

Herbert Irving Comprehensive Cancer Center
Columbia University Medical Center

DATA AND SAFETY MONITORING PLAN

Riccardo Dalla-Favera, MD, Director
Edward P. Gelmann, MD, Deputy Director For Clinical Research
Herbert Irving Comprehensive Cancer Center
Columbia University
Presbyterian Hospital 18th floor, Room 200
622 West 168th Street
New York, New York 10032
Phone: (212) 305-8615
Fax: (212) 342-3036

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 Deputy Director for Clinical Research 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 (DSM) Committee, 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 type of 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 monitored, and that reporting techniques fulfill sponsor, institutional, and governmental requirements.

Summary	2
DATA AND SAFETY MONITORING PLAN.....	4
Introduction	4
Organization and Administration	5
Protocol Review and Monitoring Committee (PRMC).....	6
PRMC membership.....	7
Quality Assurance (QA) Committee	8
Data and Safety Monitoring Committee (DSMC)	8
HICCC Clinical Research Management Office (CRMO).....	9
Adverse Event and Unanticipated Problem Reporting.....	10
Investigator Requirements and Responsibilities	10
Types of Clinical Trials and Monitoring Requirements	12
Types of Monitoring.....	13
Unanticipated Problem (UP) Reporting.....	13
Annual Continuing Review	13
HICCC Quality Assurance Program	14
Types of Trials	15
PHASE III STUDIES.....	15
A. NIH/NCI Sponsored Trials.....	15
National Cooperative Oncology Group Protocols.....	15
Other NIH Grants.....	16
Industry Sponsored Trials.....	16
B. External Peer Review Trials.....	17
C. Investigator-initiated Institutional Studies	17
Investigator-initiated Phase III protocols must include:.....	19
PHASE II STUDIES.....	19
A. NIH/NCI Sponsored Trials.....	19
National Cooperative Oncology Group Protocols.....	19
Other NIH Grants.....	20
B. Industry Sponsored Trials	20
C. External Peer Review Trials.....	20
D. Investigator-initiated Institutional Studies.....	21
PHASE I STUDIES	21
A. NIH/NCI Sponsored Trials.....	22
National Cooperative Oncology Group Protocols.....	22
Other NIH Grants.....	22
B. Industry Sponsored Trials	22
C. External Peer Review Trials.....	23
D. Investigator-initiated Institutional Studies.....	23
PRMC Responsibilities for Data Safety and Monitoring	24
Data Safety and Monitoring Boards (DSMBs)	26
DSMB Responsibilities:.....	26
DSMC Meetings.....	27

DSMC Responsibilities	27
DSMC Recommendations	28
Release of Outcome Data.....	29
Conflict of Interest.....	29
IRB Review and Approval of the Data and Safety Monitoring Plan.....	30

DATA AND SAFETY MONITORING PLAN

Introduction

The Herbert Irving Comprehensive Cancer Center (HICCC) considers the safety of participants in clinical trials to be an extremely high priority. In accordance with NIH policy, every therapeutic 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 a separate and distinct entity from the HICCC Protocol Review and Monitoring Committee (PRMC), which oversees scientific aspects of cancer clinical trials.

The HICCC DSMC, which originally received NIH approval in 2002, monitors the safety and conduct of existing therapeutic oncology trials, focusing on local investigator-initiated Phase I and II clinical trials. At the discretion of the PRMC, the IRB, or the Principal Investigator (PI), additional studies may be considered for oversight by the HICCC DSMC. For example, the DSMC monitors industry-sponsored trials that do not have provisions for external data and safety monitoring. The DSMC can initiate internal and/or external audits on a specific clinical trial, and reviews and acts on all audits undertaken by the Quality Assurance (QA) Committee, a subcommittee of the PRMC.

The responsibilities of the DSMC are to ensure that the monitoring of different types of trials is timely and effective. The HICCC Deputy Director for Clinical Research oversees the operations of the Data and Safety Monitoring Committee. The DSMC reports to the PRMC and to the Deputy Director for Clinical Research. 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.

As of February 28, 2011, there were 239 active therapeutic protocols, including 44 Phase I trials, 30 Phase I/II, 68 Phase II trials, 1 Phase II/III, 79 Phase III studies, 2 Phase IV trials, and 14 Pilot/Feasibility trials. There are 92 national cooperative group trials, 39 investigator-initiated institutional studies, 82 industry-sponsored

trials, and 28 externally peer-reviewed protocols at the HICCC.

The HICCC DSMC has primary responsibility for monitoring all investigator-initiated institutional studies. As of December 2010 there were 60 active investigator-initiated therapeutic protocols, including 6 Pilot trials, 18 Phase I trials, 5 Phase I/II, 26 Phase II studies, 3 Phase III trials and 2 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 (DSM) Plan has been developed to coordinate and provide oversight for data and safety monitoring for all therapeutic 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>) The National Cancer Institute issued a policy on June 22, 1999 for data and safety monitoring of all trials with special emphasis on randomized Phase III trials by Data and Safety Monitoring Boards (DSMBs) (<http://deainfo.nci.nih.gov/grantspolicies/datasafety.htm>).

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 AEs to the HICCC Clinical Research Management Office 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> [Unanticipated Problems: Reporting to the IRB of Unanticipated Problems Involving Risks FINALVERSION.012408.pdf](#)).

Organization and Administration

Various individuals and committees are responsible for ensuring that monitoring of different types of trials is timely and effective. . The HICCC Cancer Center Director and the Deputy Director for Clinical Research 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.

Protocol Review and Monitoring Committee (PRMC)

The Protocol Review and Monitoring Committee (PRMC) reviews the scientific merit, scientific priorities, and scientific progress of all clinical protocols involving cancer patients in the cancer center facilities. The PRMC conducts reviews of all new protocols that study risk, diagnosis or treatment of cancer of all sponsor types, including: investigator-initiated institutional studies, industry-sponsored trials, national cooperative group trials, and externally peer-reviewed protocols. Specific elements of the protocol that are addressed by reviewers include, but are not limited to, the following: whether the research question and study design are innovative, feasible, and able to be accomplished with institutional resources; whether the appropriate number of patients are available locally; and whether the planned statistical power is adequate to test the study hypothesis. Before any cancer-related study is reviewed by the Institutional Review Board (IRB), it must be approved by the Cancer Center PRMC. The PRMC also assures that HICCC resources are used optimally and that trials do not overlap in eligibility and therefore compete for the same pool of patients.

As part of the review process, the PRMC reviews and approves protocol-specific DSM plans for all therapeutic intervention trials prior to review by the CUMC IRB. No study will receive final PRMC approval without a protocol-specific description of data to be collected and adverse event reporting strategy.

PRMC membership

Name	Degree	Title	Field of Expertise and Program Affiliation
Edward Gelmann	MD	Professor of Medicine and Pathology & Cell Biology (in the Herbert Irving Comprehensive Cancer Center) Clyde '56 and Helen Wu Professor of Medicine (Clinical Oncology) and Professor of Pathology Cell Biology (in Herbert Irving Comprehensive Cancer Center)	Medical Oncology (Interim Chair)
Christine Andan	RN	Clinical Program Manager	CRMO
Bin Cheng	Ph.D.	Assistant Professor Biostatistics	Biostatistics Shared Resource
Israel Deutsch	MD	Assistant Professor of Clinical Radiation Oncology	Radiation Oncology
James Garvin	MD, PhD	Professor of Clinical Pediatrics	Pediatric Oncology
Diane George	MD	Assistant . Professor of Clinical Pediatrics	Pediatric Oncology
Victor Grann	MD, MPH	Clinical Professor of Medicine	Cancer Prevention and Control Director, RRMO
Balasz Halmos	MD	Associate . Professor of Clinical Medicine	Medical Oncology (Vice Chair)
Hanina Hibshoosh	MD	Associate Professor of Clinical Pathology	Pathology; Histopathology and Tissue Shared Resource
Zhexhen Jin	Ph.D.	Assistant. Professor of Clinical Biostatistics	Biostatistics Shared Resource
Kara Kelly	MD	Associate Professor of Clinical Pediatrics	Pediatric Oncology
Mary Ann Kral	PA-C, MsM	Executive Director for Clinical Research	CRMO
Shing Lee	Ph.D. Candidate	Associate Research Scientist	Biostatistics Shared Resource
David Leung	MD, PhD	Assistant Professor of Clinical Radiology	Radiology
Jon Levenson, *	M.D.	Associate Clinical Professor of Psychiatry	Psychiatry
Paula McKinley*	PhD	Assistant Professor of Clinical Behavioral Medicine	Psychiatry
Martin Oster	MD	Associate Professor of Clinical Medicine	Medical Oncology
Adrienne Phillips	MD	Assistant Professor of Clinical Medicine	Medical Oncology
Maria Luisa Sulis	MD	Assistant Professor of Clinical Pediatrics	Pediatric Oncology
Felice Tager	M.D.*	Assistant Professor of Clinical Behavioral Medicine	Psychiatry
Ilona Wiener	M.D.*	Assistant Clinical Professor of Psychiatry	Psychiatry
Jason Wright	M.D.	Assist ant Professor of Women's Health	Obstetrics and Gynecology
Wei-Yann Tsai	PhD	Professor of Biostatistics	Interim Director, Biostatistics Shared Resource
Antai Wang	Ph.D.	Assistant Professor of Clinical Biostatistics	Biostatistics Shared Resource
Shuang Wang	PhD	Assistant Professor of Clinical Biostatistics	Biostatistics Shared Resource
Ying Wei	PhD	Assistant Professor of Clinical Biostatistics	Biostatistics Shared Resource

Quality Assurance (QA) Committee

A quality assurance committee has been formed within the Cancer Center, as a subcommittee to the PRMC, to conduct scheduled audits of investigator-initiated, institutional studies that are actively enrolling patients or are closed to accrual, but still in the data collection phase of the study. These audits are conducted on trials of any phase (Phase I, II, or III) and are scheduled quarterly per year, with 1-3 audits conducted in each block. In September 2007, this function was outsourced to Theradex QA Services, Inc.

Data and Safety Monitoring Committee (DSMC)

The HICCC DSMC was established to monitor the safety and conduct of existing CUMC oncology trials, focusing on local investigator-initiated phase I and II clinical trials. Other selected studies may be considered for oversight by the HICC DSMC when considered appropriate by the PRMC, the IRB, or the principal investigator. This committee is specifically responsible for and dedicated to the data and safety monitoring of ongoing clinical trials, and differs from the PRMC's scientific oversight in that it will ensure the focus on subject safety issues and close review of toxicities. The DSMC is a separate and distinct entity from the HICCC PRMC, which oversees scientific aspects of cancer clinical trials.

The DSMC consists of 13 members who are appointed by the HICCC Deputy Director of Clinical Research. Members include three medical oncologists, a neuro-oncologist, two pediatric oncologists, a research pharmacist, pediatric nurse practitioner, two biostatisticians, one clinical research coordinator, the Executive Director, and an individual specializing in regulatory and compliance issues. All 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 principal investigator or co-investigator. In the event that the DSMC biostatistical member is named as a co-investigator biostatistician of a study being monitored, another biostatistician will be appointed to assist in the monitoring of that particular trial.

DSMC meetings are held on alternate Thursdays from 3:00 p.m. to 4:00 p.m. (on days that PRMC meetings are not held). The committee meets as a group one meeting per month and the second monthly meeting is conducted electronically (Virtual DSMC). The purpose of these meetings is to review all adverse events and monitoring reports for ongoing studies submitted for review by investigators conducting local, investigator-initiated trials, and other selected trials. Additional meetings may be held if deemed necessary by the IRB, the PRMC, the DSMC, or a principal investigator. Meeting agendas are sent electronically to

all committee members before each meeting in order to ensure members' attendance for timely review of adverse events and monitoring reports.

DSMC Membership:

Name	Degree	Title	Field of Expertise and Program Affiliation
J. Gregory Mears	M.D.	Clinical Professor of Medicine	Medical Oncology, Chair
Monica Bhatia	M.D.	Assistant Clinical Professor of Pediatrics	Pediatric Oncology
Michael Flamm	M.D.	Associate Clinical Professor Medicine – Oncology	Medical Oncology
Ria G. Hawks	CPNP	Instructor in Clinical Nursing	Pediatric Oncology
Mary Ann Kiernan	M.P.A.	Regulatory Manager	CRMO Regulatory Manager
Mary Ann Kral	PA-C, MsM	Executive Director- Clinical Research	Executive Director CRMO
Rose Lai	M.D.	Assistant Professor of Neurology	Neuro-Oncology
Michael Schwenk,	R.Ph	Research Pharmacist	Research Pharmacy
Maria Luisa Sulis	M.D.	Assistant Professor of Clinical Pediatrics	Pediatric Oncology
Robert Taub	M.D.	Vivian and Seymour Milstein Family Prof. of Clinical Medicine	Medical Oncology
Wei-Yann Tsai	Ph.D.	Professor MSPH Biostatistics	Biostatistics
Reena Vattakalam		Project Coordinator	Medicine
Antai Wang	Ph.D.	Assistant Professor of Clinical Biostatistics	Biostatistics Shared Resource

HICCC Clinical Research Management Office (CRMO)

The Clinical Research Management Office (CRMO) provides administrative assistance and support to the PRMC and DSMC. Additionally, the CRMO:

- Assists investigators in the preparation and submission of clinical trials for review by the HICCC, PRMC, and CUMC IRB;
- Distributes information on active cancer clinical trials to interested investigators or other interested parties by electronic and traditional means;
- Facilitates screening and identification of patients eligible for active protocols;
- Provides centralized subject registration in Velos for PRMC and IRB-approved clinical trials;
- Collects, maintains, and updates data on patients enrolled in clinical trials

- including data on accrual, toxicity, and adverse events;
- Provides information to and assists in the organization of review and monitoring of clinical studies (through the PRMC and DSMC);
- Ensures that cancer clinical trials are conducted in accordance with federal, state, and institutional regulations;
- Develops and maintains an ongoing quality assurance program for institutional studies to ensure protocol compliance and data accuracy;
- Assists in the training of investigators and clinical trial staff in the development and conduct of clinical trials.

Adverse Event and Unanticipated Problem Reporting

All serious adverse event (SAE) reports for all clinical trials conducted at the HICCC are reported by the Principal Investigator to the Regulatory Affairs Office of the Clinical Research Management Office (CRMO) for review by the DSMC, the study sponsor, and FDA (if appropriate). Unanticipated problems involving risks (UP) are reported to the CUMC IRB (via the RASCAL reporting system; www.rascal.columbia.edu). All incidents, experiences, or outcomes that are considered UPs should be reported promptly, but no later than one week (5 business days), to the IRB. By federal regulations, a UP's defined as one that is a) unexpected, b) at least possibly related to participation, and c) increases risk to the subject. This definition also includes any other event the investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect or precaution. Unanticipated Problems that do not meet the above criteria will be returned to the researcher without IRB review.

Investigator Requirements 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 protocols must include a description of a data and safety monitoring plan (description of data to be collected and the reporting mechanism for adverse events) and procedures for its implementation
- The HICCC DSMC is utilized if the proposed study was initially approved by the PRMC and does not fall under the auspices of an outside data and safety monitoring board or a study-specific DSMB formed at the HICCC (e.g., for phase III trials). The study must also be included in DSMC reviews if it includes an intervention felt to be of particularly high risk by the IRB or PRMC and warrants especially close monitoring
- A study-specific DSMB must either exist (if organized by a sponsor) or be established if the proposed study is an investigator-initiated, Phase III clinical trial. If the study is a multi-site clinical trial, the initiating PI is responsible for the formation of the DSMB and monitoring of subjects enrolled at all participating sites

- Note: PIs for studies that do not meet the above criteria for having a DSMB may still propose to have a DSMB if they feel it would be useful for their study, for example, if the study includes a high-risk intervention
- 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 (or review, at meetings held every other week)
- 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 DSMB (if one is established), the DSMC, the IRB and/or the NIH/FDA must be described. The proposed schedule should include a system for sending DSMC/DSMB reports regarding safety issues to the study Principal Investigator (PI). In multisite studies, the study PI is responsible for sending these DSMB reports to individual site PI's, who in turn are required to distribute these reports to their local IRBs.
- If the PI believes that an independent DSMB is required for adequate subject safety, the protocol should indicate the proposed frequency of meetings for the DSMB, and include a proposed list of data items to be provided to the DSMB and estimates for DSMB-related expenses in the proposed protocol budget. The PI should nominate prospective DSMB members, including such information on the nominated DSMB member as: CV, license and a list from each of the nominated DSMB members of their current affiliations with pharmaceutical and biotechnology companies including the name of the company and the type of affiliation (e.g., stockholder, consultant), as well as any other relationship that could be perceived as a conflict of interest related to the study and associated with commercial interests. These nominations are subject to approval by the Chair of the PRMC. DSMB members should have no direct involvement with the study or conflict of interest with investigators conducting the study. If the PI has not proposed a DSMB, but prior to activation of the proposed project the PRMC Chair believes an independent DSMB is required, the PI will make arrangements for a DSMB as described in the section pertaining to phase III trials.
- If the proposed protocol has additional clinical sites besides that of the HICCC, the protocol should describe procedures by which the PI will notify sites of any problems as identified by the DSMC or the DSMB (if the study is a

phase III trial and one is established). When DSMC reports regarding safety issues are sent to the study PI for multi-site studies, the study PI is responsible for sending these DSMC reports to individual site PIs, 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.
- The HICCC CRMO and PRMC are informed of actions, if any, taken by the IRB as a result of its review of DSMC or DSMB reports.

Investigators should also be aware of NIH policy "Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials" (NIH Guide for Grants and Contracts, June 11, 1999),

(<http://grants.nih.gov/grants/guide/notice-files/not-od-00-038.html>) "NIH Policy on Data and Safety Monitoring" (NIH Guide for Grants and Contracts, June 10, 1998),

(<http://grants.nih.gov/grants/guide/notice-files/not98-084.html>) and "Further

Guidance on a Data and Safety Monitoring for Phase I and Phase II Trials" (NIH Guide for Grants and Contracts, June 5, 2000);

(<http://grants.nih.gov/grants/guide/notice-files/not-od-00-038.html>) and the

OHRP guidance

<http://www.hhs.gov/ohrp/policy/advevntguid.html>

Types of Clinical Trials and Monitoring Requirements

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

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.

Types of Monitoring

Unanticipated Problem (UP) Reporting

When an unanticipated problem is experienced by a subject on a clinical trial at the HICCC, the study PI is required to report the UP to the CRMO Regulatory division, IRB, FDA and OBA (if applicable) using appropriate reporting forms in Rascal (www.rascal.columbia.edu). The DSMC will be notified of all UPs by the CRMO, and will review all reported UPs at the biweekly meetings. By federal regulations, a UP is defined as one that is a) unexpected, b) at least possibly related to participation, and c) increases risk to the subject. This definition also includes any other event the investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect or precaution. Unanticipated problems that do not meet the above criteria will be returned to the researcher without IRB. Adverse events which do not meet the definition of a UP also require timely reporting dependent upon the grade of adverse event using CTCAE v4.0 criteria, attribution, and whether the event is expected or unexpected. Safety monitoring will use the same matrix of reporting requirements and schedules as does CTEP which is available at the CTEP website at; <http://ctep.cancer.gov/guidelines/index.html>. NCI Guidelines: Expedited Adverse Event Reporting Requirements for NCI Investigational Agents dated January 2005. All expedited adverse event reports must be reported to the CRMO and the sponsor. The DSMC will review all adverse events reported for investigator-initiated trials at biweekly meetings.

UP reporting requirements for each protocol will be overseen by the IRB annually (through the continuing review process described below), and throughout the year with the review of individual UP reports.

Annual 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 from the prior annual review. This progress report includes the number of subjects entered on the trial, the number of subjects treated, a summary of all UPs in accordance with the CU IRB UP policy (using CTCAE v4.0 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 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 or have no clinical or accrual issues. These renewal applications are reviewed and presented via the agenda at the next PRMC meeting. If an ongoing study does not meet the expedited review criteria, it undergoes a full committee review. Any amendments made to the study during the prior approval period are reviewed. The consent form is also reviewed upon every amendment and revision made to the protocol throughout the previous year, to ensure inclusion of any newly documented toxicities.

The IRB will review continuing review submissions and make recommendations on whether the study should continue unchanged, require modification/amendment, or be closed based on unacceptable risk to participants.

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.

HICCC Quality Assurance Program

A quality assurance program has been formed within the HICCC CRMO, as a subcommittee to the PRMC, to conduct scheduled audits of investigator-initiated, phase I-III, institutional studies that are actively enrolling patients or are closed to accrual, but are still in the data collection phase of the study. Currently, this process is contracted to Theradex QA Services, Inc. (www.theradex.com). Audits are conducted quarterly (or more frequently if indicated), and rotate by research program. A letter is sent to the PI at least two weeks prior to the scheduled audit in order to notify him/her that the audit will take place. This letter will also include a request that the research charts and all regulatory documents be prepared for examination. At least two subject charts are randomly audited for each protocol, and 10% of charts are reviewed if the study has accrued more than 30 subjects. Quality assurance case review forms are used to evaluate subject records, including eligibility, treatment, source documentation, data quality, and regulatory administrative and regulatory information, eligibility and source documentation. Upon the completion of an audit, results are presented in writing to the PI and submitted to the PRMC for a decision on PI response requirements and any other appropriate actions that should be taken. These audits will help to ensure data accuracy and completeness, as well as protocol adherence. Any noncompliance with the federal regulations for the protection of human subjects will be reported to the IRB as well as any other state or federal institution, as needed.

Types of Trials

The phase of the individual trial directs the manner and degree 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.

PHASE III STUDIES

A Phase III Clinical Trial is a broadly based prospective clinical investigation, usually involving several hundred or more human subjects. These trials assist in either evaluating an experimental intervention in comparison with a standard or control intervention or assists in comparing two or more existing treatments to review which has the most efficacious results

Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy, standard of care, or drug licensing by the FDA. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy.

A. NIH/NCI Sponsored Trials

National Cancer Institute Cooperative Group Protocols

The HICCC conducts clinical trials of the Southwest Oncology Group (SWOG), Children's Oncology Group (COG), National Surgical Adjuvant Breast/Colorectal Program (NSABP), Eastern Cooperative Oncology Group (ECOG), Gynecological Oncology Group (GOG), and Radiation Therapy Oncology Group (RTOG).

Upon initial review of a Phase III cooperative group clinical trial, the HICCC Protocol Review and Monitoring Committee (PRMC) will verify that a DSMB exists and is overseen by the study sponsor (cooperative group) or agency. This will be recorded in the minutes of the PRMC meeting. Monitoring of adverse event reports will continue on an institutional level, as these reports will be reviewed by the CUMC IRB. DSMB responsibilities will be conducted by the cooperative group, or designee. If the DSMB oversight monitoring plan in a cooperative group protocol is not clear, the protocol will not be activated until clarification is obtained. (If the protocol is a phase I or II cooperative group protocol and has a monitoring plan not utilizing a DSMB, the plan will be examined by the PRMC to ascertain that adequate oversight is in place. See phase I and phase II studies sections.)

These trials are multi-institutional and use specific data management systems that allow safety and efficacy data to be closely monitored for each study by site and for the group as a whole. We will rely on mandated reporting mechanisms to monitor subjects on these studies, and will not require additional reporting requirements for these trials. However, all SAEs from these trials are required to be reported to the CRMO and all UP's are reported to the IRB.

Trials Supported by Other NIH Grant Mechanisms

Other types of government grants may support large, randomized, phase III trials. Any R01-funded phase III study will require the utilization of a DSMB to monitor adverse events and efficacy and to take action as necessary to protect participating subjects from unnecessary risks. Trials initiated at the HICCC will utilize a study-specific, independent DSMB to be formed (See the description of DSMBs below). The independent, study specific DSMBs will oversee monitoring for trials which may be supported through various funding mechanisms of the NIH, including PIs, etc, and also possibly trials that are receiving sufficient CCSG support to be considered NCI-supported studies. For studies not initiated at the HICCC, as in the case of cooperative group trials, the HICCC PRMC will verify that a DSMB 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 reporting, will take place on an institutional level. If the DSMB oversight monitoring plan in such a protocol is not clear, the protocol will not be activated until clarification is obtained. (If the protocol is a phase I or II cooperative group protocol and has a monitoring plan not utilizing a DSMB, the plan will be examined by the PRMC to ascertain that adequate oversight is in place. See phase I and phase II studies sections.) All study-specific DSMB reports will be forwarded to the study PI, the CUMC IRB, and the PRMC.

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 DSMB exists and is overseen by the study sponsor. This will be recorded in the minutes of the PRMC meeting. Monitoring of UP reports will continue by the IRB, DSMB responsibilities will be conducted the sponsor, or designee, as ascertained during the PRMC protocol review. Local reporting for data and safety monitoring for industry-sponsored trials will require SAEs to be reported to the CRMO, using either industry-specified report formats or the FDA MEDWATCH SAE reporting form, and UPs to the IRB.

B. External Peer Reviewed Trials

These therapeutic clinical trials often require more subjects than a single institution would be able to enroll. This has led to the conduct of these studies in multiple institutions with collaborative agreements between investigators and institutions, outside of a formal cooperative group setting. Monitoring for these studies initiated at the HICCC will be identical to local, investigator-initiated trials (See section I below).

For phase III studies among a limited number of institutions without NCI/NIH monitoring, the PI at the lead institution will be responsible for monitoring the study and establishing the use of a DSMB, if such has not been done by the sponsor. Prior to activating the study at the HICCC, upon initial review of the protocol, the PRMC will review and approve data and safety monitoring plans and verify the existence of the specified external DSMB.

As noted previously, investigators must be aware of NIH policy "Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials" (NIH Guide for Grants and Contracts, June 11, 1999) and NIH Policy on Data and Safety Monitoring" (NIH Guide for Grants and Contracts, June 10, 1998). These documents are relevant to multicenter trials.

C. Investigator-Initiated Institutional Studies

Local, investigator-initiated studies, while including many studies with NIH sponsorship, are often reliant only upon internal funding via the Cancer Center Support. These trials include studies that may receive partial or full external funding, and as a result require particular attention for local monitoring. These studies receive particularly high priority for local oversight.

Since randomized phase III studies usually require large subject populations with lengthy subject follow-up, rarely will such a trial be implemented as a local study. These investigator-initiated phase III trials (or similar randomized phase II trials) in which the study PI is a HICCC member will be monitored by a study-specific, independent DSMB (see the description of DSMBs below).

The large number of subjects required for comparative, randomized, phase III trials prescribes an emphasis on ensuring subject safety. Typically, such trials are conducted over a longer time frame than phase I and II trials. With the likelihood of a large number of subjects included, for longer exposure to investigational regimens, and with a longer period of patient recruitment, the potential for increased risks to subjects exists.

Investigator-initiated trials will be assessed at PRMC review for their data and safety monitoring plans. In the event that no monitoring is specified by external agencies, the study PI will be required to develop a local data and safety monitoring plan that adheres to the following plans.

All investigator-initiated, institutional phase III clinical trials will require regular monitoring by a study-specific, independent DSMB to be formed (see the description of DSMBs below). Since all such Phase III studies are reviewed by their specific DSMBs periodically, they will not also be additionally monitored by the HICCC DSMC.

The following policies describe HICCC requirements for local, investigator-initiated Phase III trials (i.e., when a CU faculty member is PI or the multicenter study). They do not replace existing regulations on protection of human subjects, policies and guidelines for conduct of clinical research, inclusion of women and minorities, research project administration, reporting, and financial management, or requirements of local Institutional Review Boards (IRBs). DHHS regulations for the protection of human subjects are described in 45 CFR46. The implementation of these regulations for PHS research grants involving human subjects is found in the PHS 398 form (rev. 04/2006), available on the NIH home page <http://www.nih.gov/>

This policy describes further steps to be taken in order to ensure the protection of human subjects when the study involves a potentially harmful intervention, and for other Phase III studies to ensure that participants receive an appropriate share of the benefits.

Protocols for any intervention study should clearly state whether the proposed study meets NIH's criteria for a NIH-defined Phase III trial, as well as the basis for that opinion. The PRMC will review this information. If the protocol does not include the required information for such studies (described below), the protocol will not be approved or activated until this information is received, reviewed, and approved by the PRMC.

Therapeutic protocols should describe (in the IRB protocol and consent form) whether the proposed study intervention could have harmful effects, and should list those risks. As part of the review and approval process, the HICCC PRMC and CUMC IRB will review the risks of the intervention. If the proposal for a study with a potentially hazardous intervention does not include the required information for such studies (described below), the protocol will not be activated until this information is received, reviewed, and approved.

Investigator-initiated Phase III protocols must include:

- Plans for monitoring by either an existing DSMB, or a HICCC-initiated study specific, independent DSMB, if applicable.
- A data processing and analysis unit administered by a designated individual other than the PIs of the trial. This individual may report to the PI. All data from this unit must be directly available to the DSMB upon request for review at DSMB meeting, or in the event of additional involvement by the DSMB.
- Procedures for quality assurance/quality control, data management, and analysis.
- Plans for notifying subjects of trial results alter the conclusion of the trial and providing the subjects' health providers with the appropriate information from the trial, as needed, concerning the individual subject (e.g., cessation of drugs, changes in dosage, etc.).

Local reporting for data and safety monitoring for these trials will require all reportable adverse events to be reported to the CRMO, DSMB, and the OBA or FDA (if applicable). UPs are reported to the IRB.

PHASE II STUDIES

Phase II studies are generally designed with a limited number of subjects to determine the efficacy of an agent, regimen, device, or procedure; and may include correlative biologic or pharmacologic studies. While more is known concerning the risks and benefits of the study treatment as compared with Phase I studies, more subjects are typically exposed to the study regimen. Furthermore, toxicity and outcomes can be difficult to ascertain in Phase II studies due to risk of progressive malignancy.

A. NIH/NCI Sponsored Trials

National Cooperative Oncology Group Protocols

Upon initial review of a Phase II cooperative group clinical trial, the HICCC PRMC will note that a DSMB (or other structured monitoring plan), exists, which is overseen by the cooperative group. This will be recorded in the minutes of the PRMC meeting, and no further action regarding monitoring will take place on an institutional level, aside from adverse event reporting.

These trials are multi-institutional and use specific data management systems that allow safety and efficacy data to be closely monitored for each study by site and lot for the group as a whole. We will rely on mandated reporting mechanisms to monitor subjects on these studies, and will not require additional reporting requirements for these trials. However, all SAEs from these trials are required to be

reported to the CRMO. UPs are reported to the IRB.

Other NIH Grants

In the event that an NCI or other NIH grant supports a phase II efficacy trial, data and safety monitoring will be performed in a manner identical to that for local, investigator-initiated phase II trials below (section I).

B. 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 the IRB of record. These protocol-specific plans will adhere to industry and FDA-specified guidelines. The HICCC PRMC will verify that a monitoring plan exists and is overseen by the study sponsor. This will be recorded in the minutes of the PRMC meeting, and no further action regarding monitoring will take place on an institutional level, aside from adverse event reporting. Local reporting for data and safety monitoring for industry-sponsored trials will require SAEs to be reported to the CRMO. UPs are reported to the IRB. If an external DSMB does not exist for this study (as is often seen in Phase I, I/II studies), the HICCC DSMC will be responsible for monitoring the study.

C. External Peer Reviewed Trials

Monitoring for these phase II studies will be identical to local, investigator-initiated trials. (See section D below.) For non-cooperative group, limited-institution phase II studies without NCI/NIH monitoring, the PI at the lead institution will be responsible for the monitoring plan for the study. Prior to activating the study at the HICCC, upon initial review of the protocol, the PRMC will review and approve data and safety monitoring plans.

Local reporting for data and safety monitoring for these trials will require all SAEs/UPs to be reported to the CRMO, OBA or FDA (if applicable), in accordance with the monitoring plan, federal regulations. UPs are reported to the IRB, as per IRB policies.

As noted previously, investigators must be aware of NIH policy "Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials" (NIH Guide for Grants and Contracts, June 11, 1999), "NIH Policy on Data and Safety Monitoring" (NIH Guide for Grants and Contracts, June 10, 1998), and "Further Guidance on a Data and Safety Monitoring for Phase I and Phase II Trials" (NIH Guide for Grants and Contracts, June 5, 2000). All these documents are relevant to multicenter, limited-institution trials.

D. Investigator-initiated Institutional Studies

Once an investigator-initiated, institutional phase II study has been approved by the PRMC, it will be the responsibility of the HICCC DSMC to monitor adverse events and efficacy and to take action as necessary to protect participating subjects from unnecessary risks. The PRMC, upon initial review of the protocol, will make the determination as to whether a study will require the utilization of the HICCC DSMC.

While some variation may exist in monitoring, the DSMC will normally require PIs of local, investigator-initiated, phase II studies to provide SAEs and other reportable AE reports to the DSMC for oversight of monitoring. If additional information is required, the DSMB will request that information from the PI. The DSMC will review reported AEs at regular biweekly meetings and provide the PI and PRMC with written reports following each DSMC meeting. The reports will contain written information regarding findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing, or terminating the trial. (See DSMC Policies and Procedures section below.)

The PRMC will review DSMC reports and recommendations and decide whether the study should continue unchanged, require modification or amendment, or be closed based on unacceptable risk to participants. The PRMC will then contact the study PI to relay its findings and any necessary actions on behalf of the PI and his/her study team, where applicable. Suspended or terminated trials will be reported to the NCI Program Director responsible for the grant supporting the trial, where applicable.

Local reporting for data and safety monitoring for these trials will require ongoing SAE/UPs reporting to the CRMO, DSMB, and the OBA or FDA (if applicable), in accordance with the monitoring plan, federal regulations. Ups are reported to the IRB as per local IRB policies.

PHASE I STUDIES

These studies are generally small, with limited numbers, to determine through dose escalation, a safe and tolerated dose of a drug or regimen and evaluate adverse events/toxicity. They may also include tumor response evaluation, correlative biologic studies, or pharmacologic studies. Occasionally, phase I trials will evaluate feasibility endpoints in the case of medical devices and procedures. Despite the small overall accrual, due to the unknown safety and relatively high risk to the subject of the agent, regimen, or device/procedure under study, these trials require particular attention in monitoring subject safety. The study PI carries the greatest responsibility for subject safety and monitoring in phase I trials. Typically, safety is evaluated at all

the following times: with each subject adverse experience and/or event, at each treatment level (often including three to six subjects), and after all subjects have been accrued- an overall assessment of the treatment results (often including thirty or fewer subjects).

A. NIH/NCI Sponsored Trials

National Cooperative Oncology Group Protocols

In the event of a serious and/or unexpected adverse event experienced by a subject on a phase I cooperative group trial, the NCI requires immediate reporting via the Adverse Event Expedited Reporting System [AdEERS]. New guidelines for reporting requirements went into effect on January 24, 2008. Reporting requirements and timing of reporting are dependent upon the phase of trial, grade of adverse event using CTCAE v4.0 criteria, attribution, and whether the event is expected or unexpected. A matrix of reporting requirements and schedules is available at the CUMC IRB website at : <http://www.columbia.edu/cu/irb/policies/index.html> Unanticipated Problems: Reporting to the IRB of Unanticipated Problems Involving Risks FINALVERSION.012408.pdf).

Other NIH Grants

Other grant mechanisms may provide funding for phase I/II clinical trials of agents for which the NCI/NIH may or may not be the IND holder. These grants supporting clinical trials are required to provide specific data and safety monitoring plans prior to receipt of funding.

In addition to the usual reporting of all SAEs to the CRMO, IRB, and the OBA or FDA (if applicable) other adverse events will be reported to the CRMO using the NCI's AdEERS reporting matrix.

If the study is an investigator-initiated phase I study, it will require monitoring by the HICCC DSMC (see section I). While some variation may exist in monitoring, the DSMC requires PIs to provide SAEs and other reportable AE reports to the DSMC for oversight of monitoring. If additional information is required, the DSMC will request that information from the PI.

B. 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 monitoring plan exists and is overseen by the study

sponsor and external DSMB. This will be recorded in the minutes of the PRMC meeting, and no further action regarding monitoring will take place on an institutional level, aside from adverse event reporting. If an external DSMC does not exist, the HICCC will provide monitoring and oversight. The study will be placed on the next upcoming DSMC agenda for review, determination of risk and schedule of reporting. Monitoring for these studies will be identical to local, investigator-initiated trials. Local reporting for data and safety monitoring for industry-sponsored trials will require SAEs to be reported to the CRMO and UPs to the IRB.

C. External Peer Review Trials

Monitoring for these Phase I studies will be identical to local, investigator-initiated trials. (See section D below.)

For non-cooperative group, phase I studies without NCI/NIH monitoring, the PI at the lead institution will be responsible for the monitoring plan for the study. Prior to activating the study at the HICCC, upon initial review of the protocol, the PRMC will review and approve data and safety monitoring plans.

As noted previously, investigators must be aware of NIH policy "Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials" (NIH Guide For Grants and Contracts, June 11, 1999), "NIH Policy on Data and Safety Monitoring" (NIH Guide for Grants and Contracts, June 10, 1998), and "Further Guidance on a Data and Safety Monitoring for Phase I and Phase II Trials" (NIH Guide (or Grants and Contracts, June 5, 2000). All these documents are relevant to multicenter, limited-institution trials.

D. Investigator-Initiated Institutional Studies

For phase I studies, the PRMC will require the study PI to provide a monitoring plan for subject safety within the study protocol. It will be reviewed as part of the full scientific review of the study at the PRMC meetings.

Once an investigator-initiated, institutional phase I study has been approved by the PRMC, it will be the responsibility of the HICCC DSMC to monitor adverse events and efficacy and to take action as necessary to protect enrolled subjects from unnecessary risks. Phase I studies typically require monthly summary reporting to the HICCC DSMC, as well as real-time UP monitoring via Rascal.

While some variation may exist in monitoring, the DSMC will normally require PIs of local, investigator-initiated phase I studies to provide SAEs and other reportable AE reports to the DSMC for oversight and monitoring. If additional information is

required, the DSMC will request that information from the PI.

For early phase I trials of agents or regimens with little existing data on toxicity, there is a potential for particularly high risk to subjects. If the agent or treatment technique involved is felt to be of particularly high risk (or is a new method of treatment), the investigator may be required to provide data and safety monitoring reports on a more frequent basis to the DSMC. The frequency of reporting will be determined by the DSMC and/or the PRMC for each specific protocol based on anticipated case enlistment and the specific risks anticipated. The report schedule of individual trials may be modified over the course of the study based on the safety experience of subjects treated.

The DSMC will review annual data and safety monitoring reports and make recommendations on whether the study should continue unchanged require modification or amendment, or the closed based on unacceptable risk to participants. The DSMC recommendations will be reported to the PRMC and the study PI. When applicable, suspended or terminated trials will be reported to the NCI Program Director responsible for the grant supporting the trial.

In the event of a SAE experienced by a on a subject local, investigator-initiated phase I trial, the study PI is required to report the SAE to the CRMO, and FDA (if applicable) using appropriate reporting forms. UPs are reported to the IRB.

Adverse events which do not meet the definition of a UP also require timely reporting dependent upon the grade of adverse event using CTCAE v4.0 criteria, attribution, and whether the event is expected or unexpected. Safety monitoring will use the same matrix of reporting requirements and schedules as does CTEP and which is available at the CTEP website at <http://ctep.cancer.gov/guidelines/index.html> NCI Guidelines: Expedited Adverse Event Reporting Requirements for NCI Investigational Agents dated February 25, 2011. All expedited adverse event reports must be reported to the CRMO and UPs reported to the CUMC IRB.

PRMC Responsibilities for Data Safety and Monitoring

Prior to activation of any local, investigator-initiated trial, the PRMC will review the risks of the intervention proposed in the protocol. If the information required in protocols having potentially harmful interventions is not included in the protocol, the committee will notify the PI of what items are missing and indicate, along with any other review issues, that the study will not be approved until this information is received, reviewed, and approved by the PRMC.

If the study is approved by the PRMC on scientific grounds and the PI has not

proposed the utilization of the HICCC DSMC or an independent DSMB, or has not included an appropriate monitoring plan in the protocol, the committee will determine whether the use of the DSMC or a DSMB is required (and if not, what the appropriate monitoring plan would be) for adequate subject safety.

Prior to protocol approval and activation, the PRMC will:

- Review and approve the individual protocol data and safety monitoring plan;
- Determine whether the HICCC DSMC, an existing DSMB, or an independent, study specific DSMB will be utilized for each specific protocol, and notify the PI if the protocol is required to be reviewed by the DSMC or that a DSMB should be formed;
- Include a condition in the protocol review process stating that the PI cannot recruit participants until both the PRMC and the CUMC IRB have approved the monitoring plan;
- Notify the DSMC to initiate the review process for newly approved studies.

Following protocol activation, the PRMC will:

- Evaluate regular reports of the HICCC DSMC and independent DSMBs of specific protocols monitored
- Review DSMB reports
- As needed, request that the DSMB provide advice to the study PI on trial protocol and safety issues arising over course of study, and continuation or termination of the study
- Facilitate implementation of DSMB recommendations by the HICCC
- As needed, request that the DSMB provide advice to the study PI on trial protocol and safety issues; data management, quality, and analysis; recruitment, retention, and protocol adherence issues arising over the Course of the Study and continuation or termination of the study
- Acknowledge reports of serious data discrepancies found by the DSMB, CRMO, 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 DSMB, the HICCC Deputy Director for Clinical Research, and the HICCC CRMO Director.
- Assure 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 as complete information as possible that 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. Auditors will report directly to the PRMC Chair.

Data Safety and Monitoring Boards (DSMBs)

As stated above, the PRMC will determine whether an independent DSMB will be formed and utilized for each specific trial. For all studies, the PRMC will include in the protocol review process a condition stating that the protocol will not be approved until a monitoring plan is approved by the committee. As stated above, for phase III studies, this will consist of either confirmation of the existence of an outside DSMB, or that a DSMB will be formed specifically for a particular study.

Once a DSMB is established, its initial tasks are to review the entire study protocol, the Manual of Procedures, and the informed consent form with regard to recruitment, randomization, intervention, subject safety, data management, plans for auditing of primary subject records, quality control and analysis, and to identify needed modifications. The DSMB shall then identify the relevant data parameters and the format of the information to be regularly reported. If the need for modifications to the protocol, Manual of Procedures, consent form, etc., is indicated by the DSMB and/or the PRMC, the DSMB shall postpone its recommendation for the initiation of subject recruitment until after the receipt of a satisfactorily revised protocol.

DSMB Responsibilities:

The DSMB must meet on a regular schedule (but, not less than twice a year) over the course of study (with additional meetings as needed) in order to:

- Review data (including masked data) over the course of the trial relating to efficacy, recruitment, randomization, compliance, retention, protocol adherence, trials operating procedures, form completion, intervention effects, gender and minority inclusion and subject safety;
- Identify problems relating to safety over the course of the study. Inform study PI via written report, Who in turn will ensure that all clinical site PIs receive this report;
- Identify needs for additional data relevant to safety issues and request these data from the study investigators;
- Propose appropriate analyses and periodically review developing data on safety and endpoints;
- At each meeting, consider the rationale for continuation of the study, with respect to recruitment, progress of randomization, retention, protocol adherence and compliance, data management, safety issues, and outcome data, if relevant, and make a recommendation for or against continuation of the trial;
- Provide the PI and PRMC Chair written reports following each DSMB meeting. The PI will then forward the report to the IRB;
- Provide advice on issues regarding data discrepancies found by the data auditing system or other sources. If the PRMC Chair requests this advice, it

should be provided by the DSMB in writing within two weeks of the date of the request;

- Accept submissions of manuscripts of trial results as they are submitted for publication for committee records, and forward these to the CRMO for their files;
- If there is more than one clinical site, the study PI is responsible for sending the reports to individual site PIs, who in turn are required to distribute the report to their local IRBs, as detailed in 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).

Data and Safety Monitoring Committee (DSMC) Policies and Procedures

DSMC Meetings

The HICCC DSMC meets regularly every other week to review adverse event reports submitted by investigators conducting local, investigator-initiated trials. The committee meets as a group one meeting per month and the second monthly meeting is conducted electronically (Virtual DSMC). Additional meetings will be held if deemed necessary by the IRB, the PRMC, the DSMC, or a principal investigator.

The chairman opens the meeting, and attendance is recorded. The minutes are taken as each agenda item is discussed. The meeting agenda includes the following items:

- Review of the minutes of the last meeting;
- Adverse events for initial review including SAEs;
- Re-review of unresolved SAEs;
- Review of new studies for HICCC DSMC monitoring
- List of external SAE's for administrative approval;
- Other protocol monitoring issues and discussion.

DSMC Responsibilities

The responsibilities of the DSMC are to:

- Review the protocol's plans for data and safety monitoring, and recommendations from the PRMC;
- Review data relating to, toxicity, efficacy, recruitment, accrual, compliance, retention, protocol adherence, trial operating procedures, intervention effects, and subject safety. Data will be submitted to the DSMC in the format of a reporting sheet which will be determined at the beginning of a trial;
- Identify problems relating to safety over the course of the study. Inform the study PI via written report, who will in turn will ensure that all clinical

- site PIs (where applicable) receive this report;
- Identify needs for additional data relevant to safety issues and request these data from the study investigator(s);
 - Periodically review developing data on safety and endpoints;
 - At each meeting, consider the rationale for continuation of the study, with respect to recruitment, progress of randomization, retention, protocol adherence and compliance, data management, safety issues, and outcome data, if relevant, and make a recommendation for or against continuation of the trial;
 - Prepare a report (in the form of a letter) of each study reviewed at the meeting and provide it to the PI. Unacceptable reports will be forwarded promptly to the PI and the IRB. A summary of meeting business will be sent to the PRMC Chair for review. Any significant issues will be discussed at the following PRMC meeting;
 - If there is more than one clinical site, the study PI is responsible for sending the DSMC reports to individual site PIs, who in turn are required to distribute the report to their local IRBs, as detailed in 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);
 - Inform PIs that if a trial is suspended or terminated that they are required to report this to the NCI Program Director responsible for the grant supporting the trial, where applicable;
 - Provide advice on issues regarding data discrepancies found by the data auditing system or other sources;
 - To avoid conflicts of interest, members of the DSMC will not monitor studies for which they serve as principal investigator or co-investigator. In the event that the DSMC biostatistical member is named as a co-investigator biostatistician of a study being monitored, another biostatistician will be appointed to assist in the monitoring of that particular trial.

DSMC Recommendations

DSMC recommendations should be based on results for the trial being monitored as well as on data available to the DSMC from other studies. It is the responsibility of the HICCC CRMO staff and DSMC members 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 trial principal investigator and PRMC. If the DSMC recommends a study change for subject safety or efficacy reasons, the trial principal investigator PI must act to implement the change as expeditiously as possible. In the unlikely situation that the trial principal investigator does not concur with the DSMC, then the PRMC

Chair must be informed of the reason for disagreement. The trial PI (principal investigator), 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 CRMO staff to seek advice to assist in reaching a mutually acceptable decision.

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 will disclose any potential conflicts of interest, whether real or perceived, to the trial principal investigator 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 will not monitor studies for which they serve as principal investigator or co-investigator. In the event that the DSMC biostatistical member is a named co-investigator/biostatistician of a study being monitored, a separate clinical biostatistician will be appointed by the DSMC Chair to assist in the monitoring of that 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.

If a recommendation is made to change a trial for other than subject safety or efficacy reasons or for slow accrual, the DSMC will provide an adequate rationale for its decision.

IRB Review and Approval of the Data and Safety Monitoring Plan

The HICCC Data and Safety Monitoring Plan has been approved by the CUMC IRB. 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.