Herbert Irving Comprehensive Cancer Center
Columbia University Medical Center

DATA AND SAFETY MONITORING PLAN

Stephen G. Emerson, MD, PhD, Director

Dawn Hershman, MD, MS, Associate Director of Clinical Resources

Herbert Irving Comprehensive Cancer Center
Columbia University Medical Center
1130 St. Nicholas Ave, Suite 201
New York, New York 10032
Phone: (212) 851-4680
Fax: (212) 851-4660
Table of Contents

Summary

Data Safety and Monitoring Plan

1. Introduction
2. HICCC Data Safety Monitoring: Organization and Responsibilities
3. Types of Clinical Trials and Monitoring Requirements
   3.1 NIH/NCI Sponsored Trials/National Cancer Institute National Clinical Trial Network (NCTN) Protocols
   3.2 Industry Sponsored Trials
   3.3 External Peer Reviewed Trials and Investigator-Initiated Institutional Studies
4. Protocol Review and Monitoring Committee (PRMC)
   4.1 Initial Review
   4.2 Continuing Review
   4.3 PRMC Membership
   4.4 PRMC Responsibilities for Data Safety and Monitoring
5. HICCC Clinical Protocol and Data Management (CPMD) Office
   5.1 CPMD Compliance Core Quality Review and Monitoring
   5.2 Monitoring of Investigator-initiated Trials
6. Data and Safety Monitoring Committee
   6.1 DSMC Meetings: Formats and Procedures
   6.2 DSMC Membership
   6.3 DSMC Responsibilities
   6.4 Definitions of Risk
7. DSMC Review
   7.1 Unanticipated Problems (UP)
   7.2 Serious Adverse Events – possibly/definitely related to the study drug (SAE)
   7.3 Safety Reports
   7.4 DSMC Recommendations
   7.5 Criteria for Study Suspension or Termination
8. Quality Assurance (QA): IRB Oversight
9. Release of Outcome Data
10. Conflict of Interest
11. IRB Review and Approval of the Data and Safety Monitoring Plan

Appendix A: Table of Acronyms
Appendix B: Serious Adverse Event Reporting Form
Appendix C: DSMC Safety Report – Institutional
Appendix D: DSMC Safety Report - Industrial
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 strategies 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 Director of Clinical Resources 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, the study sponsor, and the degree of risk encountered by subjects.

The HICCC DSM 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 SAFETY AND MONITORING PLAN

1. 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 safety and 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 primarily on local investigator-initiated Phase I and II 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). For example, the DSMC monitors industry-sponsored trials that do not have provisions for external data and safety monitoring. The DSMC can initiate internal monitoring on a specific clinical trial to be conducted by the Clinical Protocol Data Management (CPDM) Compliance Core, and 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 Director of Clinical Resources oversees the operations of the DSMC. The DSMC reports to the PRMC and to the Director of Clinical Resources. 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 independently from PRMC, CPDM and other entities.

As of May 2013 there were 313 interventional protocols which were active for accrual or closed to enrollment, including 38 Phase I trials, 27 Phase I/II, 100 Phase II trials, 2 Phase II/III, 115 Phase III studies, 2 Phase IV trials, 28 Pilot/Feasibility trials and 1 Extension trial. Of the 313 interventional trials that were active at CUMC, 167 were open to accrual. There were 63 National Clinical Trials Network (NCTN, formerly Cooperative Group) trials, 38 investigator-initiated institutional studies, 41 industry-sponsored trials, and 25 externally peer-reviewed protocols at the HICCC. Every effort is made to prioritize investigator-initiated trials.

The HICCC DSMC has primary responsibility for monitoring all investigator-initiated interventional protocols. As of May 2013 there were 35 active investigator-initiated interventional protocols, including 11 Pilot trials, 6 Phase I trials, 3 Phase I/II, 12 Phase II studies, and 3 trials not classified by phase.

The method and degree of monitoring done by the DSMC will vary depending on the degree of risk encountered by subjects, the phase of the study, and the degree of data and safety monitoring assumed by the study sponsor. 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, 1999 (http://grants.nih.gov/grants/guide/notice-files/not98-084.html) with further guidance issued on June 5, 2000.
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) to be reviewed by the HICCC Data and Safety Monitoring Committee (DSMC) and the study sponsor.

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 medical center IRB policy, which may be found at: http://www.columbia.edu/cu/irb/documents/SOPV4June122012FINAL.pdf

2. HICCC Data Safety Monitoring: Organization and Responsibilities

The HICCC Cancer Center Director and the Associate Director of Clinical Resources 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 investigators of NIH grants and contracts supporting clinical trials, and the principal investigators of individual clinical trials.

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 specific criteria and procedures for unblinding if needed.
- If a study is not eligible for DSMC utilization, then the study protocol should designate all individuals with access to unblinded data.
- The proposed schedule for reporting adverse events to the DSMC, the IRB and/or the NIH/FDA must be described. In multisite 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 PI's, who in turn are required to distribute 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.
3. 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 types of monitoring and trials apply to prevention and behavior modification trials, as well as therapeutic trials. All descriptions and plans for monitoring include all major classes 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.

3.1 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.

During the initial PRMC review of NCTN clinical trials, the PRMC will verify that a DSMC exists and is overseen by the study sponsor (NCTN) or agency. This will be recorded in the minutes of the PRMC meeting. If the DSMP is not clear, the protocol will not be activated until clarification is obtained. If the NCTN sponsor does not have an independent DSMC, the HICCC DSMC will assume local responsibility to ensure the safety of CUMC participants. Local monitoring of adverse event reports and UPs is required per CUMC IRB policy and will occur regardless of the NCTN agency bearing the overall responsibility for data safety and monitoring. The HICCC DSMC will track UPs, SAEs and the toxicity profile of CUMC participants. The DSMC will request a study-wide progress report to serve as a comparison to what is experienced locally at CUMC. If necessary, the DSMC will recommend suspension of local participation if patient safety is at risk.

Other types of government grants may support large, randomized, phase III trials. Any R01-funded phase III study will require the utilization of a DSMC. For studies not initiated at the HICCC, as in the case of NCTN trials, the HICCC PRMC will verify that a DSMC exists and is overseen by the study sponsor or agency. This will be recorded in the minutes of the PRMC meeting, and no further action regarding monitoring, aside from adverse event and UP reporting in accordance with CUMC IRB policy. If the DSM plan is not clear, the protocol will not be activated until clarification is obtained. If the sponsor/coordinating site does not have an independent DSMC, the HICCC DSMC will assume local responsibility to ensure the safety of CUMC participants. Local monitoring of adverse event reports and UPs is required per CUMC IRB policy and will occur regardless of the institution bearing overall responsibility for data safety and monitoring. The HICCC DSMC will track UPs, SAEs and the toxicity profile of CUMC participants. The DSMC will request a study-wide progress report to serve as a comparison to what is experienced locally at CUMC. If necessary, the DSMC will recommend suspension of local participation if patient safety is at risk.

3.2 Industry Sponsored Trials

All clinical trials initiated by pharmaceutical industry sponsors with the HICCC as a participating site will require data and safety monitoring plans that have been reviewed and approved by both the PRMC and the IRB of record. These protocol-specific plans will adhere to industry and FDA-specified guidelines. The HICCC PRMC will verify that a DSMC exists and is overseen by the study sponsor. This will be recorded in the minutes of the PRMC meeting. If the sponsor/coordinating site does not have an independent DSMC, the HICCC DSMC will assume local responsibility to ensure the safety of CUMC participants. Local monitoring of adverse event reports and UPs is required per CUMC IRB policy and will occur regardless of the institution bearing overall responsibility for data safety and monitoring. The HICCC DSMC will track UPs, SAEs and the toxicity profile of CUMC participants. The DSMC will request a study-wide progress report to serve as a comparison to what is experienced locally at CUMC. If necessary, the DSMC will recommend suspension of local participation if patient safety is at risk.

3.3 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 an CUMC investigator are required to use the HICCC DSMC for oversight and monitoring. If CUMC is not the sponsor/coordinating site and an independent DSMC is not established, the HICCC DSMC will assume local responsibility to ensure the safety of CUMC.
participants. The DSMC will determine the frequency of monitoring relative to the level of risk. Local monitoring of adverse event reports and UPs are required per CUMC IRB policy and will occur regardless of the institution bearing overall responsible for data safety and monitoring.

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.

4. Protocol Review and Monitoring Committee (PRMC)

Clinical protocol review is conducted by the Protocol Review and Monitoring Committee (PRMC). 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 of protocols for scientific merit and prioritization to assure efficient use of HICCC resources; 2. Monitor accrual and scientific progress with the responsibility to decide on protocol continuation and the authority to close trials for insufficient progress; and 3. When appropriate, to review and act on reports from the Data and Safety Monitoring Committee that have relevance for the scientific integrity of clinical research. The Protocol Review and Monitoring Committee (PRMC) reviews the scientific merit, scientific priorities, and scientific 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.

4.1 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. 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, the appropriate number of patients are available locally, and whether the statistical plan is adequate to test the study hypothesis. Before the Institutional Review Board (IRB) reviews any cancer-related study, the Cancer Center PRMC must approve it. The PRMC also ensures that trials do not overlap in eligibility criteria, which may lead to competition for the same pool of patients.

As part of the review process, the PRMC will determine if an independent external DSMC exists. If not, the PRMC will notify the HICCC DSMC that their oversight is needed. A study will not receive final PRMC approval without a protocol-specific description of data to be collected and adverse event reporting strategy.

4.2 Continuing Review

For all studies, the local principal investigator is required to submit a continuing review application for each study to the IRB and PRMC before the approval expiration date. This progress report includes the number of subjects enrolled on the trial, the number of subjects treated, a summary of all Unanticipated Problems (UPs) in accordance with the CU IRB UP policy (using current CTCAE grading, including UPs requiring immediate reporting), and significant literature developments that may affect the safety of participants or the ethics of the study. 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.

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. These renewal applications are reviewed and presented on the agenda at the next PRMC meeting. Any amendments and/or modifications to the protocol, informed consent, and personnel submitted, as part of the renewal application will be reviewed simultaneously. 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.

4.3 PRMC Membership

<table>
<thead>
<tr>
<th>Name</th>
<th>Degree</th>
<th>Title</th>
<th>Field of Expertise and Program Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edward P. Gelmann</td>
<td>MD</td>
<td>Professor of Medicine and Pathology</td>
<td>Medical Oncology</td>
</tr>
<tr>
<td>(Chair)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jasmine M. Zain</td>
<td>MD</td>
<td>Assistant Clinical Professor of Medicine</td>
<td>Hematology/Oncology</td>
</tr>
<tr>
<td>(Co-Chair)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brad Bott</td>
<td>MBA,</td>
<td>Director of Research Operations</td>
<td>CPDM</td>
</tr>
<tr>
<td></td>
<td>CCRP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frances Brogan</td>
<td>RN</td>
<td>Research Nurse Manager</td>
<td>CPDM</td>
</tr>
<tr>
<td>Simon Cheng</td>
<td>MD</td>
<td>Assistant Professor of Clinical Radiation</td>
<td>Radiation Oncology</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oncology</td>
<td></td>
</tr>
<tr>
<td>Arindam Choudhry</td>
<td>PhD</td>
<td>Assistant Professor of Biostatistics</td>
<td>Biostatistics</td>
</tr>
<tr>
<td>James Garvin</td>
<td>MD, PhD</td>
<td>Professor of Clinical Pediatrics</td>
<td>Pediatric Oncology</td>
</tr>
</tbody>
</table>
### 4.4 PRMC Responsibilities for Data Safety and Monitoring

Following protocol activation, the PRMC will:

- Evaluate regular reports of the HICCC DSMC and independent DSMBs of specific protocols monitored
- Review DSMC reports
- Facilitate implementation of DSMC recommendations by the HICCC
- As needed, 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.
5. HICCC Clinical Protocol and Data Management (CPDM) Office

The Herbert Irving Comprehensive Cancer Center 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 assists 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.

The CPDM regulatory team assists investigators in preparing new study applications for review by the Protocol Review and Monitoring Committee (PRMC) and Institutional Review Board (IRB). The PRMC is tasked with reviewing all new and continuing research studies related to the prevention or treatment of cancer at Columbia University Medical Center (CUMC). The PRMC is also tasked with reviewing and approving scientific merit, priority, and accrual monitoring. The CUMC IRB requires that the Cancer Center PRMC approve a study before conducting its own review of risks and benefits.

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 Data Applications Group (DAG) assists the CPDM with National Cancer Institute (NCI) Clinical Trials Report Program (CTRP) data submissions, including batch uploads. DAG 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.

5.1 CPDM Compliance Core Quality Review and Monitoring

The Clinical Protocol Data Management (CPDM) of the HICCC has a Compliance Core tasked with ongoing monitoring of investigator-initiated interventional trials involving CPDM resources and sponsored trials at the request of the CPDM Director of Clinical Research Operations, DSMC, and/or PRMC. 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, which serves as the HICCC clinical trials management system.

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.
5.2 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 that utilizes CPDM resources, regardless of the level of risk. Monitoring is done to verify that trial conduct follows the approved protocol and that the study data is accurate and complete.

Initial monitoring of all high- and moderate-risk investigator-initiated trials will take place after the first few subjects are enrolled. Ongoing monitoring will be performed on a schedule based upon the study type and level of risk to trial subjects. The DSMC, PRMC, CPDM Management, or the PI may request more frequent monitoring.

Monitors will verify that informed consent is properly obtained, eligibility is met, and all study procedures are conducted according to the study protocol. Monitors will also 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. Monitors will present queries and issues from their review to the clinical research nurse and/or clinical research coordinator for correction and/or completion in a timely manner. If deviations or significant deviations are noted, the monitor will review them with the clinical research nurse, clinical research coordinator, and PI, and report any significant findings to the DSMC.

The Compliance Core will be responsible for remote monitoring of participating sites. Participating sites will be asked to conduct internal monitoring and provide the HICCC Compliance Core with findings along with redacted source documents.

The compliance coordinator will review the study protocol for accuracy, consistency, and compliance with applicable regulations and GCP guidelines. The compliance coordinator will review previous reports and monitoring letters to verify that previous issues and findings have been resolved and determine whether or not new issues and findings establish a trend. For each investigator-initiated trial, the compliance coordinator will randomly select at least 10 percent of enrolled subjects (or at least three subjects, whichever is greater) for review. If fewer than three patients have been enrolled, all patient records will be reviewed. 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/CUMC SOPs. A finding with an actual or potential effect on patient safety, data integrity, or study outcome
3. Observations: represent a violation of the protocol, stated GCP guideline, regulation, or New York Presbyterian Hospital/CUMC SOPs, but which is a finding with minimal or no impact on patient safety, data integrity, or study outcome.

Findings are presented to the Principal Investigator, clinical research nurse, and clinical research coordinator. The PI is responsible for providing a timely response, which satisfactorily
resolves the issue, and a corrective action plan to prevent recurrence. The Compliance Core Coordinator will provide the DSMC with a final report complete with responses and/or corrective action plans. The report will contain a summary section of the findings and outcome. The number and significance of the findings and/or observations identified will determine the overall monitoring outcome.

Copies of the final monitoring report will be provided to the DSMC and CPDM management. Upon receipt of the final monitoring report, the DSMC will review the findings and corrective action plan to determine if additional information and clarification is needed. The committee’s action and recommendations will be sent to the PI. The PI will submit the DSMC letter and final monitoring report to the CUMC IRB via RASCAL.

6. 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 phase I, II, and III clinical 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 eight voting members who are appointed by the HICCC Director. At the time of this report members include three medical oncologists, one pediatric oncologist, one research pharmacist, one pediatric nurse practitioner, one biostatistician, and one 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 had 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.

6.1 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 alternate meetings are “Virtual”. 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 (SAE), and requested protocol safety reports. The virtual meeting conducts a review of reported UPs, SAEs, and requested protocol safety reports. The DSMC Project Coordinator will electronically distribute the 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 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.

6.2 DSMC Membership

<table>
<thead>
<tr>
<th>Name</th>
<th>Degree/Certification</th>
<th>Title</th>
<th>Field of Expertise and Program Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>J. Gregory Mears (Chair)</td>
<td>MD</td>
<td>Clinical Professor of Medicine</td>
<td>Medical Oncology</td>
</tr>
<tr>
<td>Monica Bhatia</td>
<td>MD</td>
<td>Assistant Clinical Professor of Pediatrics</td>
<td>Pediatric Oncology</td>
</tr>
<tr>
<td>Ria G. Hawks</td>
<td>CPNP</td>
<td>Pediatric Nurse Practitioner</td>
<td>Pediatric Oncology</td>
</tr>
<tr>
<td>Joseph Jurcic</td>
<td>MD</td>
<td>Professor of Clinical Medicine</td>
<td>Hematology/Oncology</td>
</tr>
<tr>
<td>Michael Schwenk</td>
<td>PharmD</td>
<td>Research Pharmacist</td>
<td>Research Pharmacy</td>
</tr>
<tr>
<td>Todd Rosenblat</td>
<td>MD</td>
<td>Assistant Clinical Professor of Medicine</td>
<td>Medical Oncology</td>
</tr>
<tr>
<td>Sharyn Lewin</td>
<td>MD</td>
<td>Clinical Professor of Medicine</td>
<td>Gynecological Oncology</td>
</tr>
<tr>
<td>Wei Yann Tsai</td>
<td>PhD</td>
<td>Professor of Biostatistics</td>
<td>Biostatistics</td>
</tr>
<tr>
<td>Reena Vattakalam</td>
<td>CCRP</td>
<td>Clinical Research Manager</td>
<td>Gynecological Oncology</td>
</tr>
</tbody>
</table>

Non-voting members

<table>
<thead>
<tr>
<th>Name</th>
<th>Degree/Certification</th>
<th>Title</th>
<th>Department</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brad Bott</td>
<td>MBA, CCRP</td>
<td>Director of Research Operations</td>
<td>CPDM</td>
</tr>
<tr>
<td>Daniel Otap</td>
<td>CCRP</td>
<td>Compliance Core Manager</td>
<td>CPDM</td>
</tr>
<tr>
<td>Monica Estrada</td>
<td>CCRP</td>
<td>Compliance Core Coordinator</td>
<td>CPDM</td>
</tr>
<tr>
<td>Guadalupe Jorge</td>
<td></td>
<td>Compliance Core Coordinator</td>
<td>CPDM</td>
</tr>
</tbody>
</table>
6.3 DSMC Responsibilities

The responsibilities of the DSMC are to:

• Review the protocol data and safety monitoring plan and based on the level of risk, determine the frequency of reporting, which may be monthly, quarterly, biannually, or annually. See the Degree of Risk section below.

• Conduct a thorough review of the unanticipated problems, adverse events, and toxicity profile associated with each study subject to its oversight. 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 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. A summary of meeting business will be sent to the PRMC Manager and will be discussed during the next scheduled meeting of the PRMC.

• If CUMC is the coordinating 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).
6.4 Definitions of Risk

The DSMC will assess risk and categorize HICCC investigator-initiated clinical trials using the following guidelines:

<table>
<thead>
<tr>
<th>Level of Risk</th>
<th>Definition</th>
<th>Examples</th>
</tr>
</thead>
</table>
| High          | Clinical trials of high complexity, high potential for toxicity to patients | • Phase I studies  
• Dose-finding studies  
• Multicenter studies  
• IND Phase II-III therapeutic studies |
| Moderate      | Clinical trials with potential of greater than minimal risk to patients | • Therapeutic phase II-III studies with no investigational new drug application (IND) |
| Low           | Clinical trials with minimal risk to patient health or safety | • Non-therapeutic studies without external oversight  
• Therapeutic or preventative studies using non-toxic agents |

7. DSMC Review

7.1 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 accordance with the CUMC IRB UP reporting policy


- 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
7.2 Serious Adverse Events – possibly/definitely related to the study drug (SAE)

All serious adverse event (SAE) reports for all clinical trials conducted at the HICCC are reported by the Principal Investigator to the Regulatory Core of the Clinical Protocol and Data Management Office (CPDM) for review by the DSMC, the study sponsor, and FDA (if appropriate). The DSMC has a required SAE form for all CUMC investigator-initiated interventional trials (See Appendix A). If the HICCC DSMC is monitoring a trial with an external sponsor, which is not assuming DSMC responsibilities, the sponsor’s standard SAE form may be substituted. Reported SAEs will be placed on the next available DSMC agenda for review and recommendation.

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

7.3 Safety Reports

The PI submits ongoing safety reports at a the frequency determined by the DSMC. The report must be signed by the PI and contain the following information relevant for efficient review (Appendix B and C):

- The number of subjects accrued at CUMC and if applicable, study-wide
- The cumulative list of study subjects, using their protocol ID number, and their study cohort or treatment arm
  - Date of Day 1 therapy, date treatment stopped, and if applicable date of withdrawal or death
  - Confirmation of whether or not each subject experienced a dose-limiting toxicity, UP, or AE
  - If a subject’s response was assessed, the report must record that response
- The cumulative list of subjects, using their protocol ID numbers, who have experienced UPs with the UP description and the date of occurrence.
- The list of study-wide ≥ Grade 3 toxicities by keyword with the number of events occurring at CUMC and the number of patients, study-wide, experiencing the toxicity

7.4 DSMC Recommendations

DSMC recommendations should 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, and the PRMC Chair 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 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.

7.5 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 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.

8. 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 findings of non-compliance 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.

9. 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.
10. 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, the DSMC will invite an appropriate individual to advise the committee.

11. 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.
Appendix A: 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 Safety and Monitoring Committee
DSMP  Data Safety and 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
Appendix B: Serious Adverse Event Reporting Form

COLUMBIA UNIVERSITY MEDICAL CENTER
HERBERT IRVING COMPREHENSIVE CANCER CENTER
Data Safety and Monitoring Committee

SERIOUS ADVERSE EVENT REPORTING FORM

1 – Trial Information
SPONSOR
CHIEF INVESTIGATOR
PRINCIPAL INVESTIGATOR NAME
IRB NUMBER
STUDY TITLE

2 – About the event
Are you reporting a SUSAR? (Suspected Unexpected Serious Adverse Reaction) Yes ☐ No ☐
Report type Initial notification ☐ Follow up ☐

3 – About the time of the event
Date Investigator informed Date of report
Date of onset Date Resolved

4 – Participant information
PATIENT ID NUMBER DOB Gender Male ☐ Female ☐

5 – Description of Event

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Causality</th>
<th>Expectedness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>Not related</td>
<td>Expected</td>
</tr>
<tr>
<td>Life threatening</td>
<td>Unlikely</td>
<td>Not expected</td>
</tr>
<tr>
<td>Hospitalization or prolongation of hospital stay</td>
<td>Possibly</td>
<td></td>
</tr>
<tr>
<td>Persistent or significant disability or incapacity</td>
<td>Probably</td>
<td></td>
</tr>
<tr>
<td>Congenital abnormality or birth defect</td>
<td>Definitely</td>
<td></td>
</tr>
<tr>
<td>Otherwise considered serious</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Brief description of event

Diagnosis

Outcome
Fatal ☐ On-going ☐ Recovered with sequelae ☐ Recovered ☐
If recovered (or recovered with sequelae) selected, enter date of recovery
If fatal enter date of death
Cause of death:
### Appendix B: Serious Adverse Event Reporting Form

#### 6 – Medication details

<table>
<thead>
<tr>
<th>Information about the CHEMOTHERAPY</th>
<th>Dose</th>
<th>Route</th>
<th>Start date</th>
<th>Stop date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relevant Concomitant Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Indication</td>
<td>Dose</td>
<td>Route</td>
<td>Start date</td>
<td>Stop date</td>
</tr>
<tr>
<td>Drug</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other clinical information, including relevant tests (laboratory, CT, ECG etc.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Appendix B: Serious Adverse Event Reporting Form

## CONTACT DETAILS

<table>
<thead>
<tr>
<th>Clinical Research Coordinator:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature:</td>
<td></td>
</tr>
<tr>
<td>Email:</td>
<td></td>
</tr>
<tr>
<td>Fax:</td>
<td></td>
</tr>
<tr>
<td>Telephone:</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Principal Investigator:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature:</td>
<td></td>
</tr>
<tr>
<td>Email:</td>
<td></td>
</tr>
<tr>
<td>Fax:</td>
<td></td>
</tr>
<tr>
<td>Telephone:</td>
<td></td>
</tr>
</tbody>
</table>
### CUMC Subject List by Protocol ID #

<table>
<thead>
<tr>
<th>Protocol ID #</th>
<th>Cohort (if applicable)</th>
<th>Date of Day 1 Therapy</th>
<th>Date Treatment Stopped</th>
<th>Dose Limiting Toxicity Y/N</th>
<th>Adverse Event Y/N</th>
<th>Unanticipated Problem Y/N</th>
<th>Response (CR, PR, SD, PD)</th>
<th>Date of Withdrawal</th>
<th>Date of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### CUMC Subjects with Unanticipated Problems (UP) - List by ID#

<table>
<thead>
<tr>
<th>UP Description</th>
<th>Date of UP occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### List Study-wide Toxicities by keyword

<table>
<thead>
<tr>
<th>Grade (≥3 events)</th>
<th>Number of CUMC events</th>
<th>Number of Patients Experiencing this Toxicity (Studywide)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CUMC Subject List by Protocol ID#</td>
<td>Date of Day 1 Therapy</td>
<td>Date Treatment Stopped</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-----------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CUMC Subjects with Unanticipated Problems (UP) - List by ID#</th>
<th>UP Description</th>
<th>Date of UP occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>List CUMC Toxicities by keyword</th>
<th>Grade (≥3 events)</th>
<th>Number of CUMC events</th>
<th>Number of Patients Experiencing this Toxicity (Studywide)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P.I. Signature

Date: