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Herbert Irving Comprehensive Cancer Center
Columbia University Irving Medical Center
New York Presbyterian Hospital

DATA AND SAFETY MONITORING PLAN

Approval:

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Table of Acronyms

CIRB	Central Institutional Review Board
COT	Compliance Oversight Team
CPDM	Clinical Protocol Data Management
CUIMC	Columbia University Irving Medical Center
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
FDA	Food and Drug Administration
HICCC	Herbert Irving Comprehensive Cancer Center
IRB	Institutional Review Board
NCI	National Cancer Institute
NCTN	National Clinical Trial Network
NIH	National Institutes of Health
PI	Principal Investigator
PRMC	Protocol Review and Monitoring Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
UP	Unanticipated Problem
WIRB	Western Institutional Review Board

Summary

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

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

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

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

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

DATA AND SAFETY MONITORING PLAN

Introduction

The Herbert Irving Comprehensive Cancer Center (HICCC) considers the safety of participants in clinical trials to be an extremely high priority. In accordance with NIH policy, every interventional trial conducted at the HICCC must include a plan for data and safety monitoring, including descriptions of data to be collected and adverse event reporting procedures. The HICCC Data and Safety Monitoring Committee (DSMC) is responsible for, and dedicated to, data and safety monitoring of on-going clinical trials.

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

It is the responsibility of the DSMC to ensure that the monitoring of different types of trials is timely and effective. The HICCC Deputy Director and HICCC Associate Director of Clinical Trials oversee the operations of the DSMC. Clinical research at HICCC ranges across all investigative phases and is supported by a broad range of sponsors. Thus, it is essential that the DSMC operate according to the DSM Plan (DSMP) and independently from PRMC, CPDM and other entities. Every effort is made to prioritize investigator-sponsored trials, and it is the primary responsibility of the HICCC DSMC to monitor these studies.

The method and degree of monitoring done by the DSMC will vary depending on the phase of the study and the degree of risk encountered by subjects. The HICCC Data and Safety Monitoring Plan (DSMP) has been developed to coordinate and provide oversight for data and safety monitoring for all interventional trials consistent with the National Institutes of Health Policy for Data and Safety Monitoring dated June 10, 1999 (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) and with NCI guidance (https://deainfo.nci.nih.gov/grantspolicies/datasafety.pdf).

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

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

The conduct of the HICCC clinical research is in full accordance with medical center IRB policy, which may be found at:
https://research.columbia.edu/sites/default/files/content/HRPO/IRB_SOP_v5.1_4.12.18_TOC_176a.pdf

HICCC Data and Safety Monitoring: Organization and Responsibilities

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

- All studies must have a structured adverse event determination, monitoring and reporting system, including procedures for referring and/or treating subjects experiencing unanticipated problems (UP). Investigator-sponsored 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 schema, and if needed, specific criteria and procedures for unblinding.
- The schedule for reporting adverse events to the DSMC, the IRB and/or the NIH/FDA must be described. In 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 PIs, who in turn are required to submit these reports to their local IRBs.

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

Types of Clinical Trials and Monitoring Requirements

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

Types of Trials

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

NIH/NCI-Sponsored Trials/National Cancer Institute National Clinical Trial Network (NCTN)/ Industry-Sponsored / Externally Peer Reviewed Protocols

Upon initial PRMC review, the committee may determine that review by the HICCC DSMC is required if there is no External DSMC/DSMB in place and if there are concerns regarding the safety profile of the Investigational Agent. These trials may be subject to DSMC review at the

discretion of the PRMC.

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

Investigator-Initiated Institutional Studies

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

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

Protocol Review and Monitoring Committee (PRMC)

Clinical protocol review is conducted by the Protocol Review and Monitoring Committee (PRMC). The HICCC PRMC is comprised of members who are appointed by the HICCC Director and Deputy Director, spanning multiple departments, divisions, and areas of expertise related to oncology research. The Protocol Review and Monitoring Committee (PRMC) reviews the scientific merit, scientific priorities, and progress of all clinical protocols involving cancer patients at the HICCC. In addition to the scientific review, the PRMC is also responsible for accrual monitoring. The PRMC meets biweekly in coordination with oncology-oriented IRB Subpanels to review newly submitted interventional protocols. The PRMC has four functions: (1) review protocol feasibility and prioritization; (2) evaluate interventional protocols for innovation, scientific merit and statistical soundness; (3) assess the accrual progress of therapeutic and interventional cancer trials at the time of continuing review (to determine whether trials should continue or be closed for lack of progress); and (4) 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.

Initial Review

The PRMC 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-consortia (e.g., ETCTN) trials are subject to review regarding feasibility and are administratively approved by the PRMC Chair. The specific elements of the protocol that are addressed by reviewers include, but are not limited to, the merit of the research question, and the innovation of the study design, feasibility, proper allocation of institutional resources, if the appropriate number of patients are available locally, and whether the statistical plan is adequate to test the study hypothesis. The PRMC also ensures that trials do not overlap in eligibility criteria, which may lead

to competition for the same pool of patients.

The submission to both the PRMC and the IRB are done simultaneously via the on-line Research Compliance and Administration System (RASCAL), the proprietary Columbia University information system for research regulatory management and compliance.

Continuing Review

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

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

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

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

PRMC membership

Name	Degree	Title	Field of Expertise and Program Affiliation in CCSG/Other
Joseph Jurcic (Chair)	MD	Professor of Medicine at CUIMC	Hematology/Medical Oncology; Tumor Biology and Microenvironment
June Hou	MD	Associate Professor of Obstetrics & Gynecology	Gynecologic Oncology; N/A
Diane George	MD	Assistant Professor of Pediatrics at CUIMC	Pediatric Oncology; N/A
Andrew Lipsky	MD	Assistant Professor of Medicine	Hematologic Malignancies; Cancer genomics and Epigenomics
Julia McGuinness	MD	Assistant Professor of Medicine	Breast Oncology; Cancer Populations Sciences
Divaya Bhutani	MD	Assistant Professor of Medicine	Hematology, Medical Oncology; Non-programmatically aligned
Brian Gill	MD	Assistant Professor of Neurological Surgery	Neurological Surgery; Tumor Biology and Microenvironment
Peter Pan	MD	Assistant Professor of Neurology	Neuro-Oncology; Non-programmatically aligned
Mark Stein	MD	Associate Professor of Medical Oncology	Hematology/Medical Oncology; Precision Oncology and Systems Biology
Jennifer Oberg	EdD	Director of Research, Developmental Therapeutics Program	Pediatric Oncology; Non-programmatically aligned
Leah Katz	MD	Assistant Professor of Radiation Oncology	Radiation Oncology; Non-programmatically aligned
Catherine Spina	MD, PhD	Assistant Professor of Radiation Oncology	Radiation Oncology; Tumor Biology and Microenvironment
Jeanine Genkinger	PhD	Associate Professor of Epidemiology	Cancer Epidemiology; Cancer Populations Science
Elnaz Anjom	PharmD	Director of Research Pharmacy	Research Pharmacy; N/A
Tony Wang	MD	Professor of Radiation Oncology (in Neurological Surgery)	Radiation Oncology; Precision Oncology and Systems Biology
Shikun Wang	PhD	Assistant Professor of Biostatistics	Biostatistics; Cancer Populations Sciences
Samuel Pan	MSc	Cancer Biostatistics Shared Resource, Manager	Biostatistics; N/A
Yifei Sun	PhD	Assistant Professor of Biostatistics	Biostatistics N/A
Xin Ma	MD	Assistant Professor of Biostatistics	Biostatistics; N/A

PRMC Responsibilities for Data and Safety Monitoring

Following protocol activation, the PRMC will:

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

HICCC Clinical Protocol and Data Management (CPDM) Office

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

Investigators negotiate sponsored budgets and contracts in cooperation with the CUIMC 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 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 120 staff.

CPDM Compliance Core Quality Monitoring

The Clinical Protocol Data Management (CPDM) of the HICCC has a Compliance Core tasked with ongoing monitoring of investigator-sponsored interventional trials being conducted at HICCC. In addition, through the Compliance Core, the CPDM oversees central subject registration. Central subject registration reduces the likelihood of accruing ineligible participants by verifying

that timely, accurate, and complete source documentation is provided during the informed consent process. The central registrars ensure the real time entry of accrual information into Velos eResearch (clinical trial management software).

Externally sponsored protocols (including industry, NCTN, non-CUIMC externally peer-reviewed or non-CUIMC investigator sponsored) that are monitored or audited by the sponsor are not routinely reviewed by the CPDM Compliance Core; however, a summary of deficiencies is requested from the sponsor following each audit visit. The Compliance Core may be requested to assist with audit preparation by performing an internal informal review in advance of an audit.

Monitoring of Investigator-Sponsored Trials

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

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

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

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

1. Critical Findings: High risk of having a major impact on the analysis of the trial, the data integrity, or result in substantial risk of regulatory authority action toward the PI or HICCC
2. Major Findings: Do not compromise trial conduct or data, but represent a departure from the protocol or a stated International Conference of Harmonization GCP guideline, regulation, or New York Presbyterian Hospital and CUIMC SOPs. A finding with an actual or potential effect on patient safety, data integrity, or study outcome
3. Minor Findings: represent a violation of the protocol, stated GCP guideline, regulation, or New York Presbyterian Hospital and CUIMC SOPs, but is a finding with minimal or no impact on patient safety, data integrity, or study outcome.

After each visit, monitoring follow-up letters will be disseminated to the PI, research team, and DSMC management. If the trial involves an IND in which a CUIMC faculty member is the Sponsor-Investigator, the CU Clinical Trials Office IND Assistance management will also be included. The final monitoring report will be reviewed by DSMC to determine if additional information and clarification is needed. If applicable, the Committee's action and

recommendations will be sent to the PI. The same process will apply to sub-sites participating in CUIMC lead multi-center trials. Monitors will conduct remote monitoring of the affiliates.

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

Data and Safety Monitoring Committee (DSMC)

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

The HICCC DSMC is comprises members who are appointed by the HICCC Director and Deputy Director, spanning multiple departments, divisions, and areas of expertise related to oncology research. Ad hoc members may be added at the request of the DSMC Chair or Program Manager to ensure adequate review as required. All voting members have extensive experience with clinical trials. To avoid conflicts of interest, members of the DSMC will not monitor studies for which they serve as the PI or Co-Investigator.

DSMC Meetings: Formats and Procedures

The DSMC meets biweekly, alternating between in-person Zoom meetings and virtual meetings conducted via email. The first meeting of each month is held as an in-person Zoom meeting, allowing for real-time discussion and interaction among committee members. The second meeting of the month is conducted virtually via email, with all correspondence and meeting materials distributed to facilitate remote participation. For both Zoom and virtual meetings, the review process maintains the same scope and rigor to ensure thorough and consistent evaluation of all protocols. Reviewers provide detailed comments, and committee members submit their votes via email for virtual meetings, while discussions and votes are recorded during Zoom meetings. Decisions are determined by a majority vote in both formats. To accommodate any urgent matters or based on recommendations from the DSMC Chair, additional meetings can be scheduled.
The review of new protocols for level of risk and frequency of ongoing reporting are reserved for full committee meetings in addition to review of reported UPs, Serious Adverse Events (SAEs), and requested protocol safety reports. The virtual meeting is a review of reported UPs, SAEs, and requested protocol safety reports. The DSMC Research Manager or Project Coordinator will electronically distribute the full committee meeting agenda and necessary review documents 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 Research Manager or Project Coordinator the day before the meeting. The day of the virtual meeting the DSMC members are emailed the agenda, the assigned reviewer's comments, and a voting sheet. The members will either accept or reject the reviewer's recommendation. A majority

vote carries the DSMC decision.

The full committee meeting is called to order by the DSMC Chair, attendance is recorded, and the minutes from the previous meeting are reviewed and either accepted with revision or deferred for revision. The DSMC Program Manager 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, violations and other relevant discussion items.

DSMC Membership

Name	Degree/ Certification	Title	Field of Expertise and Program Affiliation
Katherine Crew (Chair)	MD, MS	Professor of Medicine and Epidemiology at CUMC	Medical Oncology/Epidemiology; Cancer Population Sciences
Aya Haggiagi	MB ChB	Assistant Professor of Neurology at CUMC	Neuro Oncology; N/A
Elnaz Anjom	MD	Director of Research Pharmacy	CUIMC; N/A
Monica Bhatia	MD	Assistant Professor of Pediatrics at CUIMC	Pediatric Oncology; Tumor Biology and Microenvironment
Benjamin Herzberg	MD, MSc	Assistant Professor of Medicine at CUMC	Medical Oncology; Precision Oncology and Systems Biology
Ryan Moy	MD, PhD	Assistant Professor of Medicine at CUIMC	Medical Oncology, Cancer Genomics and Epigenomics
Karie Runcie	MD	Assistant Professor of Medicine at CUIMC	Medical Oncology; N/A

DSMC Responsibilities

The responsibilities of the DSMC are to:

- Review the protocol data and safety monitoring plan and proposed study specific monitoring plan. Based on the level of risk, the DSMC will determine the frequency of reporting, which may be monthly, quarterly, biannually, or annually.
- Conduct a thorough review of the unanticipated problems, SAEs, adverse events, and toxicity profile associated with each study subject. When it is deemed necessary, the DSMC may suspend or terminate a study based on toxicity, adverse events reported, or unanticipated problems. The DSMC may mandate revision to the protocol and informed consent to increase study monitoring and proper participant notification.

- Track safety and efficacy issues throughout the duration of the study and request additional relevant data from the PI. If needed, the DSMC will suspend or terminate the study when there is a significant concern for participant safety.
- Review requests for waivers and other significant protocol deviations.
- Review compliance and adherence to the approved protocol and mandate appropriate action when deviations are identified. If significant deviations are observed, which alters the overall integrity of the study, the DSMC may recommend suspension or termination of the study.
- Consider the rationale for continuation of the study based on overall safety and compliance.
- Prepare correspondence communicating DSMC recommendations to the PI and Study Team. Any findings of unacceptable performance will be forwarded promptly to the PI and the IRB. The PRMC/DSMC Program Manager will also inform the PRMC.
- If CUIMC is the coordinating/lead site of a multicenter study, the CUIMC PI is responsible for sending the DSMC reports to sub-site PIs. The sub-site PI is required to submit the HICCC DSMC report to the sub-site IRB pursuant to the NIH "Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials" (NIH Guide for Grants and Contracts, June 11, 1999).

DSMC Review

Unanticipated Problems (UP)

A UP is defined as any incident, experience or outcome involving risk to subjects or others in any human subjects research that meets the following criteria: a) unexpected, b) related or possibly related to participation in such research, and c) suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized. Each UP should be reported to the CUIMC 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 CUIMC IRB UP reporting policy

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

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

Serious Adverse Events

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

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

Safety reports

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

DSMC Recommendations

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

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

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

Integration with the CPDM Compliance Core

The DSMC works closely with the Compliance Core in developing and reviewing study-specific DSMPs that systematically provide accurate risk assessment of each trial. This collaboration serves to streamline and harmonize the DSMC and the CPDM Compliance Core activities, ensuring effective and efficient use of all resources. This integration has led to a comprehensive and adaptive risk-based monitoring approach, actionable items being addressed on a real-time DSMC level, and increased oversight with increased efficiency. The Committee also reviews the results of mandatory study monitoring conducted by the Compliance Core and other groups on an ongoing basis.

Study Specific Data and Safety Monitoring Plans

As of March 28, 2018, the DSMC has mandated study-specific data and safety monitoring plans (ssDSMPs) for all HICCC-led interventional investigator-sponsored studies. The DSMC reviews the protocol and ssDSMP for each new trial. The ssDSMP defines the study risk using Key Risk Indicators (KRIs), which include features of the study design (dose escalation or fixed dose, standard or adaptive design, phase), the source of funding, whether the investigator holds an IND/IDE, the number of participating centers, the complexity of the intervention, whether the agent/device is manufactured by CUIMC, the number and complexity of correlative studies, and the expected accrual rate and number. KRIs for each parameter are scored to delineate high-, moderate-, or low-risk categories, which then guide the DSMC in determining the monitoring frequency. Baseline monitoring activities and critical data points are also defined based on study-specific endpoints.

Monitoring Summary Reports

With each DSMC progress report/safety report that is submitted, the HICCC DSMC reviews the monitoring activity summary forms. These forms outline all the monitoring activities conducted during that review period, the frequency, and if these items were performed according to the predetermined plan. These reports also include a summary of major actionable findings from any on-site/remote monitoring visits during the specified reporting period along with their status of reconciliation. Findings from both CUIMC and sub-sites are included in these review summaries. The DSMC reviews and provides comments to the PI/Sponsor-Investigator and study team regarding any actionable or concerning items.

Criteria for Study Suspension or Termination

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

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

Research Non-compliance, Excessive Protocol Violations, and/or questionable Data Quality: Repeated major protocol or regulatory violations, stopping rule violations, failure to comply with

corrective recommendations of the DSMC, or incomplete or inaccurate data reporting will lead to trial suspension and possible recommendation for termination.

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

Quality Assurance (QA): IRB Oversight

The Columbia University IRB Compliance Oversight Team (COT) oversees quality assurance of all clinical research at the University. The IRB COT conducts both for cause and not-for-cause audits on a regular basis, and findings of non-compliance require formalized corrective action plans. Findings are also reported to the PIs, the HICCC Director, Associate Director for Clinical Trials and relevant institutional officials, and if it is required, federal agencies are notified.

Release of Outcome Data

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

Conflict of Interest

Individuals appointed to the DSMC and PRMC will disclose any potential conflicts of interest, whether real or perceived, to the PI and the appropriate HICCC official(s), in accordance with Columbia University policies and under the authority of Naomi Schrag, Vice President for Research Compliance, Training and Policy (in the office of the Executive Vice President). 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.

Adjudication

In the event that a Principal Investigator does not agree with the determination of either the PRMC and/or DSMC, the PI may present the matter to the Associate Director of Clinical as both committees are under his/her purview. The Associate Director of Clinical will mediate disputes between PIs and the committees and will make the final determination, in discussion with the Deputy Director and Director as needed.

IRB Review and Approval of the Data and Safety Monitoring Plan

The CUIMC 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.

HICCC DATA AND SAFETY MONITORING PLAN clean 07.29.2024

Final Audit Report 2024-08-05

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