UNIVERSITY OF COLORADO CANCER CENTER



INSTITUTIONAL DATA AND SAFETY MONITORING PLAN

FOR FURTHER INFORMATION CONCERNING THIS DOCUMENT, PLEASE CONTACT:

Peter Kabos, MD | Professor
Chair, Data & Safety Monitoring Committee
Deputy Director, Breast Cancer Research Program
University of Colorado Cancer Center
Tel. 303-724-4690
Email: DSMC@cuanschutz.edu

Sherri Wilke
Quality and Compliance Program Director
Data & Safety Monitoring Committee
University of Colorado Cancer Center
Email: DSMC@cuanschutz.edu

TABLE OF CONTENTS

DEFINITIONS & ACRONYMNS 3

1. INTRODUCTION AND OVERVIEW 6

2. INSTITUTIONAL OVERSIGHT OF CLINICAL TRIALS 6

2.1. Protocol Review and Monitoring System (PRMS) 7
2.2. Institutional Review Boards (IRB) 8
2.3. Oncology Clinical Research Support Team (OCRST) 8
2.4. Clinical Research Administration Office (CU Anschutz Office of Regulatory Compliance) 9
2.5. Clinical Trial Management Groups 9
2.6. Independent Data and Safety Monitoring Boards (DSMB) 9
2.7. CU Cancer Center Data and Safety Monitoring Committee (DSMC) 10

3. PROTOCOL SPECIFIC MONITORING AND OVERSIGHT 21

3.1.2 Tissue Banks 23
3.1.3 Trials Involving Vulnerable Participants 23
3.1.4 National or Regional Clinical Trial Network (NCTN) Trials 23

4. ADVERSE EVENT REPORTING COMPLIANCE 23

5. PERMANENT SUSPENSION OF NCI FUNDED CLINICAL TRIALS 23

6. CONFLICT OF INTEREST 24

6.1. General Conflict Management 24
6.2. Protocol-Specific Conflict Management 25

ATTACHMENT A: COMMITTEE REPORTING STRUCTURE 26

ATTACHMENT B: INFORMATION AND PROCESS FLOW 27

ATTACHMENT C: GUIDELINES FOR ESTABLISHING AND OPERATING A DSMB 28

ATTACHMENT D: DOCUMENT REVISION HISTORY 31

DEFINITIONS & ACRONYMNS

Clinical Trial: A research study in which one or more human participants 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. (NIH Definition of Clinical Trial Case Studies [Updated 1/7/19])

Clinical Trials Management System (CTMS): Software utilized by CU Cancer Center, currently OnCore®, that supports operational management of protocols, subjects, biospecimens, and financial activities throughout the clinical research lifecycle. The CTMS is used by CU Anschutz, DSMC, PRMS and Oncology Clinical Research Support Team (OCRST) for quality control and quality assurance oversight.

Conflict of Interest: A situation in which financial, professional or other personal considerations may directly or indirectly affect, or have the appearance of affecting, an employee's professional judgment in exercising any university duty or responsibility in administration, management, instruction, research or other professional activities. This can include interests that bias the nature or direction of scholarly research or influence decisions with respect to teaching and students, appointments, and promotions, use of university resources, interactions with human subjects or other matters of interest to the university. (Office of Policy and Efficiency (OPE) Administrative Policy Statement (APS) #5012)

Investigator Initiated Trial (IIT): Institutional trials involving a CU Cancer Center-held IND/IDE, a CU Cancer Center Overall PI, or where CU Cancer Center serves as the coordinating center. A protocol is an institutional IIT when it is developed and/or written by a CU Cancer Center Investigator where the CU Cancer Center PI is the driver of scientific inquiry and is in control of the protocol development and implementation.

Overall Principal Investigator (Investigator): An individual who actually conducts the research. In the event the research is conducted by a team of individuals, the investigator is the responsible leader of the team. For the research for which they are the Principal Investigator of the overall research project, this applies to all sites at which the research is conducted. For the research for which they are not the Principal Investigator of the overall research project but are the CU Cancer Center Overall Principal Investigator (such as on a multi-institutional study which CU Cancer Center is not the lead site), this applies to all sites which he/she has oversight responsibility (primary site as well as any sub-contracted sites).

Serious Adverse Event (SAE): An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the

ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (21 CFR 312.32(a))

Subcontractor: An entity that provides specific services in support of the research program but does not significantly participate in the design of the research and has no independent decision-making in the how the research program or project is to be completed. The subcontractor relationship is characteristic of a vendor relationship. (OPE APS #5012)

Subrecipient: An entity that performs substantive programmatic work or undertakes an important or significant portion of the research program or project. The other entity participates in a creative way in designing and/or conducting the research, retains some element of programmatic control and discretion over how the work is conducted. (OPE APS #5012)

Unanticipated Problems (UAPs): Any event or information that was unforeseen and indicates that the research procedures approved by the IRB and carried out as expected, cause harm (including physical, psychological, economic, or social harm) to participants or others, or indicates that participants or others are at increased risk of harm than was previously known or recognized. (COMIRB Policy & Procedures). *IRBs have different definitions and reporting criteria for expedited reporting of UAPs (non-compliance); investigators must follow reporting requirements of the IRB of record.*

Abbreviations

AE	Adverse Event
APS	University of Colorado Administrative Policy Statement
AVC	Associate Vice Chancellor
CCSG	Cancer Center Support Grant
CCTO	Cancer Clinical Trial Office
CFR	Code of Federal Regulations
CHCO	Children's Hospital of Colorado
CIRB	National Cancer Institute Central Institutional Review Board
CMP	Clinical Monitoring Plan
COIC	Conflict of Interest and Commitment
COMIRB	Colorado Multiple Institutional Review Board
CRAO	Clinical Research Administration Office
CRS	Clinical Research Support
CTRP	Clinical Trial Reporting Program
DSM	Data Safety Monitoring
DSMB	Independent Data Safety Monitoring Board

DSMC	University of Colorado Cancer Center Data Safety Monitoring Committee
DSMP	Institutional Data Safety Monitoring Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice (International Council for Harmonisation (ICH))
HCTU	Hematology Clinical Trials Unit
IIT	Investigator Initiated Trial
IND/IDE	Investigational New Drug/ Investigational Device Exemption
IRB	Institutional Review Board
LAPS	Lead Academic Participating Site
NCI	National Cancer Institute
NCTN	National Clinical Trial Network, aka Cooperative Groups
NIH	National Institutes of Health
OCRST	Oncology Clinical Research Support Team, aka Clinical Protocol and Data Management (CPDM)
OPE	University of Colorado Office of Policy and Efficiency
PI	Principal Investigator
PRMS	Protocol Review Monitoring System
SAE	Serious Adverse Event
UAP	Unanticipated Problem
UCCC	University of Colorado Cancer Center, (CU Cancer Center)
VA	Rocky Mountain Regional VA Medical Center
WCG IRB	Western Copernicus Group Institutional Review Board (formerly WIRB)

1. INTRODUCTION AND OVERVIEW

The University of Colorado Cancer Center (CU Cancer Center) is dedicated to uniting our community to overcome cancer through innovation, discovery, prevention, early detection, multidisciplinary care, and education. To fulfill this mission, the CU Cancer Center incorporates the expertise of cancer specialists, state-of-the-art technology, and careful evaluation in the conduct of its clinical trials. The CU Cancer Center is committed to ensuring the safety of clinical trial participants and to maintaining data accuracy and protocol compliance.

The CU Cancer Center Data and Safety Monitoring Plan (DSMP) has been developed to coordinate and provide oversight for the data and safety monitoring of all CU Cancer Center clinical trials, including trials conducted at both internal and external sites subject to CU Cancer Center oversight. This DSMP is consistent with the National Institutes of Health (NIH) Policy for Data and Safety Monitoring (June 10, 1998) and Further Guidance on Data and Safety Monitoring for Phase I and Phase II Trials (June 5, 2000) as well as the National Cancer Institute (NCI) Data Safety Monitoring Guidelines (Approved 9/30/2014) and Data and Safety Monitoring of NCIH-Funded Clinical Research Policy (Reviewed 9/30/2014).

2. INSTITUTIONAL OVERSIGHT OF CLINICAL TRIALS

While the Principal Investigator (PI) is ultimately responsible for the conduct and monitoring of all aspects of a clinical trial on an ongoing basis, the CU Cancer Center has developed a comprehensive infrastructure to provide robust oversight of all aspects of clinical research conducted by the CU Cancer Center, including monitoring of the research and reporting of any adverse events. All clinical trial protocols have a Data and Safety Monitoring Plan (DSMP) approved by the CU Cancer Center Protocol Review and Monitoring Committee (PRMS) and local Institutional Review Boards IRB), and align with this NCI-approved plan.

All non-exempt human subjects research conducted under the oversight of the CU Cancer Center is submitted through a central Human Subjects Research portal managed by the Clinical Research Support (CRS) office under the AVC for Regulatory Compliance. The submission triggers the Protocol Review and Monitoring System (PRMS) to review all clinical research trials including trials conducted at external and internal sites subject to CU Cancer Center oversight. The Data and Safety Monitoring Committee (DSMC) is responsible for data and safety monitoring and protocol compliance oversight for all trials submitted to PRMS. In addition, other CU Anschutz institutional research oversight committees (Institutional Biosafety Committee, Radioactive Drug Research Committee, Committee on Ionizing Radiation for Human Use, and Radiopharmaceutical Oversight Committee) ensure review of human subject research and compliance with federal regulations, state laws, and CU Anschutz/CU Cancer Center policies. Finally, the Colorado Multiple Institutional Review Board (COMIRB), the Western Copernicus Institutional Review Board (WCG IRB), the NCI Central Institutional Review Board (CIRB), or other external IRBs, depending on the trial

sponsor, ensure protection of the rights and welfare of human subjects. The committees are independent of one another; however, they collaborate and communicate with one another to provide protections for human subjects as described in this DSMP. Apart from external IRBs, all institutional oversight committees are overseen by the Associate Vice Chancellor (AVC) for Regulatory Compliance and meet regularly. All non-exempt human subjects research taking place across the CU Cancer Center system must first be submitted through a central Human Subjects Research portal managed by the Clinical Research Support (CRS) office, also under the AVC for Regulatory Compliance. This central review helps ensure that all necessary ancillary reviews by the committees above is completed in a timely fashion. The portal submission of oncology related trials triggers the PRMS review of the initial protocol. A diagram of this system can be found in Attachment A. Clinical trials are critically evaluated at the CU Cancer Center throughout protocol conception, development, approval, and performance to ensure adequate data and safety monitoring (See Attachment B).

2.1. Protocol Review and Monitoring System (PRMS)

The CU Cancer Center PRMS, in accordance with Cancer Center Support Grant (CCSG) guidelines, reviews all clinical research studies proposed by CU Cancer Center members throughout the system for scientific merit, feasibility, prioritization, and alignment with ongoing CU Cancer Center research programs. The PRMS also monitors institutional intervention studies to evaluate scientific progress, including accrual rates, new safety information, and scientific relevance to ensure timely completion of scientific aims. PRMS functions do not duplicate or overlap with the function of the IRB. Instead, the PRMS enhances the IRB functions via protocol review by members of disease groups with proper qualifications to review concepts and protocols within each area of expertise.

The PRMS includes a Chair appointed by the Cancer Center Director and a Deputy Chair appointed by the PRMS Chair. PRMS Committee members are nominated and selected by the PRMS Chair to ensure diverse expertise and include senior and junior investigators as well as biostatisticians at each scientific review committee meeting. Members represent the diversity of the cancer center including cancer prevention, medical oncologists, radiation oncologists, and surgical oncologists. If specialized expertise is required, PRMS solicits additional ad hoc reviews as appropriate. All protocols are reviewed to ensure a DSMP is documented in compliance with this plan. DSMC administrative personnel perform an additional review of institutional protocols that are submitted to PRMS to ensure appropriate DSMC oversight as described in this plan, with added input from DSMC Chair and Committee on a continuous basis as needed. This DSMC evaluation is included in each PRMS trial portfolio and provided to the respective trial PI. Protocols are reviewed at scientific review committee meetings led by the Chair or Deputy chair. Discussion includes evaluation of potential enrollment and inclusion of catchment area populations. Decisions (approved, approved with stipulations, approved with modifications, or disapproved) is determined by a majority vote. PRMS and DSMC membership are distinct and

separate from one another and do not overlap. Current PRMS Committee membership can be located at: https://medschool.cuanschutz.edu/colorado-cancer-center/clinical-trials/protocol-review-and-monitoring-system

All CU Cancer Center trials have a system of oversight and monitoring in place, commensurate with study risk and approved by PRMS and the IRB, to safeguard the well-being of study participants and ensure study integrity. Further details on the processes and procedures of PRMS, including roles of the Scientific and Executive committees can be found by contacting the PRMS Chair or Program Director, whose contact information is posted on the PRMS website noted above.

2.2. Institutional Review Boards (IRB)

The Colorado Multiple Institutional Review Board (COMIRB) serves as the IRB for the CU Cancer Center and reports to the University of Colorado Associate Vice Chancellor (AVC) for Regulatory Compliance (part of the CU Anschutz Office of Regulatory Compliance). Trials may utilize WCGIRB, CIRB or other external IRBs depending on the trial sponsor. As such, each IRB provides scientific and ethical review of all protocols and is the final arbiter of whether a protocol is or is not approved and activated. The IRBs review and process Serious Adverse Events (SAEs) and Unanticipated Problems (UAPs) with their respective policies. Each IRB stipulates the frequency of Continuing Reviews based on risk assessment and reviews these in detail on an ongoing basis.

Continuing Reviews occur as required by the IRB. This review focuses on the risks, benefits, adverse event reports, protocol deviations, and unexpected problems. Additionally, amendments are reviewed by the IRB and the IRB determines when it is necessary to inform participants of changes in the level of risk that may affect their willingness to participate in the trial.

All non-exempt human subjects research must first be submitted through a central Human Subjects Research portal managed by the Clinical Research Support (CRS) office under the AVC for Regulatory Compliance. The CRS office facilitates University IRB reliance arrangements for research proposing to rely on an external IRB; otherwise, the research is submitted to COMIRB.

2.3. Oncology Clinical Research Support Team (OCRST)

The OCRST provides central management and oversight functions for coordinating, facilitating, and reporting on cancer clinical trials conducted under the oversight of the CU Cancer Center in accordance with the CCSG. The OCRST Program Director reports to the Assistant Director of Clinical Research, who in turn reports to the Associate Director (AD) of Clinical Research. The OCRST provides a variety of essential services, including CU Cancer Center staff onboarding and education, quality control of OnCore® and centralized CTRP reporting/quality control oversight.

In addition, the OCRST provides centralized IIT program support including protocol development, regulatory functions, and monitoring services, as well as budget and contract support. OCRST staff engage DSMC staff in protocol development process to ensure appropriate language related to data and safety monitoring is included in protocols. The DSMC audit team and OCRST monitoring team maintain open communication to ensure consistent messaging on best practices as well as the escalation and/or resolution of potential findings. Finally, the OCRST Program Director assists in the oversight of a CU Cancer Center Working Group charged with the development and management of Standard Operating Procedures (SOPs) applicable across the CU Cancer Center. More information regarding the services of the OCRST, as well as the SOP Working Group Charter is available at:
https://olucdenver.sharepoint.com/sites/OCRST/sitepages/policies-and-procedures.aspx
(CU Cancer Center staff log-in required).

2.4. Clinical Research Administration Office (CU Anschutz Office of Regulatory Compliance)

The Clinical Research Administration Office (CRAO) ensures accountability, safety, and compliance for all research activities within the entire University of Colorado community and includes a variety of services, oversight committees and research support. More information can be found at: http://www.ucdenver.edu/research/ORC/Pages/ORC.aspx.

2.5. Clinical Trial Management Groups

Oncology research is conducted by many investigators and clinical teams across the CU Cancer Center system. The Cancer Clinical Trial Office (CCTO) and the Hematology Clinical Trial Unit (HCTU) conduct the majority of the clinical trials at CU Cancer Center. Investigators and their clinical trials groups conduct protocol prioritization and feasibility reviews prior to PRMS submission. Investigators are responsible for the development of appropriate department-specific SOPs and best practices to ensure subject safety and data integrity through the lifecycle of a clinical trial, including compliance with all applicable regulatory and institutional reporting requirements.

2.6. Independent Data and Safety Monitoring Boards (DSMB)

A Data Safety and Monitoring Board (DSMB) is an independent, impartial group of experts that periodically reviews and evaluates accumulated trial data for participant safety, trial conduct and progress; and makes recommendations to the trial investigators concerning the continuation, modification or termination of the trial when significant benefits or risks have been uncovered or when it appears that the clinical trial cannot be concluded successfully. The DSMB considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study. The National Institute of Health (NIH) requires data and safety monitoring, generally, in the form of DSMBs for phase III clinical trials, particularly for randomized

phase III IITs. For earlier trials (phase I and II), an independent DSMB may be appropriate if the studies have multiple clinical sites, are blinded or employ particularly high-risk interventions or vulnerable populations. A DSMB might be considered for practical reasons such as for trials with a high chance of early termination for safety or efficacy reasons, or to have an independent review group that may help to add validity to the trial. NIH policy provides flexibility to implement the requirement for data and safety monitoring as appropriate for its clinical research activities.

The CU Cancer Center requires a DSMB for phase III or large (e.g., >100 subject) phase II, randomized, multi-site clinical trials involving interventions that entail potential risk to the participants. If not specified in the protocol, the need for an independent DSMB will be at the discretion of the CU Cancer Center DSMC Chair and/or Committee. The DSMC Chair, or DSMC Committee if the Chair has a COI (refer to DSMC Conflict of Interest SOP #03 for more information), will make the final decision on the necessity of an independent DSMB and the reason will be documented. The requirement for an independent DSMB is identified and documented by the CU Cancer Center DSMC during protocol development or at the time of PRMS submission if CU Cancer Center DSMC is not consulted during the development of the protocol.

Guidelines for establishing and operating an external DSMB are outlined in Attachment C. CU Cancer Center leadership and the DSMC may assist the PI in setting up an adequate DSMB (in accordance with guidelines outlined in Attachment C) and the PI will be responsible for submitting all independent DSMB reports on IITs to the CU Cancer Center DSMC in a timely manner.

2.7. CU Cancer Center Data and Safety Monitoring Committee (DSMC)

The DSMC reports to the Associate Director (AD) for Clinical Research who, in turn, reports to the Director of the CU Cancer Center. The DSMC ensures that research data generated by CU Cancer Center investigators are of high quality, reliable, and verifiable. Additionally, the DSMC is responsible for ensuring the safety of clinical trial participants. The DSMC provides oversight through:

- Review of DSM progress reports for drug/device interventional IITs
- Conduct of internal audits
- Ongoing monitoring of all Serious Adverse Events (SAEs) and Unanticipated Problems (UAPs) for all studies
- Supervision of independent DSMBs for CU Cancer Center investigator-initiated large randomized trials that otherwise do not have an external DSMB assigned

The DSMC meets quarterly on a recurring basis; however, meetings can be held at any time as necessary to address urgent situations. Agendas include, but are not limited to, review of reported adverse events, internal and external DSMB reports, internal and external audit reports, review of

pharmacy safety trends, educational activities, and progress reports for IITs (see section 2.7.2). The meeting minutes and reports on specific protocol actions are maintained by the DSMC Manager (or the Quality and Compliance Program Director) and are available to the Cancer Center Director, AD for Clinical Research, COMIRB, and the AVC for Regulatory Compliance upon request.

The expertise of the DSMC includes Physicians from across the CU Cancer Center, Oncology Nurses, Research Pharmacists, Biostatisticians, and Research Administration staff. Investigator members of DSMC are eligible to conduct clinical research and are recognized authorities in their scientific discipline. Members of the DSMC serve staggered, renewable three-year terms designed to maintain an appropriate distribution of expertise. The committee may supplement its membership at any time to ensure proper review. The Chair serves by appointment of the CU Cancer Center Director. The chair selects members in consultation with the AD for Clinical Research. The current DSMC membership roster can be found at: https://medschool.cuanschutz.edu/colorado- cancer-center/clinical-trials/dsmc

2.7.1 Clinical Trial Risk Assessment

Protocol risk varies substantially based on several factors. The following are considered when determining risk of a trial:

- Risk inherent to the population being studied
- Possible risks of the study intervention(s)
- Whether the protocol is an institutional IIT
- Whether an IIT is single or multi-center trial
- Whether the protocol involves an IND or medical device (IDE) held by a CU Cancer Center Investigator
- Protocol-specific requirements including, but not limited to, trial phase, national/international experience with the agent(s) or device(s) under study, the inclusion of vulnerable populations, monitoring and/or auditing by non-CU Cancer Center entities, and complex dosing requirements (including dose escalation/de-escalation)
- Site and/or investigator-specific factors including, but not limited to, experience of the investigator and/or research team, local experience with the drug(s) or device(s) under study, response to monitoring findings, prior internal/external audit outcomes, potential conflict of interest or special circumstances as determined by the IRB, PRMS, OCRST, or DSMC

Per NIH guidance, oversight should be commensurate with risk; therefore, characterization of risk is a critical component in the evaluation of a clinical trial. The CU Cancer Center DSMC has established the following risk categories based on the risk factors described above. Research that qualifies under one of the federally recognized exempt categories, for example, retrospective

chart reviews and secondary use of data trials are considered to have no risk under this risk assessment.

Table 1: Clinical Trial Risk Categorization

Extremely High Risk	**Trials involving greater than minimal risk which may or may not have a direct benefit to the subjects. Risks may be high in relation to anticipated benefit.** *Examples include cell/gene therapy, first in human trials, products manufactured on campus, new interventions with high/severe pre-clinical toxicity.*
High Risk	**Intervention commensurate with those inherent in expected medical, social, or educational situations. Institutional responsibility is high based on CU Cancer Center's ownership of the protocol and increased regulatory responsibilities as a sponsor. Risks are reasonable in relation to anticipated benefits and anticipated knowledge gained.** *Examples include IITs with CU Cancer Center-held IND/IDE and Multi-center IITs where a CU Cancer Center investigator serves as Overall PI or CU Cancer Center is the coordinating institution*
Moderate Risk	**Intervention commensurate with those inherent in expected medical, social, or educational situations. Risks are reasonable in relation to anticipated benefits and anticipated knowledge gained.** *Examples include drug/device interventions (IND-Exempt, NSR, 510K), therapeutic research including but not limited to surgery, radiation therapy, chemotherapy, vaccines, biologics.*
Low Risk	**Probability of harm or discomfort not greater than daily life or routine physical/psychological exams.** *Examples include behavioral intervention, tissue banks, survey research, venipuncture and observational studies, non-invasive procedures.*

2.7.2 Data Safety Monitoring (DSM) Progress Reports

The DSMC reviews CU Cancer Center investigator-initiated drug or device interventional trials at regular intervals (see Table 2) to ensure appropriate data and safety monitoring. This includes trials where an IND/IDE is held by a CU Cancer Center investigator and multi-center investigator-initiated trials where the CU Cancer Center investigator is the Overall PI or sponsor or when CU Cancer Center is the coordinating center. Trials with external data and safety monitoring review may submit documentation of external review in lieu of DSM progress reports with CU Cancer Center DSMC Chair approval.

In accordance with NIH guidance, an independent DSMB is required for Phase III institutional IITs. For earlier phase IITs, an independent DSMB may be appropriate at the discretion of the DSMC Chair and/or Committee as described in section 2.6 and Attachment C.

Table 2: DSM Reviews by Risk

Extremely High Risk	Reviewed every 3-6 months
High Risk	Reviewed every 6-9 months
Moderate Risk	Reviewed every 9-12 months
Low Risk	Not subject to DSM Report requirements

Trials that require DSM Progress Reports are identified during the protocol development and approval process and the determination is documented as part of the DSMC administrative review at PRMS submission. If there is question regarding risk assessment or whether a trial requires the submission of DSM progress reports, the DSMC Chair, or alternate DSMC physician-member if the Chair has a COI (refer to DSMC Conflict of Interest SOP #03 for more information), will make the final decision and the reason will be documented. It is the responsibility of the study PI to provide a DSM progress report to the CU Cancer Center DSMC beginning six months following the initiation of treatment for the first trial participant. The DSM progress reports include a protocol summary, current enrollment figures, a summary of toxicity data to include specific SAEs, UAPs and AEs, dose modifications, protocol deviations, interim analysis (if applicable) and protocol amendments. The DSM reports also include, if applicable, final efficacy analysis, annual IND report, minutes from monthly safety teleconferences for multisite studies, and verification of monitoring activities. DSM reports must contain data from all participating sites if trials are conducted at multiple sites. See DSMC Reporting SOP #02 for more information.

The DSMC conducts a formal review of DSM Progress Reports during regularly scheduled meetings in accordance with study risk assessment (See Table 2) and votes on a determination. Investigators with a conflict of interest can participate in the discussion of a protocol but are excused before voting and do not count towards quorum. A quorum consists of a minimum of 5 voting members, including at least 2 physicians and a biostatistician. Voting members include DSMC Chair, Physicians, Research Pharmacists, Biostatisticians and Program Director. Studies are initially reviewed at six-month intervals beginning six months after the first participant is treated. After the initial review, studies considered moderate risk (as outlined in Table 1 & 2) may be reviewed at twelve-month intervals as voted on by the DSMC.

Studies with no enrollment or safety events since the last review may qualify for expedited review by the DSMC Chair, or a designee of the Chair should there be a conflict of interest (DSMC Conflict of Interest SOP #03). The determination would then be shared at the DSMC quarterly meeting.

DSM Review Determinations	Criteria
Approved	Study is approved to continue
Approved with stipulations	Study is approved to continue pending PI response to DSMC questions, or compliance with DSMC recommendations
Approved with modifications	Study is approved to continue *only* if the PI modifies the investigational plan as noted by DSMC
Disapproved	Study is not approved to continue at this time; further action is required
More Information Needed	Determination cannot be made without additional information

The DSMC provides determination letters to the Overall PI and should be submitted to the IRB of record at time of Continuing Review. DSMC may recommend modifications be made to the trial. If a response is required, the due date will be noted in the determination letter, generally within 14 days. The determination letter will also include the due date for the next DSMC progress report. Once the study no longer has subjects on treatment or in active follow-up the letter will indicate the DSM reporting requirement has been fulfilled.

PRMS and the IRB of record will be copied on DSMC determination letters for any protocol determined to be *Disapproved* or *Approved with modifications* to determine if the findings significantly alter the scientific value and safety of the trial. PRMS will also receive any new safety information that DSMC becomes aware of that may significantly alter the scientific value and safety of any trial to determine whether a trial should be closed by PRMS.

For multi-center trials, the Overall PI must provide DSMC determination letters to all participating sites. DSMC determination letters should also be submitted to the IRB of record at the time of Continuing Review as they aid the IRB in their review. If modifications to the trial are recommended, the Overall PI will be notified so that they may alert all investigators involved in the trial of the potential action. The DSMC may recommend an amendment to the protocol but may also recommend study suspension or closure based on findings. Following notification, the Overall PI may submit additional information to the DSMC that could affect the DSMC's decision. If study suspension or closure is recommended, the Overall PI must notify all investigators involved with the study, the IRB, the trial sponsor (if applicable), the funding agency, and provide written documentation of these notifications to the DSMC.

2.7.3 Internal Audits

The DSMC performs internal audits of clinical trials subject to CU Cancer Center oversight to evaluate study protocol adherence, source verification, participant eligibility, AE reporting and informed consent procedures. The DSMC prioritizes internal audits of CU Cancer Center (including VA and CHCO) institutional IITs, CU Anschutz held IND/IDEs, and NCTN trials. Audit priority of institutional IITs is further stratified based on risk as described in Table 1. External sites participating in CU Cancer Center institutional IITs, particularly those involving a CU Cancer Center -held IND/IDE, may be audited as determined by the CU Cancer Center DSMC. Audit requirements are identified and documented during protocol submission to PRMS, both at initial submission and any amendments that may affect risk (e.g., adding a site). Audits may be routine, for-cause, or targeted (narrowly focused to a specific area(s)). The goals of the DSMC auditing process are:

- To ensure ongoing clinical protocol compliance with IRB guidelines, FDA regulations, and Institutional, as well as CU Cancer Center, policies, and procedures
- To educate the clinical research staff and to promote greater awareness and understanding of policies, procedures, and objectives, and to increase efficiency and consistency in the performance of clinical trials
- To identify system changes needed within the CU Cancer Center to ensure quality improvement

All protocols at the CU Cancer Center are eligible for audit; however, priority is given to higher risk protocols not subject to frequent external auditing and monitoring, including IITs and NCTN trials. The DSMC may adjust the audit schedule as needed to ensure effective oversight is maintained. In collaboration with the DSMC, Chair and Program Director, auditors will monitor activity on IITs and NCTN trials on a continuing basis and adjust audit planning, as necessary. IITs are selected for routine audit based on risk:

Extremely High Risk: Initial audit conducted within approximately 3-6 months of first subject enrolled (treated) and approximately every 3-6 months until all subjects have completed protocol requirements.

High Risk: Initial audit conducted within approximately 6-9 months of first subject enrolled (treated) and approximately every 6-9 months until all subjects have completed protocol requirements.

Moderate Risk: Initial audit conducted within approximately 9-12 months of first subject enrolled (treated) and approximately every 9-12 months until all subjects have completed protocol requirements only if auditors are current on all higher-risk audits.

Low Risk: Subject to audit if auditors are current on all higher-risk audits or at the request of COMIRB, PRMS, PI, DSMC, etc.

NCTN trials are selected for routine audit as outlined in the DSMC Internal Audit SOP #01, with priority given to trials designed for potential registration with the FDA.

Auditing is coordinated and performed by the DSMC audit team as described below. Each audit team is comprised of at least one DSMC auditor and a non-conflicted DSMC physician. The DSMC physician is not required to attend the audit in person but will be reachable during the audit to provide guidance on clinical questions that may arise. Investigators and their team are contacted approximately two to four weeks before audit for routine audits. Less notice may be provided for targeted or for-cause audits. The PI will receive a letter with the audit details and expectations (including date, time, case selection, etc.). The auditor will select approximately 10% of accrued cases for full review and select additional cases based on any observed trends. Audits are conducted in a secure fashion to assure the confidentiality of data. If a true or perceived conflict of interest exists, the protocol will be assigned to another auditor in accordance with DSMC Conflict of Interest SOP #03. No member of the audit team shall audit any protocol for which he/she has a true or perceived conflict of interest as determined by the DSMC Chair (or designee if the Chair is conflicted).

Extremely High- and High-Risk audits include 100% review of informed consents (ICF) and full case review of a minimum of 10% of all cases accrued to verify federal, institutional, and protocol compliance. Additional cases may be selected based on potential trends identified during initial case review. For trials audited multiple times, the audit team may select only participants enrolled and/or active since the last audit. Pharmacy records and regulatory documents (including IRB submissions, continuing review submissions, etc.) will be reviewed. Sponsor Trial Master File (TMF) will be reviewed for IITs where the CU Cancer Center investigator serves as the sponsor investigator.

Moderate Risk audits include 100% review of informed consents (ICF) and full case review of a minimum of 10% of all cases accrued to verify federal, institutional, and protocol compliance. Additional cases may be selected based on potential trends identified during initial case review. For trials audited multiple times, the audit team may select only participants enrolled and/or active since the last audit. For studies with a very large number of participants (200+), less than 10% of cases may be selected. If multiple protocols are reviewed as part of the same audit, less than 10% of cases on an individual protocol may be selected. Pharmacy records and regulatory documents (including IRB submissions, continuing review submissions, etc.) will be reviewed. Sponsor Trial Master File (TMF) will be reviewed for IITs where the CU Cancer Center investigator serves as the sponsor investigator.

Low Risk audits include a review of at least 10% of informed consents (ICF) and full case review of 10% of all cases accrued to verify federal, institutional, and protocol compliance. Additional cases may be selected based on potential trends identified during initial case review. For trials audited multiple times, the audit team may select only participants enrolled and/or active since the last audit. For studies with a very large number of participants (300+), less than 10% of cases may be selected. If multiple protocols are reviewed as part of the same audit, less than 10% of cases on an individual protocol may be selected. Regulatory documents (including IRB submissions, continuing review submissions, etc.) will be reviewed. Sponsor Trial Master File (TMF) will be reviewed for IITs where the CU Cancer Center investigator serves as the sponsor investigator.

The auditor will discuss the preliminary audit findings with the PI and study team as part of an exit interview within 72 hours of the audit. If the exit interview is delayed due to PI's schedule or other reasons, the reason will be documented in the audit notes by the auditor.

The lead auditor will draft the audit report and it will be peer-reviewed by the DSMC audit team and approved by the DSMC Manager or Quality and Compliance Program Director, and DSMC Chair. The approved final report will be issued to the PI, IND/IDE Office (if applicable)and AVC for Regulatory Compliance as close as possible to three weeks of the audit. If the audit report is significantly delayed, then this will be documented by the auditor or DSMC Manager. The audit report will indicate what follow-up is required and provide a timeline for response.

Per ICH GCP E6, "to preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case-by-case basis when evidence of serious GCP non-compliance exists, or in the course of legal proceedings."

DSMC will provide the investigator with an audit certificate to document that the internal audit occurred. The audit certificate should be filed in the protocol-specific documentation at the investigator's discretion in accordance with their applicable SOPs.

DSMC audits are rated on the following performance outcomes:

Audit Outcomes	**Criteria**
Exceptional	Superior source documentation, data quality, protocol, and regulatory compliance. No response required.
Satisfactory	Source documents with minor deficiencies/deviations that do not impact participant safety or interpretation of data. Requires correcting deficiencies. No response required.

Acceptable, with follow-up	Findings indicating action is needed but do not violate participant safety, are not life threatening or indicate a concern for misconduct or fraud. These types of findings may require a written corrective/preventive action plan with deadlines and timelines for implementation. May require in-service education/training for research staff.
Unacceptable	Findings indicating repeated minor, and major findings that indicate potential critical systemic issues that must be addressed immediately. Major finding(s) that if discovered during an FDA inspection may individually result in regulatory enforcement, such as a violation to participant safety, are life threatening, or indicate concern for misconduct or fraud. Such findings require, at a minimum, a written corrective/preventive action plan and implementation of recommendations, but may require temporary or permanent closure by the IRB or PRMS at the recommendation of the DMSC for participant safety or study conduct concerns. Temporary or permanent closure may also occur upon recommendation of PRMS or the IRB for lack of scientific progress.

If the DSMC Chair (or designee if the Chair has a COI) determines the audit outcome may be 'Unacceptable', the report and relevant supplemental materials will be sent for full-board DSMC review. The DSMC will discuss and vote on the outcome (either in-person or via email) and determine if immediate action is warranted (e.g., temporary or permanent suspension of accrual). The DSMC may elect to defer action until the PI's response is received.

In the event that the DSMC recommends suspending the protocol or permanently or temporarily closing the trial, the trial is placed on hold. PRMS and the IRB are copied on DSMC's determination. The audit report and any other supplemental materials relevant to the decision are provided to PRMS and the IRB to determine if the findings significantly alter the scientific value and/or safety of the trial. If action is required following an audit, the final audit report is submitted to site-specific leadership, as well as the IRB of record and PRMS if DSMC recommends accrual to be temporarily or permanently suspended. If a trial requires suspension, this is immediately reported by the DSMC to the PI, the above-named stakeholders, the AD for Clinical Research, collaborating groups, as well as the sponsor of the trial. In the case of temporary or permanent suspension of an NCI-funded clinical trial or trial investigator, this action will be reported to the appropriate NCI Program Director, other appropriate agencies, and co-sponsors.

If the audit report requires a response, the PI must provide a written response and submit it to the DSMC by the deadline noted in the audit report. Deficiencies noted in the audit report should be documented, corrected, and further mitigated through a plan of Corrective and Preventive Action (CAPA) plan. CAPA plans may be requested as a result of audit findings. The development and execution of a CAPA plan should serve to correct audit findings and prevent future issues of non-compliance.

While the investigator is responsible for creating, implementing and updating CAPA plans, the DSMC offers guidance documents, worksheets and support to assist investigators and their teams in conducting meaningful root cause analysis and comprehensive corrective and preventive action in response to internal or external audit findings.

CAPA plans required in response to DSMC internal audits are due with the response and are reviewed by the DSMC lead auditor, DSMC Manager and/or Quality and Compliance Program Director and Chair and may be reviewed by the full- board DSMC at the discretion of the DSMC Chair, or Quality and Compliance Program Director if the Chair has a COI. CAPA plans in response to Unacceptable audits will be reviewed and approved by the DSMC and will also be sent to PRMS, IRB, etc. as appropriate. The DSMC may follow up on corrective/preventive action plans resulting from an audit to determine progress.

2.7.4 Centralized Monitoring of SAEs and UAPs

The CU Anschutz Administrative Policy (#6005) titled, *Utilization of OnCore for Clinical Research*, specifies CTMS (currently OnCore) data entry requirements for human subject research based on study type, including requirements for SAE and deviation entry. The Administrative policy provides the basis for the CU Cancer Center OnCore utilization SOPs that further specify data entry requirements in the CTMS for clinical trials subject to CU Cancer Center oversight.

The DSMC monitors and reviews SAEs and UAPs occurring on all clinical trials subject to CU Cancer Center oversight as outlined in this section. Reporting and oversight activities are primarily accomplished via the CTMS. Reporting timelines for expedited reporting to DSMC are described below in Table 3:

Table 3: SAE & UAP Reporting Timelines to DSMC (via CTMS entry)

Trial Type	Unexpected, Fatal or Life-Threatening SAE or UAP	Expected, Non-Life-Threatening SAEs	Expected, Non-Life-Threatening UAPs
Institutional IIT	Within 7 calendar days	Within 15 calendar days	Within 15 calendar days
All Other Trials	Within 7 calendar days	Within 15 calendar days	Quarterly summaries to DSMC

SAEs and UAPs occurring on all trials are required to be entered in the CTMS, or otherwise reported to DSMC, in alignment with all applicable policies and SOPs, within the timelines noted in Table 3. Non-fatal SAEs and UAPs on all trials are reviewed and discussed during the DSMC quarterly meetings. Fatal events are initially reviewed on an event-specific basis by the DSMC Chair or an oncologist on the committee and can trigger a full-board DSMC review for concerning toxicity or compliance trends. Cumulative reports of these events are also reviewed and discussed in the DSMC quarterly meetings. Cumulative protocol-specific SAE and UAP reports for IITs are reviewed by the DSMC Chair or an oncologist on the committee at the following intervals based on risk: **Extremely High-Risk** trials will be monitored via a monthly cumulative protocol-specific report. **High and Moderate Risk** trials will be monitored via a quarterly cumulative protocol-specific report. **Low Risk** trials will be reviewed on an event- specific basis.

The PI will ensure data required for appropriate oversight of participant safety is reported to the IRB, CU Cancer Center DSMC, Independent DSMB (as applicable), and that all serious adverse events (SAEs) are reported to the CU Cancer Center DSMC, IRB, and the sponsor using NIH and applicable FDA guidelines for either commercial or investigational agents (or as required in the protocol). In general, expedited reports are required for life-threatening events, first occurrence of unexpected events, death on study, or death within 30 days of last treatment. Applicable trials must submit to at least an annual review of study data if participants are undergoing study treatment or are being followed for study purposes. These annual Continuing Reviews are performed by the IRB for applicable trials.

2.7.5 Education

The DSMC Chair and/or Quality and Compliance Program Director provide ongoing education for investigators, oncology nurses and clinical research staff in the preparation for and performance of audits, including techniques for continuous quality assurance and quality improvement. The Quality and Compliance Program Director or designee also serves as a resource for ongoing enhancement of trial management skills.

3. PROTOCOL SPECIFIC MONITORING AND OVERSIGHT

3.1. Data and Safety Monitoring

All CU Cancer Center clinical trials have a system of oversight and monitoring in place to safeguard the well-being of study participants and to ensure study integrity. Data and Safety Monitoring Plans (DSMPs) based on trial risk are described in detail in each protocol and approved by the PRMS and IRB before implementation of the study. Incorporation of stopping rules and details concerning specific interim analyses for safety and efficacy endpoints is encouraged, as appropriate, to enhance scientific merit and participant safety. All institutional investigator-initiated trials (IITs) submitted to PRMS are reviewed concurrently by DSMC Manager or Quality and Compliance Program Director, Chair, or designee, to ensure adequate data and safety monitoring is commensurate with study risk as outlined in this DSMP. DSMC administrative review of institutional IITs at initial protocol submission and applicable amendments is documented and incorporated into PRMS feedback letters to investigators.

Interventional institutional IITs involving drug(s) and/or device(s) must have a documented clinical monitoring plan (CMP) and multi-center trials also require a PI Oversight Plan. SAEs and UAPs are reported to the DSMC and IRB in accordance with DSMP and IRB policies. The number of participants, significant toxicities, dose modifications, and treatment responses/outcomes should be discussed at regular disease-oriented working group meetings as appropriate. Audits by the DSMC audit team will be conducted based on risk (Table 1) and DSMC recommendations.

Non-drug/device interventional institutional IITs will have data safety monitoring and PI oversight commensurate with the risk of the trial as determined by the sponsor or sponsor investigator and will be approved by the PRMS and IRB. SAEs and UAPs are reported to DSMC and IRB in accordance with DSMP and IRB policies. Trials may be audited by the DSMC based on risk (Table 1) and DSMC recommendations.

Non-interventional institutional IITs will have data safety monitoring and PI oversight commensurate with the risk of the trial as determined by the principal investigator and will be approved by the PRMS and IRB. Trials may be audited by the DSMC.

The PI is responsible for developing and incorporating the DSMP for CU Cancer Center institutional IITs without external oversight. The PI is responsible for ensuring that trial conduct is monitored for participant safety, and data quality, as well as protocol and regulatory compliance through a trial specific CMP. The development and execution of this monitoring plan is the PI's responsibility; however, the PI may delegate specific monitoring tasks to a monitor or data manager as appropriate. The PI is also encouraged to collaborate with clinical trial staff, OCRST, as well as additional resources as applicable when developing a trial specific monitoring plan.

In all cases, the PI has primary responsibility for ensuring compliance with the Code of Federal Regulations (CFR) and Good Clinical Practice (GCP). The PI is responsible for the overall conduct of the trial in accordance with the IRB-approved protocol. Therefore, all investigators and staff participating in clinical trials subject to CU Cancer Center oversight are required to complete training in Good Clinical Practices (GCP), and basic clinical trial training as offered by the CU Cancer Center, the Colorado Clinical Translational Science Institute, or the web-based CITI course (as applicable). In addition, eligibility checklists, the DSMC internal audit program, consistent clinical data monitoring, protocol-specific DSMPs, and regular oversight by PIs ensure data accuracy and protocol compliance.

3.1.1 Multi-Center Trials

The sponsor or sponsor investigator is responsible for the data and safety monitoring of the study. If the CU Cancer Center is the lead institution or the CU Cancer Center PI is the Overall PI or IND/IDE holder, the CU Cancer Center PI will be responsible for the data and safety monitoring of the trial at all participating sites as outlined in the CMP. Each participating institution and their respective DSMC/DSMB will be expected to comply with all CU Cancer Center DSMC determinations.

The sponsor or sponsor investigator is responsible for site selection, which includes evaluating site feasibility, including the anticipated involvement of local quality assurance and DSMC/DSMB oversight. External sites participating in IITs, in which the CU Cancer Center is the lead institution, or the CU Cancer Center Investigator is the Overall PI, may be audited by the CU Cancer Center DSMC.

Each participant's treatment outcomes will be monitored at least monthly by a conference call with the investigators and CRAs from all participating institutions. Data regarding the number of participants, significant toxicities, dose modifications, and responses will be discussed and documented in meeting minutes (or as outlined in site-specific policies and procedures).

SAEs and UAPs are reported to the CU Cancer Center DSMC, IRB and sponsor investigator per protocol and section 2.7.3.

The sponsor or sponsor investigator will provide a DSM progress report, inclusive of all sites, to the CU Cancer Center DSMC every three, six or twelve months, as determined by the DSMC. The DSM report will include a protocol summary, current enrollment numbers, and summary of toxicity data to include specific SAEs, UAPs and AEs (inclusive of reportable AEs), any dose modifications, all protocol deviations, documentation of monitoring activities, audit reports, and protocol amendments. The DSM progress report submitted to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted. Results and recommendations from the review of this progress report by the DSMC will then be provided to the sponsor or

sponsor investigator in a DSMC determination letter. The sponsor or sponsor investigator is then responsible for ensuring this letter is submitted to all participating institutions for submission to their IRBs of record in accordance with their IRB policy.

3.1.2 Tissue Banks

The lead institution/PI is responsible for the specimens and data obtained during tissue banking and will be responsible for the monitoring of the tissue bank specimen and data collection. Tissue banks that utilize methods of specimen collection that could result in SAEs, UAPs, and AEs, must report all SAEs and UAPs to the DSMC as outlined in section 2.7.3.

3.1.3 Trials Involving Vulnerable Participants

High-risk trials for vulnerable participants such as children might consider a consent monitor or Certified Research Participant Advocate. Data and safety of all trial participants will be discussed at regularly scheduled disease-oriented working group meetings, and the discussion documented in the minutes which will be submitted to the DSMC within the DSM progress report.

3.1.4 National or Regional Clinical Trial Network (NCTN) Trials

NCTN or Cooperative group trials are generally monitored at the cooperative group level. Data and safety are monitored by set DSM committees at the cooperative group level. However, these trials are subject to routine DSMC internal auditing and SAE reporting as outlined in section 2.7.3.

4. ADVERSE EVENT REPORTING COMPLIANCE

All UAPs and SAEs are reported to the DSMC, IRB, and the sponsor using NIH guidelines for either commercial or investigational agents (or as required in the protocol). In general, expedited reports are required for life-threatening events, first occurrence of unexpected events or death on study, or death within 30 days of last study treatment. All UAPs and SAEs must be reported to the IRB-of-record per IRB policy and to DSMC as outlined in section 2.7.3.

PIs or their designee are responsible for reporting to the IRB (per IRB policy) any unexpected event that impacts the safety of, or risk to, their participants. These reports should be completed in a timely fashion. At the same time, the PI will notify the study sponsor, NCTN/Cooperative Group, the FDA, the DSMC, or other agencies as appropriate.

5. PERMANENT SUSPENSION OF NCI FUNDED CLINICAL TRIALS

Temporary or permanent closures of NCI-sponsored (non-NCTN) clinical trials as a result of DSMC recommendations will be reported by the DSMC to the appropriate NCI Grant Program Director.

Protocols that are closed due to non-compliance or safety concerns by the IRB or DSMC will be reported immediately to the site-specific leadership, AD for Clinical Research, PRMS and the NCI Grant Program Director.

6. CONFLICT OF INTEREST

6.1. General Conflict Management

The University of Colorado Denver and IRBs require all persons involved in the design, conduct, or reporting of research to comply with the CU Administrative Policy Statement for Conflicts of Interest and Commitment in Research and Teaching (COIC Administrative Policy Statement #5012), CU's COIC Procedures, disclosure process and management plans as applicable, sponsor requirements, and federal regulations concerning conflict of interest and commitment management. Covered individuals include employees, consultants, subrecipients and subcontractors involved in the design, conduct and reporting of research. Disclosures are required on an annual basis and within 30 days of a change. Disclosures that list a significant financial interest (See the CU Procedure on Disclose of Interests APS #4013) are reviewed in accordance with CU Procedure on Conflicts of interest and Commitment (Effective August 12, 2019) and receive management plans accordingly. Management plans are project specific and will be reviewed at a minimum on an annual basis.

The IRB Chair (or designee for Expedited) or Full-Board will review the conflict management plan to determine if the conflict will adversely affect the protection of human subjects and if the management plan is adequate. Based on the significance of the conflict and the potential adverse effects on the protection of subjects, conflict management plans can include:

- Disclosure to participants through the consent process
- Modifications in the research plan
- Monitoring by independent reviewers
- Divestiture of financial interests
- Appointment of a non-conflicted Principal Investigator
- Prohibition of the conduct of research

The IRB Chair (or designee) or Full-Board can:

- Accept the management plan and recommend approval
- Recommend changes in the management plan
- Refer the review to the Full-Board

A copy of the final, approved conflict management plan will be kept on file in the IRB Office, as

well as in the Office of Regulatory Compliance.

6.2. Protocol-Specific Conflict Management

The IRB application asks protocol-specific questions regarding conflict of interest for investigators and key personnel. As part of its review process, the IRB's panel will determine whether the conflict adversely affects the protection of human subjects. If the answer is yes and an approved conflict management plan exists, the IRB panel will review to determine if it adequately protects the human subjects in that protocol. If no approved conflict of interest management plan exists, the IRB panel will forward the conflict information to the appropriate institutional office charged with overseeing and managing conflicts of interest for the institution (for the University of Colorado Denver this office is the Office of Regulatory Compliance).

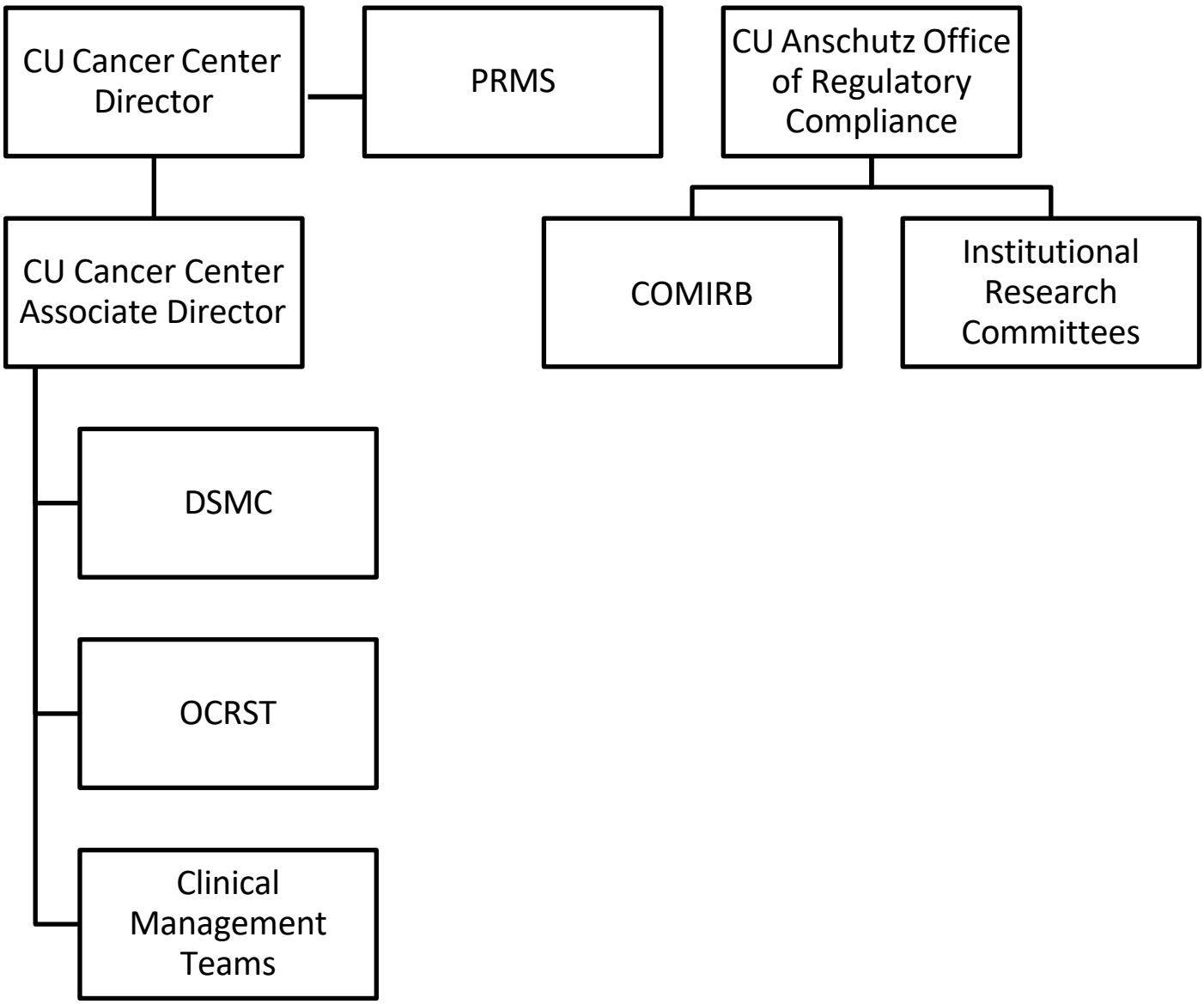
Review of conflict management plans are documented in the panel minutes for full-board review and in the protocol file for expedited review. If a conflict of interest exists, final IRB approval cannot be given until an approved conflict management plan that adequately protects the human subjects in the protocol is in place.

If the conflict of interest status of an investigator or key personnel changes during a study, the individual is required to notify the IRB Office and the institution's conflict of interest management program within 30 days of the change. The IRB panel will review the change as a modification to the protocol.

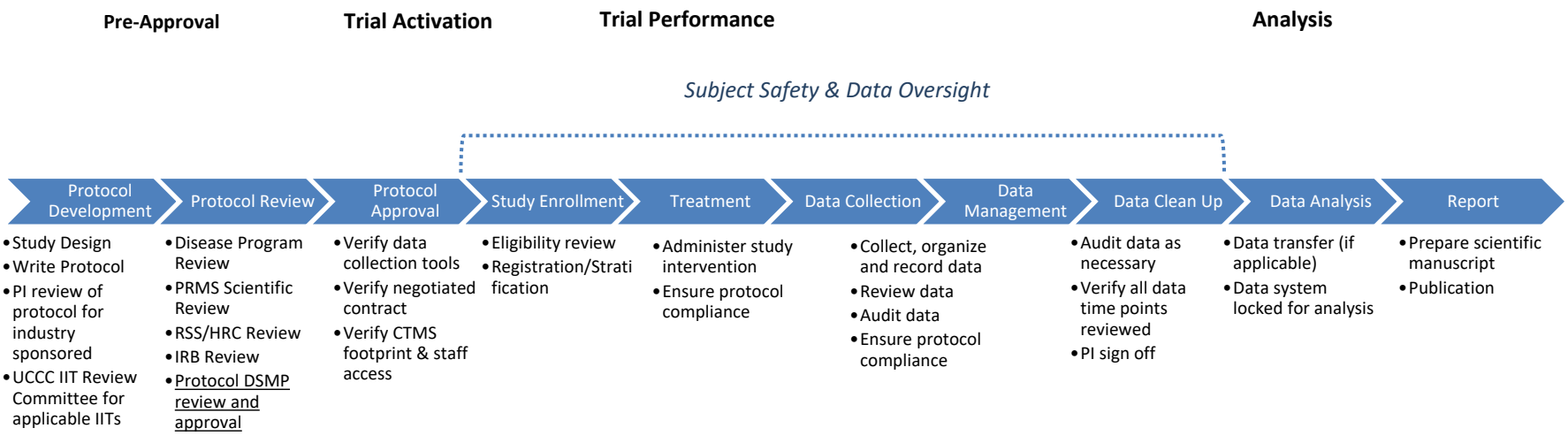
At the time of continuing review, the investigator and key personnel will be asked whether there has been any change in the conflict of interest status relating to the research. The IRB panel will review conflict of interest as part of its continuing review.

Potential conflicts, which develop during a member's tenure on a DSMB/DSMC, must also be discussed and addressed in accordance with the University of Colorado Conflict of Interest policies.

ATTACHMENT A: COMMITTEE REPORTING STRUCTURE



ATTACHMENT B: INFORMATION AND PROCESS FLOW



ATTACHMENT C: GUIDELINES FOR ESTABLISHING AND OPERATING A DSMB

1. Membership

a) Monitoring activities should be conducted by experts in all scientific disciplines needed to interpret the data and ensure participant safety. Clinical trial experts, biostatisticians, bioethicists, and clinicians knowledgeable about the disease and treatment under study should be part of the monitoring group or be available for consultation if warranted.

b) Voting members may be from within or outside the institution, but the majority should not be affiliated with the institution. Members should view themselves as representing the interest of participants and not that of the institutions. Investigators directly involved with the conceptual design or analysis or treatment/enrollment of the particular trial are not eligible to serve on the DSMB.

2. Meeting Procedures

a) Frequency: DSMB meetings will be held at least every six months and more often depending on the nature and progress of the trial being monitored.

b) Elements for Review

(1) A written summary of status, toxicity and outcome of the clinical trial will be prepared by the assigned statistician. The summary will be submitted to DSMB members allowing enough review time prior to meeting.

(2) This summary will also address specific toxicity concerns as well as concerns about the conduct of the trial. It may contain recommendations for consideration by the DSMB concerning whether to close the trial, report the results, or continue accrual or follow-up.

c) Meeting Structure DSMB - Meetings will be divided into three sessions as follows:

(1) **Open Session** - members of the clinical trial team present review of the trial conduct and answer questions from DSMB members. Focus is on accrual, protocol compliance, and general toxicity.

(2) **Closed Session** - Includes DSMB members and the clinical trial statistician(s). The statistician presents and discusses outcome results with DSMB.

(3) **Executive Session** - DSMB members only discuss the general conduct of trial, all outcome results including toxicities as described in the protocol, all adverse events and develop

recommendations.

3. Recommendations

a) It is the responsibility of the PI, the clinical trial statistician(s), and individual DSMB members to ensure that the DSMB is kept apprised of non-confidential results from other related studies that became available, and any programmatic concerns related to the clinical trial being monitored. It is the responsibility of the DSMB to determine the extent to which this information is relevant to its decisions related to the specific trial.

b) DSMB recommendations will be given to the PI, the CU Cancer Center DSMC and the sponsor. The DSMB must provide an adequate rationale for any recommendations made to change the trial for other than safety or efficacy reasons or for slow accrual.

c) The PI is responsible for implementing the change recommended by the DSMB as expeditiously as possible.

d) The sponsor must be informed of the reason for disagreement in the unlikely situation that the PI does not agree with the DSMB recommendation.

e) The sponsor, DSMB Chair, and PI will be responsible for reaching a mutually acceptable decision about the study.

4. Release of Outcome Data

a) In general, outcome data should not be available to individuals outside of the DSMB until accrual has been completed and all participants have completed their treatment.

b) The DSMB may approve the release of outcome data on a confidential basis to the PI for planning the preparation of manuscripts and/or to a small number of others for future trial planning purposes (if applicable).

c) Any release of outcome data before the DSMB recommendation for general dissemination of results must be reviewed and approved by the DSMB.

5. Confidentiality

a) No communication, either written or verbal, of the deliberations or recommendations of the DSMB will be made outside of the DSMB.

b) Outcome results are strictly confidential and must not be divulged to any non-member, except as indicated above, until the recommendation to release the results are accepted and

implemented.

c) Each member of the DSMB, including non-voting member, must sign a statement of confidentiality.

6. Conflict of Interest

a) DSMB members are subject to Federal regulations and CU's COIC Procedures regarding standards of conduct.

b) Individuals invited to serve on the DSMB (voting or non-voting) will disclose any potential conflicts of interest, whether real or perceived, to the PI and the appropriate institutional officials, in accordance with the CU's COIC Procedures. Conflict of interest can include professional interest, proprietary interest, and miscellaneous interest as described in the NIH Grants Policy Statement, Page II-12, and 45 CFR Part 94.

c) Decision concerning whether individuals with potential conflicts of interest or the appearance of conflicts of interest may participate in the DSMB will be made in accordance with the CU's COIC Procedures.

d) Potential conflicts, which develop during a member's tenure on a DSMB, must also be disclosed and addressed in accordance with the CU's COIC Procedures.

ATTACHMENT D: DOCUMENT REVISION HISTORY

January 2007	Editorial changes throughout for clarity. Bone Marrow Transplant (BMT) trials, including pediatric BMT has internal DSMB monitors to provide oversight.
Revised January 2011	Editorial changes throughout. Clarified conflict of interest for PQASC auditors. Stipulated quarterly meetings for protocol review. Added audit outcomes and outlined audit processes. Clarified AE/SAE reporting requirements and PI responsibilities for AEs. Deleted Protocol Auditing
NCI Approved October 2014	Editorial changes throughout for clarity. Updated administrative terms, titles, and organization structure. Emphasizes template language for PI oversight and DSMC oversight of clinical trials, including internal audits, high-risk protocol review and SAE oversight. Added sections on DSMB Oversight, Education, and IRB involvement. Deleted PRMS relevant sections since PRMS is separate committee not reporting to PQASC/DSMC. Added potential DSMP requirements by study type and clarified multi-center trial requirements. Added Conflict of Interest section. Removed PQASC membership from attachments.
Revised August 2020	Added Definitions and Acronyms section for clarity. Multiple clarifications that DSMP covers trials under Cancer Center oversight, not only those at the Cancer Center. Inserted updated Risk Assessment (table 1) per EAB recommendations in incorporated into DSMC sections throughout. Updated Policy contact information, institutional titles, and terms throughout for consistency. Editorial changes throughout for clarity. Clarified real time SAE review for NCTN/Industry trials. Removed expedited reporting requirement throughout for Reportable AEs as reporting of those events are protocol and/or IRB-specific and will be reported to DSMC as appropriate as SAEs or UAPs. Clarified that DSMC members are not required to be CU Cancer Center members; explained DSMC meeting parameters for expedited Chair review and updated handling/storage of meeting minutes. Updated protocol risk-assignments and corresponding references in Table 1. Updated audit process section to reflect changes to streamline processes, better reflect industry practice and account for CCSG requirement for PRMS to close trials that do not make scientific progress. Updated audit outcomes for more inclusive criteria that allows DSMC greater discretion to intervene independent of a numerical threshold. Updated section 2.1.2 and removed 'high-

	risk language to align with updated risk assessment table and clearly define the studies that require DSM progress reports. Added requirement for verification of monitoring to DSM report materials. Clarified that determination letters, not meeting reports are sent to PI. Removed requirement for blinded Ph II to have DSMB to reflect NIH Further Guidance on Data and Safety Monitoring for Ph I and Ph II trials (Released June 5, 2000). Section 2.2 updated to reflect Common Rule 2018 changes. Edited for clarity, deleted redundant information in Section 4. Updated Section 6 to reflect 2017 update to applicable campus policy on Conflicts of Interest. Updated Attachment A and B with current process flows and titles. Removed DSMC membership from Attachment C and inserted link to current DSMC membership list in DSMP. DSMB Guidelines moved to Attachment C and inserted Revision History as Attachment D
Revised September 2025	Updates to Acronyms list Updated WIRB to match current business name of WCGIRB Added communication and escalation of concerning study conduct from OCRST monitoring team to DSM auditing team Table 2 revised to align with narrative in Internal Audits section Added placement of DSMP review and approval to Att. B