CPDM Director of Research Operations, and the CPDM Compliance Core Manager, and Compliance Core Coordinators are non-voting members of the DSMC. All voting members have extensive experience with clinical trials. To avoid conflicts of interest, members of the DSMC will not monitor studies for which they serve as the PI or Co-Investigator. In the event that the DSMC biostatistician is named as a co-investigator of a study being monitored, an alternate biostatistician will be appointed to assist in the monitoring of that particular trial.

DSMC Meetings: Formats and Procedures

DSMC meetings are convened biweekly in one of two formats: Once a month there is

a full committee meeting in person and a “virtual” meeting. The virtual meeting is conducted via email correspondence. Additional meetings may be held if deemed necessary by the IRB, the PRMC, or the DSMC members.

The review of new protocols for level of risk and frequency of ongoing reporting are reserved for full committee meetings in addition to review of reported UPs, Serious Adverse Events (SAEs), and requested protocol safety reports. The virtual meeting is a review of reported UPs, SAEs, and requested protocol safety reports. The DSMC Project Coordinator will electronically distribute the full committee meeting agenda and necessary review documents no later than five business days before the scheduled meeting regardless of the meeting format. For virtual meetings the assigned reviewers are required to email their review comments and recommendations to the DSMC Project Coordinator the day before the meeting. The day of the virtual meeting the DSMC members are emailed the agenda, the assigned reviewer’s comments, and a voting sheet. The members will either accept or reject the reviewer’s recommendation. A majority vote carries the DSMC decision.

The full committee meeting is called to order by the DSMC Chair, attendance is recorded, and the minutes from the previous meeting are reviewed and either accepted with revision or deferred for revision. The DSMC Project Coordinator takes note of each committee discussion item to aid in the transcription of the meeting’s minutes. The agenda begins with a discussion of new protocols, UPs, SAEs, safety reports, and other relevant discussion items.

DSMC Membership

Name	Degree/ Certification	Title	Field of Expertise and Program Affiliation
Joseph Jurcic	MD	Professor of Clinical Medicine	Medical Oncology
Monica Bhatia	MD	Assistant Clinical Professor of Pediatrics	Pediatric Oncology
Margaret Chen	MD	Assistant Professor of Clinical Surgery	Breast Surgery
Frances Brogan	MSN, RN. OCN, CCRP	Associate Director of Clinical Operations	CPDM
Emerson Lim	MD	Assistant Professor of Medicine	Medical Oncology
Todd Rosenblat	MD	Assistant Clinical Professor of Medicine	Medical Oncology
Wei Yann Tsai	PhD	Professor of Biostatistics	Biostatistics
Reena Vattakalam	CCRP	Clinical Research Manager	Gynecological Oncology

Non-voting members	Degree/ Certification	Title	Department
Moshe Kelsen	MBA	Executive Director	CPDM
Daniel Otap	CCRP	Associate Director of Regulatory Affairs	CPDM
Mariamne Reyna	CCRC	Compliance Core Coordinator	CPDM
Lauren Blumberg	MS	Compliance Core Coordinator	CPDM
Tiffany Negri	CCRP	CPDM, Multi-Center Manager	CPDM

DSMC Responsibilities

The responsibilities of the DSMC are to:

- Review the protocol data and safety monitoring plan and proposed study specific monitoring plan. Based on the level of risk, the DSMC will determine the frequency of reporting, which may be monthly, quarterly, biannually, or annually.
- Conduct a thorough review of the unanticipated problems, SAEs, adverse events, and toxicity profile associated with each study subject. When it is deemed necessary, the DSMC may suspend or terminate a study based on toxicity, adverse events reported, or unanticipated problems. The DSMC may mandate revision to the protocol and informed consent to increase on study monitoring and proper participant notification.
- Track safety and efficacy issues throughout the duration of the study and request additional relevant data from the PI. If needed, the DSMC will suspend or terminate the study when there is a significant concern for participant safety.
- Review requests for eligibility waivers and other significant protocol deviations
- Review compliance and adherence to the approved protocol and mandate appropriate action when deviation is identified. If significant deviation is observed, which alters the overall integrity of the study, the DSMC will recommend suspension or termination of the study.
- Consider the rationale for continuation of the study based on the overall safety and compliance
- Prepare the PI with correspondence stating the DSMC recommendation. Any findings of unacceptable performance will be forwarded promptly to the PI and the IRB. The PRMC/DSMC Manager will also inform the PRMC
- If CUMC is the coordinating/lead site of a multicenter study, the CUMC PI is responsible for sending the DSMC reports to sub-site PIs. The sub-site PI is required to submit the HICCC DSMC report to the sub-site IRB pursuant to the NIH "Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials" (NIH Guide for Grants and Contracts, June 11, 1999).

DSMC Review

Unanticipated Problems (UP)

A UP is defined as any incident, experience or outcome involving risk to subjects or others in any human subjects research that meets the following criteria: a) unexpected, b) related or possibly related to participation in such research, and c) suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized. Each UP should be reported to the CUMC IRB promptly, but not later than one week following the occurrence of the UP or the PI acquiring knowledge of the UP, by using the Unanticipated Problem Report module in RASCAL. This procedure is in accordance with the CUMC IRB UP reporting policy

<http://www.columbia.edu/cu/irb/policies/documents/UnanticipatedProblemsPolicy.FINALVERSION.012408.pdf>

- The HICCC DSMC monitors the UP queue daily for preliminary review. The UPs are reviewed by the DSMC Manager and/or Project Coordinator to determine whether or not expedited or committee review is required
 - HICCC is not the DSMC of record
 - Events which occur at any institution other than CUMC are administratively approved
 - Events which occur at CUMC are administratively approved and recorded on the next available DSMC agenda and minutes
 - HICCC is the DSMC of record
 - Events are placed on the next DSMC agenda for review and recommendation

Serious Adverse Events

All serious adverse event (SAE) reports for all CUMC investigator initiated interventional trials are submitted by the Principal Investigator and the responsible Clinical Research Nurse, Clinical Research Manager, or Clinical Research Coordinator to the HICCC DSMC for review and the FDA (if appropriate). The DSMC has a required SAE form for all CUMC investigator-initiated interventional trials (See Appendix A). Reported SAEs will be placed on the next available DSMC agenda for review and recommendation.

Each SAE must be reported to the DSMC Manager and Project Coordinator promptly. Reporting should occur within 24 hours of knowledge of the SAE occurring at CUMC or sub-sites.

Safety reports

The PI submits ongoing safety reports at a frequency determined by the DSMC. The report must be signed by the PI. An instruction document is provided to the PI and all applicable study team members (Appendix B and C):

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DSMC Recommendations

DSMC recommendations will be based on the results of the trial being monitored as well as on the information available to the DSMC from other published clinical data. It is the responsibility of the PI, study team, and the HICCC, CPDM staff to ensure that the DSMC is kept apprised of non-confidential results from other related studies that become available. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored. A written copy of DSMC recommendation(s) will be given to the PI, the PRMC, the IRB, and the CPDM.

In the case of study suspension or recommendation of permanent closure, the PI will be given 10 working days to respond to the DSMC's concerns. The study will remain suspended until the DSMC receives and approves an acceptable response from the PI. If the DSMC recommends a study change for patient safety or efficacy reasons, or that a study be closed early, the trial PI must act to implement the change within 10 working days.

In the event that the PI does not concur with the DSMC, then the PRMC Chair must be informed of the disagreement and be provided with the necessary review documents and correspondence. The PI, DSMC Chair, PRMC Chair and if applicable, CPDM leadership will be responsible for reaching a mutually acceptable decision about the study. Confidentiality must be maintained during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and HICCC, CPDM staff to seek advice; and to assist in reaching a mutually acceptable decision.

Notification of suspension and any recommendations for permanent closure are forwarded to the IRB, PRMC, NCI, or other sponsoring agency as required. If the study is NIH-funded, as required, a copy of this information will be provided to the responsible NIH program Director.

Criteria for Study Suspension or Termination

The following criteria are used by the DSMC for suspending or recommending termination of a clinical trial:

Toxicity/AEs: Excessive toxicity relative to the proposed risk and potential subject benefit will necessitate study suspension. The study may be reactivated pending DSMC and PRMC review and approval of a protocol amendment that reduces risk without jeopardizing scientific goals. Study suspension or termination may also be recommended if adequate treatment delivery cannot be achieved because of toxicity, subject compliance, or technical problems.

Research Non-compliance, Excessive Protocol Violations, and/or questionable Data Quality: Repeated major protocol or regulatory violations, stopping rule violations, failure to comply with corrective recommendations of the DSMC, or incomplete or inaccurate data reporting will lead to trial suspension and possible recommendation for termination.

Regardless of the reason, the IRB and CPDM Compliance Core and other relevant bodies will be informed of any decision to suspend.

Quality Assurance (QA): IRB Oversight

The Columbia University IRB Compliance Oversight Team (COT) oversees quality assurance of all clinical research at the University. The IRB COT conducts both for

cause and not-for-cause audits on a regular basis, and any findings of non-compliance will require formalized corrective action plans. Findings are also reported to the PIs, the HICCC Director, Associate Director for Clinical Research and relevant institutional officials, and if it is required, federal agencies are notified.

Release of Outcome Data

In general, outcome data should not be made available to individuals outside of the DSMC until accrual has been completed and all subjects have completed their treatment. At this time, the DSMC may approve the release of outcome data on a confidential basis to the trial principal investigator for planning the preparation of manuscripts and/or to a small number of other investigators for purposes of planning future trials. Any release of outcome data prior to the DSMC's recommendation for general dissemination of results must be reviewed and approved by the DSMC.

Conflict of Interest

Individuals appointed to the DSMC and PRMC will disclose any potential conflicts of interest, whether real or perceived, to the PI and the appropriate HICCC official(s), in accordance with Columbia University policies. Conflict of interest can include professional interest, proprietary interest, and miscellaneous interest as described in the NIH Grants Policy Statement, <http://grants.nih.gov/grants/policy/coi/> and 45 CFR Part 94. Potential conflicts that develop during a member's tenure on the DSMC must also be disclosed.

Members of the DSMC or PRMC will not review or monitor studies for which they serve as principal investigator or co-investigator. In the event that the DSMC or PRMC biostatistician is named as a co-investigator of a study being monitored, an alternate biostatistician will be appointed to assist in the monitoring of that particular trial. If other DSMC members are investigators in a reviewed protocol and by being excused from protocol review a quorum no longer exists, the DSMC Chair will appoint an additional individual on an *ad hoc* basis to monitor that protocol only. Also, if additional expertise on a particular protocol is deemed necessary by the DSMC Chair or by the DSMC, then the DSMC will invite an appropriate individual to advise the committee.

IRB Review and Approval of the Data and Safety Monitoring Plan

The CUMC IRB has approved the HICCC Data and Safety Monitoring Plan. Individual protocol data and safety monitoring plans will also be reviewed and approved by the IRB as a part of the comprehensive full board review for all relevant studies.

Table of Acronyms

CIRB	Central Institutional Review Board
COG	Children's Oncology Group
COT	Compliance Oversight Team
CPDM	Clinical Protocol Data Management
CUMC	Columbia University Medical Center
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GOG	Gynecological Oncology Group
HICCC	Herbert Irving Comprehensive Cancer Center
IRB	Institutional Review Board
NCI	National Cancer Institute
NCTN	National Clinical Trial Network
NIH	National Institutes of Health
NSABP	National Surgical Adjuvant Breast and Bowel Project
PI	Principal Investigator
PRMC	Protocol Review and Monitoring Committee
RTOG	Radiation Therapy Oncology Group
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SWOG	Southwest Oncology Group
UP	Unanticipated Problem
WIRB	Western Institutional Review Board