



AT THE FOREFRONT

**UChicago** **Medicine**

Comprehensive Cancer Center

# Data Safety and Monitoring Plan

Version	Revision Date
2.0	March 7, 2023
1.0	December 2016

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## Acronyms

<b>Abbreviation</b>	<b>Term</b>
AD	Associate Director
AE	Adverse Event
BSD	Biological Sciences Division
CAPA	Corrective and Preventative Action
CET	Clinical and Experimental Therapeutics
CFR	Code of Federal Regulation
COE	Community Outreach and Engagement
COI	Conflict of Interest
CPDM	Clinical Protocol and Data Management
CTMS	Clinical Trials Management System
CROAC	Cancer Research Oversight and Advisory Committee
CTEP	Cancer Therapy Evaluation Program
CTMB	Clinical Trials Monitoring Branch
CTSO	Clinical Trials Support Office
DLT	Dose Limiting Toxicity
DSMB	Data & Safety Monitoring Board
DSMC	Data & Safety Monitoring Committee
EDDOP	Early Drug Development Opportunity Program
ETCTN	Experimental Therapeutics Clinical Trials Network
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
HIRO	Human Imaging Research Office
HSP	Human Subject Protection
HTRC	Human Tissue Resource Core
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
MDT	Multidisciplinary Disease Team
NCI	National Cancer Institute
NCTN	National Clinical Trials Network
NIH	National Institutes of Health
OCR	Office of Clinical Research
PI	Principal Investigator
PRMC	Protocol Review and Monitoring Committee
PRMS	Protocol Review and Monitoring System
QU	Quality Unit
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
UC	University of Chicago
UCCCC	University of Chicago Medicine Comprehensive Cancer Center

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UCM	University Chicago Medicine
UCMC	University of Chicago Medical Center
UP	Unanticipated Problem
URA	University Research Administration

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## 1. INTRODUCTION

This document outlines the policies established by the University of Chicago Medicine Comprehensive Cancer Center (UCCCC) for the appropriate oversight and monitoring of the conduct of **cancer-focused clinical research** conducted at University of Chicago Medicine and its network sites. This document also outlines procedures for oversight and monitoring of multi-site cancer-focused clinical research conducted at, sponsored by, and/or coordinated by the UCCCC.

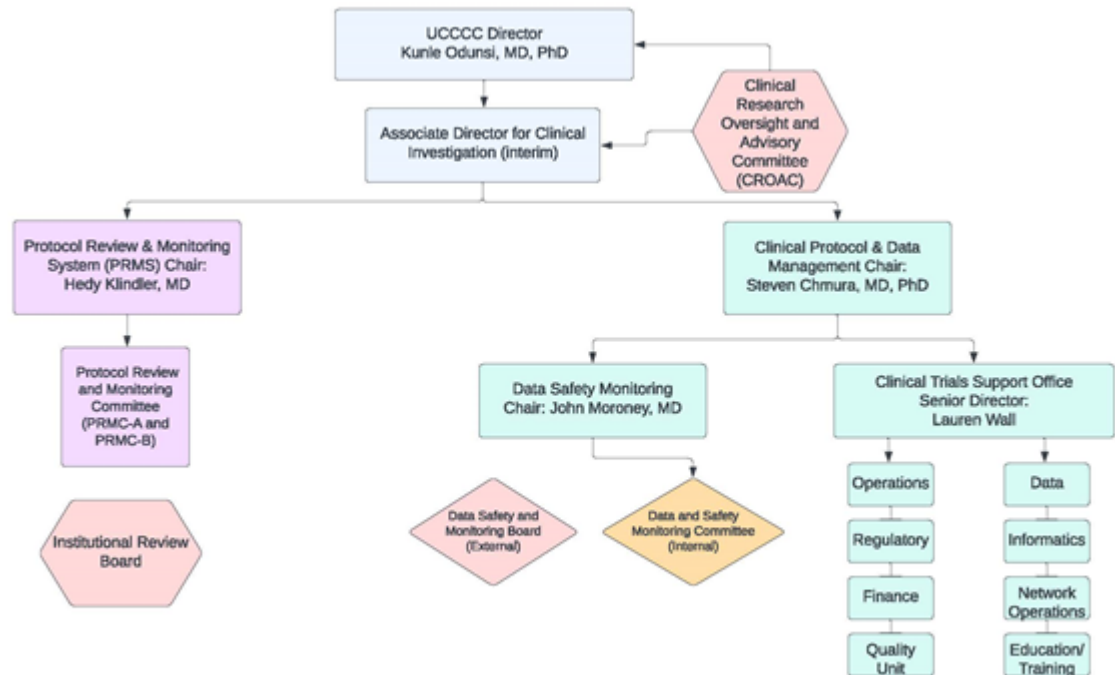
The purpose of these policies is to ensure the safety of participants, the validity of data, and the scientific progress of cancer-focused clinical research including termination of studies for which significant risks have been uncovered or when it appears that the project cannot be conducted successfully. These policies apply to all cancer-focused clinical research as defined in Section 9 of this document regardless of study sponsorship or source of support.

Adherence to these policies is a requirement of Cancer Center membership. Failure to comply with the policies and procedures outlined in this document may result in suspension of UCCCC membership privileges including access to, or discounts on, shared facilities as well as other Cancer Center resources (e.g., access to services of the Cancer Center's Clinical Trials Support Office [CTSO] and review by the Protocol Review and Monitoring Committee [PRMC, which is required for Institutional Review Board (IRB) approval]).

The UCCCC Clinical Trials Support Office (CTSO) serves as the centralized infrastructure that supports system-wide monitoring and oversight of all clinical research activities. All prospective cancer-focused trials in UCCCC go through a central protocol review and monitoring system (PRMS) managed by the UCCCC. In addition, the CTSO is responsible for coordinating, facilitating, and reporting UCCCC cancer-focused trials and ensuring that they are conducted in a consistent and cohesive manner. The CTSO is comprised of research staff responsible for clinical research quality assurance, clinical research education, clinical research informatics, clinical research data management, and inter-institutional operations coordination. The CTSO also works closely with the University's Biostatistics Laboratory & Research Computing Group, for clinical research analytics and reporting.

The committees that provide institutional oversight are the Protocol Review and Monitoring Committees (PRMC), BSD/UCMC Institutional Review Boards (IRB), the Clinical Research Oversight and Advisory Committee (CROAC), Data and Safety Monitoring Committee (DSMC), and Data and Safety Monitoring Boards (DSMB). Individuals from the University of Chicago Medicine (UCM) and unaffiliated individuals serve as members on committees as appropriate.

**Figure 1: UCCCC Organizational Chart**



## 2. COMMITTEE OVERVIEW AND MEMBERSHIPS

### 2.1. Data & Safety Monitoring Committees (DSMC)

#### 2.1.1. Overview

The UCCCC Data & Safety Monitoring Committee (DSMC) is responsible for providing ongoing data and safety monitoring of all active cancer focused clinical trials conducted by a UCCCC investigator. This includes all multi-site trials sponsored, or otherwise coordinated, by an UCCCC investigator.

The DSMC meets once monthly and is tasked with providing ongoing monitoring of safety, data compliance, and overall study progress of cancer clinical trials. The DSMC advises the IRB and Associate Director (AD) for Clinical Investigation of any recommended actions, and reports directly to the AD for Clinical Investigations who informs the Director.

#### 2.1.2. Membership

Consisting of internal UCCCC faculty and staff, voting members include faculty physicians, biostatisticians, and other scientists based on their experience, reputation for objectivity, absence of conflicts of interest, and knowledge of clinical trials methodology.

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DSMC members are appointed by the UCCCC Director in consultation with the AD for Clinical Investigation and the Clinical Research Oversight and Advisory Committee (CROAC). Appointments to the DSMC are generally for a three-year term; however, members may be re-appointed and serve longer at the discretion of the Chair and AD for Clinical Investigation.

The UCCCC DSMC is comprised of members including representatives from gynecologic oncology and medical oncology, including at least one member with a hematologic specialty, nursing, pharmacy and a biostatistician. Quorum consist of five voting members. Additional ad hoc members are invited as appropriate (e.g., radiation oncology, pediatrics, pharmacy, etc.) to provide necessary input to facilitate review of ongoing trials. Representatives from the CTSO regulatory, clinical operations leadership and CTSO Quality Unit team serve as non-voting members.

### **2.1.1. Management of Conflicts of Interest(s)**

Conflicts of Interest (COI) including professional or commercial activities external to the University or financial interests of the investigator (including their spouse or dependent children) are managed at an institutional level in compliance with the applicable policies and processes as described in Section 7 of this document.

As part of the DSMC submission packet, the submitting investigator is required to provide details of any conflicts of interest they may hold related to the protocol and those of any sub-investigator or other staff member that is anticipated to make significant contributions to the study design or data. Any institutional conflicts (e.g. patents or propriety interest in sponsor company) must also be disclosed. The DSMC will discuss all such conflicts as part of their review to ensure that the COI has not impacted the integrity of the study data or study conduct at the UCCCC.

DSMC submissions are assigned to reviewers by the DSMC Chair (or Vice-Chair) who ensure that the assigned reviewer(s) are not assigned to review submissions on which they are principal investigator, those submitted from within their Multidisciplinary Team(s) (MDT), or which they might otherwise serve as a sub-investigator and make significant contributions to the study design or data. At each meeting, members are asked to announce any COI with the trials under review. Investigators with a conflict of interest can participate in the discussion of a trial but must abstain from voting on any trial on which they serve as PI, sub-investigator, statistician, or any other supporting consultive role (e.g. medical monitor, member of steering committee, external DSMB member, etc.). Any disclosed COI and the record of each absentia vote are documented in the DSMC meeting minutes.

## **2.2. Data & Safety Monitoring Boards (DSMB)**

### **2.2.1. Overview**

A Data & Safety Monitoring Board (DSMB) is an independent group of experts that serve in an individual capacity and provide their expertise and recommendations related to continued conduct of a specific clinical trial. All randomized, controlled, phase 3 clinical trials



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conducted at the UCCCC must have an independent DSMB convened by the trial sponsor. Selected high-risk clinical trials, as requested during the formal scientific review process conducted by the Protocol Review and Monitoring Committee (PRMC), may also be required to convene a DSMB.

For clinical trials sponsored and/or coordinated by a UCCCC investigator, it is the responsibility of the sponsor-investigator to ensure that an independent DSMB is convened and meets regularly.

Once a clinical trial is activated, the DSMB should convene as often as necessary as specified in their DSMB charter, but at least once annually, to examine the accumulated safety and enrollment data, review study progress, and discuss other factors (internal or external to the study) that might impact continuation of the trial as designed. A DSMB meeting may be requested by DSMB members, industry collaborator(s), IRB, or Principal Investigator(s) at any time to discuss safety concerns. Decisions to hold ad hoc meetings will be made by the DSMB Chair.

The main responsibilities of the DSMB are to review data and safety monitoring reports at periodic intervals. They will also monitor patient accrual, submit requests for additional analyses as deemed necessary, evaluate the performance of the participating clinical sites, evaluate the performance of the Coordinating Center, and provide recommendations regarding the protocol as to continue, query, or stop the clinical trial. They will review reports of adverse events to ensure patient safety as well as efficacy analyses.

For clinical trials sponsored and/or coordinated by a UCCCC investigator, the CTSO Quality Unit may assist the sponsor-investigator with the establishment of the DSMB and will provide administrative support and coordinate the meetings. They will retain all documentation related to actions taken by the DSMB and issue an outcomes letter of the findings. All required documentation is centrally maintained in this office.

### **2.2.2. Membership**

DSMB members are appointed by the trial sponsor (or sponsor-investigator as applicable) and membership should reflect the appropriate medical disciplines, and other specialties necessary to interpret the data from the clinical trial and to fully evaluate participant safety.

Following National Institutes of Health (NIH) and Food and Drug Administration (FDA) guidance, the number of DSMB members depends on the trial and its complexity, design, and risk level, but generally consists of three to seven members including, at a minimum:

- Expert(s) in the clinical aspects of the disease/patient population being studied;
- One or more biostatisticians; and,
- Investigators with expertise in current clinical trials conduct and methodology.

For clinical trials sponsored and/or coordinated by a UCCCC investigator, UCCCC members and other UChicago staff, without direct involvement in study implementation; and who

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meet other membership criteria may participate as Board Members with voting rights. However, the majority of DSMB voting members should not be affiliated with the University of Chicago.

At least one representative from the UCCCC Quality Unit may serve as a non-voting member and provides administrative support as described in the prior section.

### **2.2.3. Management of Conflict of Interest**

The majority of the DSMB members are external, and therefore eliminates the potential for study reviewer conflicts and/or bias. Final DSMB charter and membership list will be reviewed approved by CROAC to assure independence and no COI. At every DSMB meeting all voting members must indicate verbally any COI, and this will be recorded in the minutes of the meeting.

## **2.3. Protocol Review and Monitoring Committee (PRMC)**

### **2.3.1. Overview**

A critical activity for Cancer Centers is a mechanism for assuring rigorous scientific review of cancer clinical research activities. Documentation that all protocols are reviewed through a two-stage scientific review is a National Cancer Institute (NCI) mandate.

At the UCCCC scientific review is required to assess scientific merit, feasibility, and prioritization of all cancer clinical trials. This review is conducted by one of two Protocol Review and Monitoring Committees (PRMC-A or PRMC-B). Both of these two committees have identical responsibility and authority. Non-interventional cancer focused research undergoes an administrative review by PRMC staff. This administrative review focuses on ensuring compliance with all aspects of data safety monitoring and auditing including plans for registration and accrual reporting in the UCCCC CTMS.

For cancer-focused clinical trials, a PRMC approval is a requirement for review by the Institutional Review Board (IRB) so that no cancer-focused clinical trial can be activated without appropriate UCCCC oversight.

The CTSO provides administrative support and retains all documentation related to actions taken by the PRMC. All required documentation is centrally maintained in this office. The CTSO Director reports directly to the UCCCC AD for Cancer Center Administration.

### **2.3.2. Membership**

PRMC members are appointed by the AD for Clinical Investigation in consultation with the UCCCC Director and Chairs/Vice-Chairs of the PRMC based on interest and experience with clinical trials and research. The current Committees have broad representation including Medicine, Surgery, Pediatrics, Radiation and Cellular Oncology, Radiology, Pharmacy, and Biostatistics. Non-voting members including from the CTSO, the Human Imaging Research Office (HIRO), and research phlebotomy and the Human Tissue Resource Center (HTRC)

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serve as a feasibility sub-committee to ensure appropriate resources and prioritization of the research based on available UCCCC and institutional resources.

Patient advocate members are appointed by the AD for Clinical Investigation in consultation with the COE director and the UCCCC Director.

### **2.3.3. Management of Conflicts of Interest(s)**

Conflicts of Interest (COI) including professional or commercial activities external to the University or financial interests of the investigator (including their spouse or dependent children) are managed at an institutional level in compliance with the applicable policies and processes as described in Section 7 of this document.

As part of the PRMC submission packet, the submitting investigator is required to provide details of any conflicts of interest they may hold related to the protocol and those of any sub-investigator or other staff member that is anticipated to make significant contributions to the study design or data. Any institutional conflicts (e.g. patents or propriety interest in Sponsor Company) must also be disclosed (if known). The PRMC will discuss all such conflicts as part of their review. Trials which have a significant institutional or investigator conflict of interest will be designated as High Risk (as described in Table 2) and will be subject to quarterly review by the UCCCC DSMC.

PRMC submissions are assigned to reviewers by the PRMC Chairs (or Vice-Chairs) who ensure that the assigned reviewer(s) are not assigned to review submissions on which they are principal investigator, those submitted from within their Multidisciplinary Team(s) (MDT), or which they might otherwise serve as a sub-investigator and make significant contributions to the study design or data. At each meeting, members are asked to announce any COI with the trials under review. Investigators with a conflict of interest can participate in the discussion of a trial but must abstain from voting on any trial on which they serve as PI, sub-investigator, statistician, or any other supporting consulting role (e.g. medical monitor, member of steering committee, etc.). Any disclosed COI and the record of each absentia vote are documented in the PRMC meeting minutes.

## **2.4. Institutional Review Board (IRB)**

### **2.4.1. Overview**

The University of Chicago Biological Sciences Division (BSD) and The University of Chicago Medical Center (UCMC) Institutional Review Boards (IRB) [hereafter referred to as the BSD IRB] is charged by the University with the responsibility for review and surveillance of research involving human subjects carried out in the BSD and UCMC or by a BSD/UCMC investigator.

All clinical or behavioral research in the BSD or UCMC conducted by University of Chicago investigators and involving human subjects, regardless of its source of financial support, must be approved by the IRB; unless the IRB determines it to be exempt from their review or

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the Office of Clinical Research (OCR) determines that review by another IRB may be accepted in lieu of BSD IRB review (e.g. allows for single or central IRB review).

No UCCCC or other institutional committee, office, or official may permit human subjects research to proceed that has not been approved or exempted from review by the IRB or its designee.

The BSD IRB has three committees, each of which meets on a monthly basis to ensure timely review and protocol initiation. Two of the committees primarily review new protocol submissions and amendments, whereas the third primarily provides continuing review of active protocols. However, each committee may review any type of research/change as necessary. No IRB meeting will be conducted without the necessary quorum, and no Committee decisions will be made lacking the vote of at least one non-scientist and at least one scientist. If a quorum fails for any reason, no further actions are taken until quorum is restored.

The Chair, with the assistance of the Vice-Chair(s) and the IRB administrative staff, are responsible for correspondence to the Principal Investigator regarding necessary revisions, approval or deferral of the study. Copies of the outcomes letters are sent to the Principal Investigator and the designated regulatory contact(s).

#### **2.4.2. Membership**

The BSD IRB follows the IRB membership requirements as outlined at 45 CFR 46.107 and 21 CFR 56.107.

The IRB membership of each Committee comprises faculty members from a broad range of disciplines and each Committee includes at least one community (unaffiliated) member, a member without scientific expertise, and at least one member with scientific expertise. In addition, representatives from University and Medical Center Legal Counsel, Pharmacy, and Nursing serve as members of the IRB Committees. The term of membership is three years. All terms are renewable.

The UCCCC Director, in consultation with leaders from the respective departments and sections, may recommend to the Dean of BSD and/or IRB Chair, UCCCC members for inclusion on the IRB based on an interest in, and experience with, clinical trials and research.

The OCR provides administrative support and retains all documentation related to actions taken by the IRB. All required documentation is centrally maintained in that office.

#### **2.4.3. Management of Conflicts of Interest(s)**

Conflicts of Interest (COI) including professional or commercial activities external to the University or financial interests of the investigator (including their spouse or dependent children) are managed at an institutional level in compliance with the applicable policies and processes as described in Section 7 of this document.

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As part of any IRB submission of a specific protocol, investigators are required to disclose any potential conflict of interest resulting from their (or any other personnel listed on the submission) involvement in the proposed study and if, they have not already done so, they are instructed to complete the internal disclosure form described in Section 7.

IRB submissions are assigned to reviewers by the IRB staff who ensure that the assigned reviewer(s) are not assigned to review submissions on which they are principal investigator or are otherwise involved (e.g. listed on study personnel list), those submitted from within their section/department, or where the reviewer has known financial conflict with the submission. Reviewers with a conflict of interest may be asked to recuse themselves from the discussion of any research on which they are conflicted. Reviewers must abstain from voting on any trial on which they serve as PI, sub-investigator, statistician, other research personnel, or if they have any other supporting roles or financial conflicts related to the research. Any disclosed COI and the record of each absentia vote are documented in the IRB meeting minutes.

The BSD IRB is charged with ensuring that human subjects research is conducted in compliance with any potential conflicts and any University-issued conflict of interest management plans. The IRB Committee will review and discuss any investigator or institutional conflicts of interest as part of initial and continuing protocol review. The IRB may also consult the University's Office of Legal Counsel on conflict of interest issues. The IRB Committee has final authority to determine whether the management of a disclosed interest is sufficient to permit the approval of associated human subject research.

The BSD IRB will not grant final approval to a protocol until the University approves any applicable COI management plan(s) and all necessary amendments to the study documents have been made. In the event, the IRB believes there is a COI that was not revealed to the University, the IRB will identify the potential conflict and require the PI or other study personnel (e.g. sub-investigator) to provide proof of institutional disclosure or to submit an updated disclosure to the University for evaluation as appropriate. The IRB may also recommend disclosure of the COI on the patient consent form(s).

## **2.5. Cancer Research Oversight and Advisory Committee (CROAC)**

### **2.5.1. Overview**

The Cancer Research Oversight and Advisory Committee (CROAC) is advisor to the Director and AD for Clinical Investigation as relates to the following:

- Prioritization and progress of CTSO process improvement initiatives including the ongoing work of the task force outcomes,
- Advise on DSMC and PRMS policies and procedures,
- Engagement of CPDM elements with UCCCC membership, and
- Engagement of Community Outreach and Engagement (COE) within UCCCC clinical trials infrastructure.

The meetings are held quarterly with additional meetings on an as-needed basis. If the issues in question require additional input, the appropriate individuals (e.g., Departmental or Section leadership) will be invited to attend.

**2.5.2. Membership**

The CROAC is comprised of senior UCCCC leadership and other senior investigators including representation from pediatric and hematologic malignancies. Other staff and investigators are invited to join based on experience and interest in clinical research.

CROAC members are appointed by the UCCCC Director, in consultation with the AD for Clinical Investigation and current CROAC members.

**2.5.3. Managing Conflict of Interest**

The committee members are notified of the conflict of interest policy on every agenda, and members recuse themselves if there is a conflict of interest with the protocol(s) being reviewed. If a conflict of interest exists between a reviewers and his/her assignment, it is the reviewer’s responsibility to notify the CTSO meeting coordinators upon receipt of the meeting packet.

At every CROAC meeting all voting members must indicate verbally any COI, and this will be recorded in the minutes of the meeting.

**Table 1: CROAC Membership**

<b>Members</b>	<b>Role</b>
Kunle Odunsi, MD, PhD	UCCCC Director
Eileen Dolan, PhD	Deputy Director
Russell Szmulewitz, MD (interim)	AD for Clinical Investigation
Steven Chmura, MD, PhD	CPDM Chair
Hedy Kindler, MD	PRMS Chair
John Moroney, MD	DSMC Chair
Susan Cohn, MD	Director of Clinical Sciences, Dept. of Pediatrics
Wendy Stock, MD	CET Program Leader
Nita Lee, MD	COE Leader
Drew Memmott, MPhil, MA	AD for Administration
Lauren Wall, MS	Sr. Director of CTSO

**3. OVERSIGHT OF CLINICAL RESEARCH PRE-ACTIVATION**

**3.1. Overview**

All cancer-focused clinical research conducted at the UCCCC and its network sites requires a multi-step review process to assess feasibility, ensure appropriate availability of resources

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needed to conduct the trial, scientific merit, and overall level of risk. Oversight is provided by the multidisciplinary teams (MDTs), PRMC, IRB, and other ancillary internal review committees as required by the design of the clinical trials (e.g. Institutional Biosafety or Radiation Safety Committees).

**Figure 2: Pre-activation Processes**



### **3.2. Multidisciplinary Teams Review (1<sup>st</sup> Stage Review)**

Multidisciplinary teams (MDT) are organized on a disease focused basis (e.g. breast or lung cancer) and program focused basis (e.g. Developmental Therapeutics, Cellular Therapy). They review and approve all proposed cancer focused clinical trials for feasibility and determine priority within the MDT. During this process, the resource requirements and logistical needs of the protocol are evaluated to ensure the protocol can be conducted properly and safely by each participating disease program.

Investigators developing new investigator-initiated clinical trials must present the preliminary trial design to the MDT early in the process. This initial concept review is intended to ensure that there is consensus from the group regarding the overall merit of the trial and trial design and to ensure that the planned protocol requirements, funding plans, and overall feasibility are appropriate and the trial does not compete with other ongoing or planned trials.

### **3.3. Scientific Review (2<sup>nd</sup> Stage Review)**

All prospective cancer-focused clinical trials must be submitted to the PRMC. The PRMC will conduct formal scientific review, as part of PRMS activities, to assess the scientific merit of the trial, appropriateness of the research question and study design, and overall feasibility of conduct of the trial at our centers.

Other prospective cancer focused clinical research which does not qualify as a clinical trial, will be administratively reviewed by the PRMS administrator or their designee.

All new clinical research which undergoes PRMC review or administrative assessment is assigned a level of risk according to the in Table 2.

**Table 2: PRMS Risk Definitions**

<b>Risk Level</b>	<b>Definition</b>	<b>Example</b>
Minimal	Clinical research which involves no intervention(s).	<p>Observational research</p> <p>Research studies involving long-term follow-up-only</p> <p>Sample and/or questionnaire collection studies</p>
Low	Clinical trial which involves the use of an intervention but does not meet criteria for Moderate or High Risk	<p>Externally-sponsored Phase 3 clinical trial which is routinely monitored by the sponsor</p> <p>Interventional trials which do not involve a drug/device/or similar (e.g. imaging, education or behavior intervention, etc.)</p>
Moderate	<p>Clinical trial which meets <u>any one</u> of the following criteria:</p> <ul style="list-style-type: none"> <li>• Externally-sponsored Phase 1 or Phase 2 clinical trial which is routinely monitored by the sponsor</li> <li>• National clinical trial of any phase (e.g. NCTN or ETCTN/EDDOP trials)</li> </ul>	
High	<p>Clinical trial of any phase which meets <u>any one</u> of the following criteria:</p> <ul style="list-style-type: none"> <li>• Investigator-initiated trial (IIT)</li> <li>• Life-threatening toxicity is expected in the majority of participants and which would not be expected in the context of standard management of the patient.</li> <li>• Additional oversight required as determined by the PRMS</li> </ul>	<p>Trials that require inpatient hospitalization for administration of the study agent, except for trials involving acute patients where admission is routinely required for the clinical management of the patient (e.g. leukemia and/or cell therapy trials)</p> <p>Trials involving products manufactured in-house under Good Manufacturing Practices (GMP) guidelines,</p>



Risk Level	Definition	Example
		<p data-bbox="1047 268 1398 373">Trials with significant institutional or investigator conflict of interest</p> <p data-bbox="1047 415 1373 520">Trials involving first in human studies of cellular therapy products</p>

PRMC review/approval or administrative acknowledgment must occur prior to formal IRB review. Cancer-focused clinical research, with the exception of those considered PRMS Exempt, will not be sent for formal review or approved by the IRB without appropriate PRMC documentation.

### 3.4. IRB Review

All clinical research must be reviewed and approved by the BSD IRB unless the IRB determines it to be exempt from their review. When the IRB allows for reliance on another IRB (e.g. allows for single or central IRB review), an abbreviated IRB application must be submitted to the BSD IRB for local review and acknowledgment. No clinical research conducted at the UCCCC may begin without the appropriate review and approval or acknowledgment from the BSD IRB.

### 3.5. Additional Review of Investigator-Initiated Multi-Site Clinical Trials

In addition to other required internal reviews, all new cancer focused investigator-initiated, multi-site clinical trials must undergo a review by the CTSO Quality Unit prior to PRMC or IRB submission. This review is to ensure that the sponsor-investigator has the appropriate resources to conduct the multi-center trial and will have the appropriate oversight of trial conduct at all sites.

The PI is responsible for developing a comprehensive study manual/plan which outlines how the study is to be monitored and procedures for conduct at the external affiliate sites. The manual describes in a stepwise manner all of the responsibilities of the UCCCC as coordinating site, the research sites, how data flows between sites to the UCCCC and sites, shipment of investigational products, monitoring and auditing, data sharing, management of events etc.

Minimally this is to include the following information. The CTSO Quality Unit will provide templates and support in preparing these documents.

- Locations at which the trial is to be conducted (if known) or number of planned sites if specific sites have not yet been identified
- Proposed activation timeline for each site (if known)

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- Description of how eligibility will be confirmed
  - Description of regulatory essential document collection requirements
  - Description of data collection plan (e.g. RedCap or Velos data forms)
  - Description of deviation reporting and tracking plan
  - Description of sample collection and shipment requirements (if applicable)
  - Details on how to order the investigational product(s)
  - Description of adverse event reporting plan (including plan for reporting serious adverse events or other events requiring expedited reporting). This must include details and timelines for reporting events to any funders or collaborators supporting the research.
  - Data and site monitoring plan include plan to ensure timely data entry by the sites and plans for risk based source data monitoring
  - Audit plan

This plan must be reviewed and approved by the Quality Unit before the study can open at any external affiliate sites.

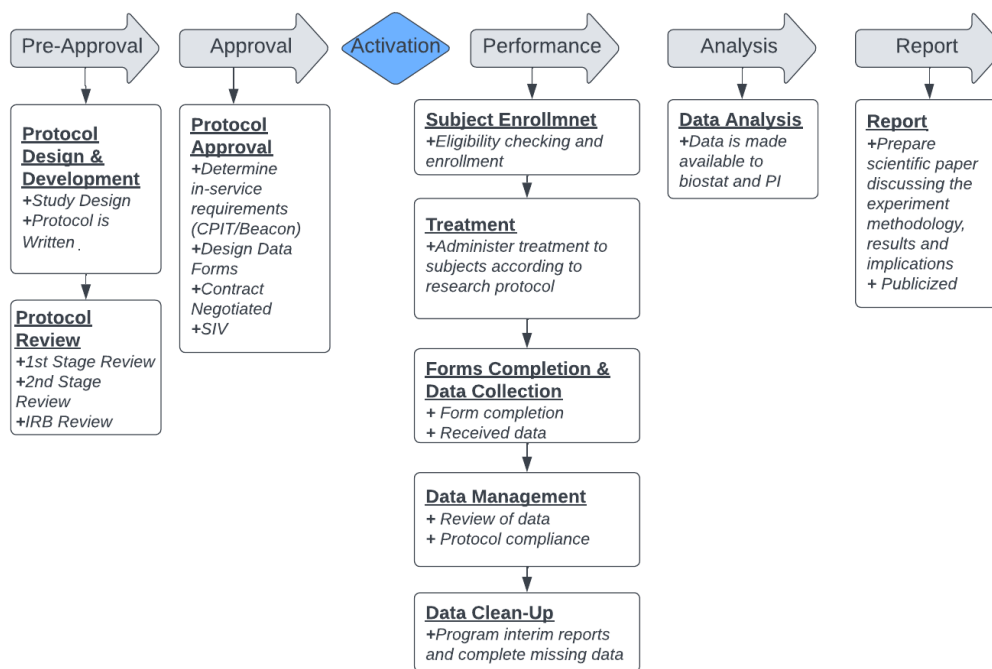
#### **4. Oversight of Trials Post-Activation**

All cancer-focused clinical trials conducted at the UCCCC requires a multi-step monitoring and oversight process to ensure the safety of trial participants, the validity of trial data, the scientific progress of studies, and to ensure closure of studies for which significant risks have been uncovered or when it appears that the trial cannot be completed successfully.

The DSMC and CTSO together serve to provide the necessary oversight, monitoring, and auditing of these clinical trials. See Figure 2. The PRMC and IRB provide additional oversight related to trial progress, scientific merit, and accrual as per their policies and procedures.

During the conduct of a trial, oversight is provided through close coordination between multiple committees and departments. The oversight committees may request a corrective action plan based on the observed and/or reported deficiencies or non-compliance in trial management. If an issue could potentially affect subject safety, the IRB is notified. The committees may also request follow-up information on AEs/SAEs and makes recommendations regarding the status of the study or protocol or consent form modifications if there are concerns about safety or quality.

**Figure 2: UCCCC Trial Oversight Process**



## 4.1. Scientific Review

The PRMC is responsible for monitoring the accrual, evaluating the ongoing scientific merit, and assuring compliance with the approved data safety monitoring plan for all active cancer focused clinical trials.

### 4.1.1. Amendment Review

The PRMC is responsible for reviewing all significant changes to active cancer-focused clinical trials prior to implementation, to ensure that the changes to the research do not result in a change to scientific merit, PRMS-defined Risk Level, or otherwise change the reasonability of continuing to conduct the study at the UCCCC.

Routine changes to the Investigator Brochure or other documents not required as part of the PRMC initial submission packet do not require PRMC re-review (e.g. consent form edits).

### 4.1.2. Continuing Review

All active clinical trials are subject to continuing review by the PRMC. An initial review will occur six months after the trial opens to accrual. Subsequent reviews will occur at 6 or 12 month timepoints based on accrual to date or other concerns related to trial feasibility or continued merit.

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Monitoring zero and slow-accruing trials maximizes subject contributions by minimizing the likelihood that research will fail to complete its objectives. All active clinical trials are thus reviewed for slow or inadequate accrual, based on the goals approved by the PRMC as part of their initial (or most recent) review. The PRMC has the authority to close trials due to slow accrual or other concerns regarding study progress or safety.

Monitoring of rapidly accruing trials identifies research that requires close monitoring to ensure adequate resources, prospective data collection and appropriate safety review.

## **4.2. IRB Review**

The IRB has the authority to observe and/or monitor UCCCC research to whatever extent they consider necessary to protect human subjects. They also have the authority to suspend or terminate research for serious or continuing non-compliance with the Common Rule, DHHS regulations, and FDA regulations, or its own findings, determinations and requirements.

All UCCCC cancer-focused trials fall under the jurisdiction of the BSD/UCMC IRB, unless there is an established reliance agreement designating an external IRB as the IRB of record.

The BSD/UCMC IRBs (or other IRB of record) routinely review Amendments, Continuing Reviews, and reports of Major Deviations/Noncompliance or other Unanticipated Problems. These committees perform a detailed review of all submissions and associated documents. If additional information is needed to complete the review and make a determination, the committee will query the PI. At the completion of the review, the IRB is authorized to take any action deemed necessary to ensure subject safety, protocol compliance and data integrity. The IRB's determination is binding.

### **4.2.1. Amendment Review**

All proposed changes to approved clinical research must be submitted to the IRB of record for review and approval. Amendments to approved protocols may not be initiated until IRB approval has been obtained, except where necessary to eliminate apparent immediate hazards to the subject.

The IRB determines when it is necessary to inform subjects of any new findings that reveal additional risk or information that may alter their willingness to participate in the research.

### **4.2.2. Continuing Review**

The IRB will perform continuing review of ongoing clinical research in accordance with applicable federal regulations. In most cases, the IRB will perform continuing review at intervals appropriate to the degree of risk, not less than once per year.

At the time of Continuing Review, the IRB will review and assess subject enrollment progress, protocol deviations, safety information (including any internally reported SAEs),

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DSMC minutes, external DSMB reports, and potential change in level of risk. Investigator conflicts of interest will also be reviewed as applicable.

#### **4.2.3. Review of Major Deviations/Noncompliance and other Unanticipated Problems**

The BSD IRB requires reporting and review of all unanticipated problems (UPs) involving risks to subjects or others, including all problems, events or information that is not expected, given the nature of the research procedures and the subject population being studied; and which suggests that the research places subjects or others at a greater risk of harm or discomfort related to the research than was previously known.

All UPs must be reported by the PI to the IRB using their electronic submission system in a timely manner.

In order to ensure adequate protection of the welfare of subjects, the IRB will review the UP and consider whether the event impacts the risk/benefit ratio and whether the study needs to be stopped, require modifications to the study, or if the timetable for continuing review requires revision. The IRB may suspend or request further changes to ongoing clinical research due to safety concerns.

#### **4.3. DSMC Review**

All clinical trials conducted at, or coordinated by, the UCCCC are subject to review by the DSMC. The frequency of DSMC review is dependent on the risk level assigned during PRMC review. See Table 3. The initial review by the DSMC is triggered based on the first subject accrual to a protocol. DSMC reviews continue until the DSMC feels there are no subject safety concerns that require further monitoring.

**Table 3: Data and Safety Monitoring Requirements and Frequency**

<b>PRMS Risk Level</b>	<b>DSMC</b>
Low	Every 12 Months
Moderate	Every 6 Months
High	Every 3 Months
<b>Review Requirements</b>	Accrual Progress at UCCCC Overall Study Progress Serious Adverse Events Protocol Deviations Unanticipated Problems Data Progress/Timeliness Audit Findings DSMB outcomes (IIT only)
<b>Outcome Report to</b>	
Continue	PI MDT Lead PRMC <sup>1</sup> IRB <sup>1</sup>
Query	PI MDT Lead PRMC <sup>1</sup> IRB <sup>1</sup> NCI <sup>2</sup>
Close	PI MDT Lead PRMC <sup>1</sup> IRB <sup>1</sup> NCI <sup>2</sup>
<sup>1</sup> DSMC outcome letters will be sent to the PRMC and IRB at time of IRB Continuing Review	
<sup>2</sup> DSMC recommendations to halt or close a trial for safety reasons or noncompliance will be reported to the NCI (Protocol Information Office) for all NCI-sponsored (non cooperative group) trials.	

**4.3.1. Meeting Structure**

The DSMC meets at least monthly to clinical trials for toxicity, protocol and data submission compliance, and compliance with internal policies and process. The DSMC may choose to increase or decrease the frequency based on the protocol status, accrual rate, and review of ongoing safety indicators. Members will recuse themselves from voting if a conflict of interest exist for a given protocol.

The DSMC requests information from the PI, study team, and the Quality Unit to facilitate

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review. The information includes:

- Accrual progress
- Overall study progress
- Current dose level information
- Dose-limiting toxicity information (if applicable)
- SAEs and other significant safety updates (e.g. participant deaths)
- Protocol deviations
- Unanticipated Problem Reports reported to BSD IRB and/or external IRB of record
- Data entry progress and timeliness
- Audit Finding and corrective action plans (as applicable)
- External DSMB outcomes (as applicable for UCCCC-sponsored trials only)

For multi-site trials sponsored or coordinated by the UCCCC, information about accrual progress, SAEs and safety updates, and data progress for the external affiliate sites must be submitted to the DSMC.

All trial and participant information remain confidential.

DSMC reviewers assigned to each protocol receive the requested information in advance. During the meeting, the assigned reviewer presents the trial, raises any concerns for discussion, and makes recommendations to the committee as to the frequency of review. DSMC meeting minutes are maintained by the CTSO Quality Unit.

#### **4.3.2. Meeting Outcomes and Requirements**

The DSMC may recommend a trial *continue*, *query the PI* and request additional information, or recommend a trial for *closure* based on their discussion and review as per the below definitions. All DSMC recommendations will be based on available data from the trial, including, information on primary and secondary efficacy measures, adverse events, and quality of trial conduct, as recorded in the CTMS and/or Case Report Form system for the trial, along with relevant information external to the trial.

- Continue – No concerns and trial may proceed as planned.
- Query – DSMC requires additional information to complete their review or has other concerns regarding the continued conduct of the study. This may include a recommendation to pause new enrollment, pause treatment of subjects, or recommendation to amend the protocol or other trial documents.
- Closure – DSMC has major concerns regarding the trial progress and recommend trial be closed.

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DSMC outcome letters will be provided to the PI, MDT leader(s) and research manager, designated regulatory contact, and PRMC.

PI written response to DSMC queries must be provided to the DSMC within 60 days of the date the outcome letter is issued. Requests for extension may be considered by the DSMC Chair, if requested by the PI (or their designee).

Lack of response will be assumed to be due to lack of interest in continuing the study by the submitting PI and the study will be recommended for closure.

In the event that a trial is requested to be closed, the DSMC administrative team will update the trial status in the UCCCC's CTMS to prevent further patient enrollment.

A copy of each DSMC outcome letter will be shared with the IRB and PRMC at the time of their respective continuing reviews.

#### **4.4. Study Closure**

All temporary and permanent study closures and reason for closure will be documented in the UCCCC's CTMS to prevent further patient enrollment. CTRP and clinicaltrials.gov (if applicable) will be updated to report the closure date.

For multi-site trials, sponsored or coordinated by the UCCCC, a temporary or permanent closure notification will be sent to the external participating sites to notify them of enrollment status.

All temporary or permanent closures or suspension of NCI-sponsored clinical trials (non-cooperative group) will be reported by the CTSO to the Protocol Information Office (PIO) of the Cancer Therapy Evaluation Program (CTEP). NCI-sponsored (non-cooperative group) protocols that are closed by the IRB or the DSMC for non-compliance or safety concerns will be reported immediately to the PIO.

CTSO staff are responsible for reporting such closures or suspensions in IRB approval to the appropriate regulatory agency when required.

#### **4.5. DSMB Review**

The PRMC, IRB, and/or Quality Unit will identify protocols to be reviewed by an independent DSMB (as described in Section 2).

Externally sponsored trials with a DSMB will follow the DSMB charter put in place by the trial sponsor. For trials sponsored, or coordinated, by the UCCCC and which require an external DSMB, the following requirements must be met.



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#### **4.5.1. Meeting Structure**

Once a clinical trial is activated, the DSMB should convene as often as necessary and as described in the DSMB charter, but at least once annually, to examine the accumulated safety and enrollment data, review study progress, and discuss other factors (internal or external to the study) that might impact continuation of the study as designed.

A DSMB meeting may be requested by DSMB members, industry collaborator(s), IRB, or study Principal Investigator(s) at any time to discuss safety concerns. Decisions to hold ad hoc meetings will be made by the DSMB Chair.

The DSMB may request information from the PI, study team, and the CTSO Quality Unit to facilitate review. This information includes up-to-date accrual, current dose level information, dose-limiting toxicity information, all unexpected and related adverse events, and participant deaths. Other information may be requested for multi-center trials or as requested by the committee.

Each meeting has three parts:

- An open session in which members of the trial team, including the statistician, may be present, at the request of the DSMB, to review the conduct of the trial and to answer questions from members of the DSMB. The focus of this open session may be on accrual, protocol compliance, and general toxicity issues. Outcome results must not be discussed during this session.
- A closed session of the DSMB is to be held to allow discussion of the general conduct of the trial and all outcome results, including toxicities and adverse events, as well as develop recommendations and take necessary votes.
- A summary executive session follows to summarize and evaluate the overall meeting, and to plan the next meeting. The meeting may occur by conference call if necessary.

After all members have provided their input and expressed their concerns, the DSMB will make their recommendations, and these will be documented in an outcome letter.

#### **4.5.2. Meeting Outcomes and Requirements**

At the conclusion of the review, the DSMB provides a written recommendation based on its review of the data and the progress report.

Recommendations made are based on the overall risk benefit assessment; consideration is given to whether the potential benefits of the investigational intervention have been established or whether the risks appear greater than previously anticipated.

The DSMB will recommend to:

- Continue
- Query

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- Close the trial

Recommendations about early trial termination or continuation must be based on all available data from the trial, including information on primary and secondary efficacy measures, adverse events, and quality of trial conduct, along with relevant information external to the trial.

DSMB may also include recommendations regarding:

- Eligibility criteria
- Sample size
- Participant recruitment rate
- Participant withdrawals

In the event that a trial is requested to modify its protocol, a copy of the outcome letter will be shared with IRB and PRMC as part of an amendment submission.

A copy of each DSMB outcome letter will be shared with the IRB and PRMC at the time of their respective continuing reviews.

## **5. Event Reporting**

Adverse events must be reported to the trial sponsor, UCCCC, DSMC, IRB, and regulatory agencies as outlined below.

Protocol deviations/violations/exceptions (other events) must also be reported to the sponsor, UCCCC, DSMC, IRB, and regulatory agencies as outlined below.

### **5.1. Adverse Event Reporting**

All adverse events including serious events or other events requiring expedited reporting (e.g. pregnancy, secondary malignancies, or events of special interest) must be reported to the trial sponsor (or their designee) as outlined in the approved protocol document(s). All clinical trials conducted at the UCCCC are required to have a section describing the adverse event reporting requirements.

#### **5.1.1. Expedited Adverse Event Reporting**

##### **5.1.1.1. Events Occurring at the UCCCC**

All serious adverse events or other events requiring expedited reporting which occur at the UCCCC must be reported to the trial sponsor (or their designee) as outlined in the approved protocol document(s).

In addition to the protocol mandated reporting, all such events must be reported in the Cancer

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Center's CTMS within 1 *business* day of investigator awareness. Event report must include the following information:

- Details of the event including PI notification date
- Whether or not the event meets BSD IRB reporting criteria as an Unanticipated Problem (UP).
- For events which occur on a trial conducted under an IND/IDE held by a UCCCC sponsor-investigator, the event report should also indicate whether or not FDA reporting as IND safety report is required.

Events which meet the BSD IRB UP reporting criteria must be reported using their electronic submission system as per their policies and procedures. Events should be reported as soon as possible after the event has been deemed to meet reporting criteria. Events which do not qualify as a UP are to be reported at the time of IRB Continuing Review.

Events which occur on a study conducted under an IRB reliance agreement (e.g. central IRB study) must be reported to the IRB of Record according to their policies and procedures. All such events must also be reported to the BSD IRB if they meet local UP reporting requirements.

Events which occur on a trial conducted under an IND/IDE held by a UCCCC sponsor-investigator and which meet FDA expedited reporting criteria as an IND safety report, must be reported to the FDA within the following timelines:

- 7 *calendar* days for life-threatening or fatal events
- 15 *calendar* days for other reportable events

A delegated member of the study team (e.g. clinical research coordinator) is responsible for:

- Reporting all SAEs and other protocol-defined important events requiring expedited reporting to the sponsor (or designee) using the forms and process as specified in the current approved protocol and/or study manual (e.g., Medwatch, CTEP-AERS)
- Recording the event in the CTMS
- Completing the IRB e-submission form and forwarding the report to the PI for submission to the IRB
- Forwarding the completed Medwatch 3500A (or equivalent) to the CTSO regulatory team for reporting to the FDA (as applicable)

A member of the CTSO regulatory team is responsible for reporting all events to the FDA as applicable.

#### 5.1.1.2. Events Occurring at External Sites (Multi-Site Investigator-Initiated Trials)

All serious adverse events or other events requiring expedited reporting which occur at an external site on a trial sponsored, or coordinated by, the UCCCC must be reported to the UCCCC PI (or their designee) as outlined in the approved protocol document(s).

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The designated staff at the site at which the event occur is responsible for:

- Reporting the SAE (or other reportable event) to the PI (or their designee) within 24 hours of local PI's knowledge of the event via email
- Entering the event in the study database (eCRFs)

CTSO staff are responsible for reporting the SAE (or other reportable events) to:

- Any collaborators or funders as outlined in the approved protocol document
- UCCCC PI
- Cancer Center, BSD IRB, and FDA (if applicable) as described above

Events which are reported to the BSD IRB or FDA will be distributed to all participating external affiliate sites for reporting to their local IRB as per their policies and procedures.

### **5.1. Deviation Reporting**

All protocol deviations or violations must be reported to the trial sponsor (or their designee) as outlined in the approved protocol document(s) or supplemental trial materials provided by the sponsor.

#### **5.1.1. Events Occurring at the UCCCC**

In addition to the sponsor mandated reporting, all such events must be reported in the Cancer Center's CTMS. Event report must include the following information:

- Details of the event
- Major or Minor deviation categorization

Major deviations or other events which meet the BSD IRB UP reporting criteria must be reported using their electronic submission system as per their policies and procedures. Events should be reported as soon as possible after the event has been deemed to meet reporting criteria. Events which do not qualify as a UP are to be reported at the time of IRB Continuing Review.

Events which occur on a study conducted under an IRB reliance agreement (e.g. central IRB study) must be reported to the IRB of Record according to their policies and procedures. All such events must also be reported to the BSD IRB if they meet local UP reporting requirements.

Deviations to protect the life or physical wellbeing of a subject and which occur on a trial conducted under an IDE held by a UCCCC sponsor-investigator must be reported to the FDA within the following timelines:

- 5 *working* days after the event occurred

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### **5.1.2. Events Occurring at External Sites (Multi-Site Investigator-Initiated Trials)**

All protocol deviations which occur at an external site on a trial sponsored, or coordinated, by the UCCCC must be documented in a deviation log at the site.

Deviations should be reported to the local IRB of record according to their policies and procedures.

Major deviations which impact the overall quality of the trial data will be reported to the BSD IRB in addition to any local reporting requirements.

The deviation logs and records of local IRB reporting (as applicable) are to be made available to the UCCCC PI (or their designee) as part of routine site monitoring and auditing activities (see Section 6).

Events which are reported to the BSD IRB or FDA will be distributed to all participating external affiliate sites for reporting to their local IRB as per their policies and procedures.

## **6. Quality Control and Quality Assurance**

It is the expectation of the UCCCC that the trial sponsor develop and implement a plan for monitoring and oversight of the trial appropriate to the design and risk of the trial. For investigator-sponsored trials, the PI is responsible for describing the monitoring plan (as described in Section 3.5) and as detailed below in Table 4.

In addition to the overall trial monitoring plan prepared by the sponsor, every Principal Investigator has a responsibility to monitor the safety, conduct and progress of each trial conducted at the UCCCC. This includes ongoing review of the following:

- Accrual progress at the UCCCC
- Review of SAEs and protocol deviations
- Review of DLTs (if applicable)
- Review of data entry progress and timeliness

Regular reports of the above must be made to the DSMC as described in Section 4.3.

Investigator-initiated trials and those without routine source data verification/monitoring performed by the sponsor (e.g. National trials, certain trials from other academic institutions, foundation, or consortia) will be subject to additional monitoring as described in the next section.

The UCCCC will perform monitoring and auditing of ongoing clinical trials as described in this section and in Table 4.

**Table 4: Monitoring and Auditing Requirements**

Review at MDT Research Meeting	Internal Monitoring including SDV Required	Internal Monitoring Frequency	Internal Auditing Required	Internal Auditing Frequency	Percentage of Trials Audited
<b>PRMS-Exempt or Minimal-Risk Research</b>					
No	No	N/A	No	N/A	N/A
<b>PRMS Low Risk</b>					
Yes	No	N/A	For Cause	For Cause	For Cause
<b>PRMS Moderate Risk</b>					
Yes	Yes*	At least once per year	Yes	Annually	10% of trials annually with a minimum of 10% of new patient cases <sup>^</sup>
<b>PRMS High Risk</b>					
Yes	Yes*	At least twice per year	Yes	Annually	20% of trials annually with a minimum of 20% of new patient cases <sup>^</sup>

\* Internal monitoring by the quality unit will be performed for all Moderate-Risk and High-Risk studies unless the trial is already being monitored on routine basis by the study sponsor or coordinating center.

<sup>^</sup> Internal auditing will be performed unless the trial is subject to routine audits by the study sponsor or coordinating center.

### **6.1.1. UCCCC Monitoring of Active Trials**

Monitoring is the act of overseeing the progress of a clinical trial and ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), Good Clinical Practices (GCP), and applicable regulatory requirements.

A risk-based approach is used to determine the appropriate level of monitoring. This includes considering the complexity of the study design, study endpoints, clinical complexity, study population, geography, experience of the participating investigators, experience of the sponsor in conducting these types of trials, data capture requirements, known safety profile of the investigational product, and stage of the study.

The CTSO Quality Unit provides dedicated monitoring support of all investigator-initiated trials and those which are not subject to routine source data verification/monitoring performed by the sponsor. See Table 4.

Each clinical trial will be assigned to Data Monitor(s) within the Quality Unit. The monitor

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will be tasked with source data verification as well as monitoring for overall compliance with the protocol, Good Clinical Practices, applicable regulations, and internal standard operating procedures.

Monitoring tasks include:

- Precise tracking of patient accrual
- Ongoing assessment of patient eligibility and evaluability
- Adequate measures to ensure timely submission of study data
- Confirmation of timely reporting of adverse events and treatment-related morbidity information
- Periodic evaluation of outcome measures and patient safety information
- Review of Investigational Product Records
- Review of Investigator Site File

The monitor will review regulatory, pharmacy, and subject files utilizing the same categories and major deficiency criteria as outlined in the current NCI/CTEP's CTMB Audit Guidelines document.

The monitor will also be responsible for preparing monitoring follow-up letters and ensuring all deficiencies are addressed in a timely manner.

For UCCCC investigator-initiated trials, the Quality Unit will prepare regular monitoring progress reports summarizing overall trial progress, data completion, and monitoring activities. These reports will be sent to the PI and the DSMC for their review.

Trials are subject to monitoring by the Quality Unit until all data collection for primary and secondary endpoints are completed and verified.

#### **6.1.2. UCCCC Monitoring of Active Trials Conducted at External Sites**

For all multi-site investigator-initiated trials, the Quality Unit will assign Data Monitor(s) who will be responsible tasked with source data verification as well as monitoring for overall compliance with the protocol, Good Clinical Practices, applicable regulations, and internal standard operating procedures at each participating site.

Monitoring tasks for the affiliate sites include all of the same activities and tasks as detailed in Section 6.1.1 as well as verifying that all applicable documents for the affiliate sites are present in the UCCCC trial master files.

#### **6.1.3. UCCCC Auditing of Active Trials**

Auditing is a systematic and independent examination of trial-related activities and

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documents to determine whether the evaluated trial-related activities were conducted, recorded, analyzed, and accurately reported according to the protocol, sponsor's SOPs, GCP, and the applicable regulatory requirements.

The goals of the audit process are to:

- Ensure and confirm ongoing protocol compliance in accordance with UCCCC guidelines, policies and operations, and U.S. federal regulations;
- Educate the clinical research faculty and staff and promote greater awareness and understanding of policies, operations and objectives, and to increase efficiency and consistency in the conduct of clinical trials at the UCCCC;
- Identify areas where systemic process improvement in UCCCC policies and operations is needed to ensure compliance and enhance participant safety; and
- Allow for corrective and preventive action plans.

A risk-based approach is used to determine the appropriate level and frequency of auditing. Trials will be audited based on the PRMS Risk Level and according to the frequency noted in Table 4 **Error! Reference source not found.**

Audit reports will be sent to the Principal Investigator and study team. A written corrective and preventive action (CAPA) plan will be required for all major findings. Audit reports and CAPAs will be reviewed by the AD for Clinical Investigation, applicable CTSO leadership, and the DSMC (for investigator-initiated trials).

If audit findings are deemed significantly unacceptable reports will also be sent to the DSMC, CROAC, and BSD Office of Clinical Research to review and decide if further action is necessary.

CTSO leadership will work with the PI and study teams to ensure proposed CAPAs are appropriate and that the appropriate education, training/re-training, and process changes are implemented in a timely manner.

#### **6.1.4. Institutional Office of Clinical Research (OCR) Audit Program**

All trials conducted at the University of Chicago or under our University of Chicago Medical Center Federal Wide Assurance are subject to undergo scheduled audits at a frequency and scope that will be determined by Office of Clinical Research (OCR) based on prioritization categorizations. For cause audits may result from requests by other University or Divisional offices or any allegation or other indication of possible noncompliance or risk to safety of human subjects enrolled in research studies, and any protocol for which the institutional research injury policy is invoked. Scientific misconduct allegations are handled by the Office of the Provost.



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### **6.1.5. Research Misconduct**

UCCCC is committed to the responsible conduct of research, and has policies and procedures in place for responding to allegations of misconduct in science. Allegations of research misconduct will be reviewed promptly, thoroughly, and objectively, with concern for the rights, reputations, and privacy of all those involved.

Definitions of Research Misconduct:

- Misconduct in science is defined as fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.
- Fabrication is making up data or results and recording or reporting them.
- Falsification is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record. This includes failure to report Significant Financial Interests related to ongoing research related activities.
- Plagiarism is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit.

When allegations of misconduct arise, a number of individuals with oversight of research may become involved, this includes unit/department/cancer center leadership, Office of Provost, BSD IRB, and BSD OCR. The person with primary responsibility is the Associate Vice President for Research Administration, Director of University Research Administration.

## **7. Conflict of Interest**

The University of Chicago's Conflict of Interest/Conflict of Commitment Policy requires that all individuals with the designation of faculty, or other academic appointment, file annually a Conflict of Interest-Conflict of Commitment Disclosure. Furthermore, any individual that is engaged in the design, conduct or reporting of research, or is considered "key personnel," must comply with the policy. This is a University-wide policy and applies regardless of whether the faculty or academic is engaged in research or receives external research funding, and regardless of whether they have a full-time or part-time appointment. As of August 2012, The University's Conflict of Interest-Conflict of Commitment Disclosure process was revised to capture both the new federal requirements, as well as The University of Chicago and the University of Chicago Medical Center requirements.

All faculty must also complete Conflict of Interest Training every 4 years.

Conflict of Interest is assessed and monitored at two levels: 1) at the level of the University Research Administration office (URA) and the Office of the Provost, 2) at the level of the BSD IRB. The University, Office of the Provost, then has the responsibility for determining if the disclosed interests could directly and significantly affect the performance of University responsibilities and to require the management, reduction or elimination of the conflict.

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## **7.1. Disclosure of Outside Interest**

All investigators at the University must disclose any financial (or other) conflicts of interest (COI) on an ongoing basis (no less than annually) of any financial arrangements with external industry partners of any dollar amount. These disclosures are made using the university's online COI management system. The content or value of any faculty member's COI disclosure and their management plan is confidential and is only available to the Institutional Review Board (IRB) Committee(s), COI administrators, and appropriate institutional leadership.

In addition to these institutional disclosures, investigators are required as part of the PRMS and IRB review process to disclose any relevant conflicts held by themselves or the sub-investigators or other personnel making direct and significant contributions to the study data. All such disclosures are reviewed by the PRMC and IRB as part of their decision making process regarding research to be conducted at the UCCCC.

All UCCCC Committee members (DSMC, PRMC) are required to disclose any applicable conflicts and recuse themselves from voting on any research on which they are conflicted.

## **8. Training of Research Personnel**

All clinical research faculty and staff are required to complete Human Subject Protection (HSP) and Good Clinical Practice (GCP) training. Researchers must complete the appropriate HSP and GCP courses prior to participating in research. Re-certification is required every three years.

All faculty are also required to complete Conflict of Interest training as detailed in Section 7.

All faculty intending to serve as principal investigator of a clinical trial are required to complete mandatory training on their responsibilities, the processes, and expectations incurred as an investigator with the UCCCC. This training is offered in person/virtually approximately once a year. Additional ad hoc training will be offered as needed.

All clinical research staff (coordinators, regulatory, data management, nursing, and mid-level providers) are expected to participate in mandatory fundamentals of oncology clinical research training. This training is offered in person/virtually approximately 3 times per year. Modules include Intro to Clinical Research, Clinical Trial Protocol, Adverse Event and Serious Adverse Events, Investigational Drug and Drug Accountability, Consenting and Eligibility Review, and Roles and Responsibilities of Regulatory Affairs.

Additional training opportunities include:

- **Research Staff Education Series:** This series provides a forum for education and discussion regarding the issues that investigators and research staff confront. Topics cover ethical issues in clinical research, barriers to day-to-day trial management, and clarifications about how to apply regulations and guidelines to current practices.

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- **Fundamentals of Clinical Research:** This series offered by the University's Office of Clinical Research serves to educate investigators and research staff on the regulatory and other aspects of conducting clinical research at the University of Chicago. Emphasis is placed on local policies and procedures along with code of federal regulations.
  - **Clinical Research Support Website:** An online resource that investigators and research staff may use to access current policies, operations and guidance, as well as e-learning modules and other educational resources for conducting research at UCCCC. Modules include: human subjects protection, IRB submission, informed consent, reportable events, and good documentation practices.

## 9. Definitions

### **Cancer-Focused Research:**

For the purposes of these policies, cancer-focused research is defined as research with a primary or secondary aim(s) that meets any one of the following criteria:

- Research to understand the causes, trends, nature and mechanisms of cancer and its development including identifying the biological mechanisms, environmental causes, or other factors associated with cancer risk
- Research aimed at cancer detection and screening
- Research aimed at the diagnosis, treatment, or prevention of cancer
- Research aimed at the diagnosis, treatment, or prevention of symptoms or side effects associated with cancer and/or cancer treatment including interventions to improve quality of life
- Research related to the costs of cancer treatment or care, screening, diagnosis and/or prevention
- Research involving the inclusion of oncology providers or oncology-focused clinical, support, and/or research staff as study participants if the primary aims of the research is related to the care or treatment of cancer patients, oncology clinical research, and/or education or surveys related to oncology clinical practice.
- Research in these populations that does not have a primary aim(s) that is directly related to one of the previously defined research categories will be exempt.
- Any other research receiving Cancer Center funding or other material support (i.e. Pilot Project Grants)
- Any other research which enrolls patients with a cancer diagnosis, those that have previously had cancer and/or received cancer treatment, and/or those at risk of developing cancer as a primary population per the protocol inclusion/exclusion criteria
- Research into benign tumors

All cancer-focused research must be reviewed by the Cancer Center Protocol Review and Monitoring System (PRMS) in addition to the Institutional Review Board and are subject to ongoing monitoring and oversight as defined in this document including periodic reporting of enrollment metrics to the UCCCC.

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**Clinical Trial:**

For the purposes of this policy, a clinical trial will be defined as a clinical research project which meets any of the following criteria:

- Research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. Examples of interventions include: drug(s), biologic(s), device(s), radiation, surgical or other procedures, behavioral strategies (e.g. diet, education, exercise), treatment strategies, prevention strategies, and diagnostics.
- Prospective imaging research
- Treatment given as part of a multi-patient expanded access, compassionate use, or rollover protocol for the purposes of treating cancer and/or symptoms or side effects associated with cancer and its treatment will be considered cancer-focused clinical research for the purposes of this policy.

**Network Site:**

For the purposes of this policy, a network site is one which is operated by the University of Chicago (UC)/University of Chicago Medicine (UCM) and which conducts cancer-focused research under the direction of a UC/UCM principal investigator.

**Affiliate Site:**

For the purposes of this policy, an affiliate site is one which is external to the University of Chicago/University of Chicago Medicine and which operates under its own policies and procedures and under the direct oversight of a non-UCCCC/UCM principal investigator.

**10. References**

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