University of Colorado Cancer Center

A NATIONAL CANCER INSTITUTE-DESIGNATED CONSORTIUM COMPREHENSIVE CANCER CENTER

INSTITUTIONAL DATA AND SAFETY MONITORING PLAN

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1. INTRODUCTION AND OVERVIEW

The University of Colorado Cancer Center (CU Cancer Center) is dedicated to excellence in cancer research, education, prevention, and treatment. In order 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 (DSM) Plan has been developed to coordinate and provide oversight for the data and safety monitoring of all CU Cancer Center clinical trials. This DSM plan is consistent with the National Institutes of Health (NIH) Policy for Data and Safety Monitoring (June 10, 1998) and the Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by the National Cancer Institute (April 2001).

For the purpose of this document, the operational definition of a clinical trial as defined by the National Cancer Institute (NCI) is: "a prospective study involving human subjects designed to answer specific questions about the effects or impact of particular biomedical or behavioral interventions; these may include drugs, treatments, devices, or behavioral or nutritional strategies. Participants in these trials may be patients with cancer or people without a diagnosis of cancer but at risk for it." The implementation of the CU Cancer Center DSM Plan is conducted through the activities of the Data and Safety Monitoring Committee (DSMC) and Institutional Review Boards (IRBs). Trials at the CU Cancer Center are overseen by the Colorado Multiple Institutional Review Board (COMIRB), the Western Institutional Review Board (WIRB), the NCI Central Institutional Review Board (CIRB), or other external IRBs depending on the trial sponsor.

2. INSTITUTIONAL OVERSIGHT OF CLINICAL TRIALS

The Principal Investigator (PI) is responsible for individual trial oversight; however, the DSMC and IRBs oversee data and safety monitoring for all clinical trials at the CU Cancer Center. The DSMC reports directly to the Associate Director (AD) for Clinical Research who, in turn, reports to the Director of the CU Cancer Center. The Colorado Multiple Institutional Review Board (COMIRB) reports to the University of Colorado Assistant Vice Chancellor (AVC) for Research. Close interaction and communication between the two committees is critical to the ongoing data and safety monitoring of clinical trials at the CU Cancer Center (See 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).

Committees and groups with responsibilities in data and safety monitoring include the:

- CU Cancer Center Data and Safety Monitoring Committee (DSMC)
- Institutional Review Boards (IRBs)

- Site Specific Clinical Trial Management
- Individual Data and Safety Monitoring Boards (DSMBs)

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

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:

- Conduct of internal audits
- Real-time review of treatment-related SAEs, UAPs and other reportable AEs
- High-risk protocol review
- 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 on a quarterly basis; however, meetings are held at any time as necessary to address urgent situations. Agendas include, but are not limited to, review of reported adverse events, internal DSMB reports, internal and external audit reports, pharmacy safety trends, educational activities and data and safety monitoring reports from high risk trials (see section 2.1.2). The meeting minutes and reports on specific protocol actions are provided to the AD for Clinical Research, COMIRB, and the AVC for Research and Compliance.

The expertise of the DSMC includes Physicians, Oncology Nurses, Research Pharmacists, Biostatisticians, and Research Administration staff. Investigators on the DSMC must be eligible to conduct clinical research at the CU Cancer Center. 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 by the CU Cancer Center Director (See Attachment C). The chair selects members with the concurrence of the AD for Clinical Research.

A quorum consists of a minimum of 5 of the voting members, including at least 2 physicians and a biostatistician.

2.1.1 Auditing

The DSMC performs internal audits of CU Cancer Center trials to evaluate study protocol adherence, source verification, subject eligibility, AE reporting and informed consent procedures. The goals of the DSMC auditing process are:

- To ensure ongoing clinical protocol compliance with IRB guidelines, FDA regulations, and CU Cancer Center policies and procedures

- To educate the clinical research staff to promote greater awareness and understanding of policies, procedures, and objectives, and to increase efficiency and consistency in the clinical trial
- 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 protocols not subject to frequent external auditing and monitoring, such as CU Cancer Center investigator-initiated trials. At least one protocol will be selected for each CU Cancer Center team conducting clinical trial research annually. At the end of each calendar year, all eligible trials are reviewed by the DSMC Manager and Chair and a protocol audit list is created and sent to the DSMC for review and final approval. Auditing is coordinated by the DSMC and is performed by Audit Teams. Each Audit Team is comprised of at least one non study-related Physician Investigator, two to three other staff with expertise in study coordination or regulatory requirements and a DSMC auditor. At the discretion of the DSMC Chair, there may be instances when a full audit team is not required to be convened. Each audit team will receive written and verbal instructions regarding the role of the audit team from the lead auditor. The PIs and their study teams of the protocol that will be audited are contacted at least four weeks prior to audit. Each PI and study team to be audited will receive a letter listing the information about the audit (including date, time, etc.), a list of the cases to be audited, a copy of the audit policies and data and regulatory forms. Audits are conducted in a secure fashion to ensure confidentiality of data. No member of the audit team shall audit any protocol for which he/she has a true or perceived conflict of interest. If a conflict of interest exists, the protocol will be assigned to another audit team. The DSMC reviews and approves audit reports and makes recommendations regarding significant findings.

The process continues as follows:

- For all treatment trials selected, auditing includes a random check of study conduct, data completeness and accuracy based upon a minimum of 5 cases per trial or 10% of all cases accrued (whichever is greater).
- For large tissue banking only studies, a random selection of 10% or more cases will be audited.
- For trials that are audited multiple times, the audit team may select to audit only new patients enrolled since the last audit.
- The selected participants' records, pharmacy records and protocol regulatory documents (including IRB submissions, continuing review submissions) will be reviewed.
- The selected participants' records, including consent forms, source documentation of eligibility, response, toxicity, drug accountability and handling and data quality will be reviewed.
- The audit team will discuss the audit outcome with the PI and Study Team within 72 hours of the audit.

- The final written audit report is submitted by the audit team within three weeks of the audit to the PI and site-specific clinical research team.
- If a follow-up response is required, the PI must provide a written response to the DSMC within 30 days. If corrective action is required as a result of the audit, the DSMC Manager will follow up with the study team and PI to determine progress.
- If immediate action is required (in the event of an unacceptable audit rating), the DSMC has the authority to require accrual be temporarily or permanently suspended.
- If action is required following an audit, the final audit report is submitted to site-specific leadership, the CU Cancer Center AD for Clinical Research, the IRB of record and the CU Vice Chancellor for Research. If a trial requires suspension, this is immediately reported to the PI, the above-named groups, 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.

The DSMC audits are rated on the following performance outcomes:

Audit Outcomes	**Criteria**
Exceptional	Evidence of source documents, data quality, regulatory compliance. No response required.
Acceptable	Source documents with minor deficiencies/deviations. Requires correcting deficiencies.
Acceptable, requires follow-up	Irregularities in consent forms/IRB Submissions. Requires, at a minimum, a written or corrective plan with deadlines and timelines for implementation. May require in-service education/training for research staff.
Unacceptable	Major violation(s) present. Major consent deviations. 50% or more dose errors. Requires, at a minimum, a written corrective plan and implementation of recommendations. May require temporary closure at the recommendation of the DMSC and may result in temporary or permanent closure upon recommendation of the PRMS/IRB.

2.1.2 High-Risk Protocol Review

The DSMC reviews high-risk Phase I and Phase II protocols for data and safety monitoring. Protocols defined as high-risk are CU Cancer Center investigator-initiated treatment trials without external data and safety monitoring. This includes trials where an IND is held by a CU Cancer Center investigator, and multi-site investigator-initiated trials where the CU Cancer Center is the coordinating center.

High-risk trials are identified during the protocol development and approval process. It is the responsibility of the study PI to provide a DSM report to the CU Cancer Center DSMC every 6 months beginning at the time of the first trial subject enrollment. The DSM reports include a protocol summary, current enrollment figures, a summary of toxicity data to include specific SAEs, UAPs and AEs, dose modifications, protocol deviations and protocol amendments. The DSM reports also include, if applicable, final efficacy analysis and minutes from monthly safety teleconferences for multi-site studies. DSM reports must contain data from all participating sites if trials are conducted at multiple sites.

The DSMC performs a formal review of all high-risk protocols every six months during regularly scheduled meetings. The DSMC provides meeting reports to the PI and their site specific clinical research team and may recommend modifications be made to the trial. For multi-site trials, the PI must provide DSMC meeting reports to all participating sites. DSMC meeting reports should also be submitted to the IRB of record at the time of Continuing Review.

If modifications to the trial are recommended, the PI will be notified in order that he/she may alert all investigators involved in the trial with regard to the potential action. The DSMC may recommend an amendment to the protocol, but also may recommend study suspension or closure based on findings. Following notification, the PI may submit additional information to the DSMC that could affect the DSMC's decision. If study suspension or closure is recommended, the 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.

2.1.3 Centralized Review of SAEs, UAPs and reportable AEs

The DSMC provides an ongoing and real-time review of all treatment-related SAEs, UAPs and reportable AEs to identify safety-driven milestones within trials and across trials of similar targeted therapeutics. All SAEs, UAPs and reportable AEs are reported to the DSMC, IRB and the sponsor using NIH guidelines for either commercial or investigational agents (or as required in the protocol) (see section 4. AE Reporting Compliance). The DSMC chair or an oncologist on the committee performs an initial review which serves as a triage and can trigger a full-board DSMC review for concerning toxicity or toxicity trends. Cumulative reports of these events are discussed in the DSMC quarterly meetings in order to provide consistency and “longevity” to AE analysis.

2.1.4 DSMB Oversight

For CU Cancer Center investigator-initiated phase III trials or blinded phase II trials, an independent DSMB will be required as data may need to be unblinded for analysis. Guidelines

for establishing and operating an external DSMB are outlined in Attachment D. The DSMC may assist the PI in setting up an adequate DSMB (in accordance with guidelines outlined in Attachment D) and the PI will be responsible for submitting independent DSMB reports to the DSMC.

2.1.5. Education

The DSMC Manager provides ongoing education for physician 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 manager or designee also serves as a resource for enhancement of trial management skills.

2.2. Institutional Review Boards (IRBs)

COMIRB serves as the IRB for the CU central system, however, trials may utilize WIRB or 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 all SAEs. Each IRB stipulates the frequency of Continuing Reviews based on risk assessment and reviews these in detail on an ongoing basis. DSMC reviews and monitoring systems aid IRBs in their evaluations.

Continuing Reviews occur at least annually for all trials that are more than minimal risk. 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.

The DSMC provides their reviews of high-risk trials (see section 2.1.2) to be submitted to the IRB at the time of Continuing Review.

3. PROTOCOL SPECIFIC MONITORING AND OVERSIGHT

3.1. Data and Safety Monitoring

All CU Cancer Center clinical trials must 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 (Table 1) must be described in detail in each protocol, and approved by the IRB prior to 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 subject safety.

Table 1: Clinical Trial Risk Categorization

High Risk	**Moderate Risk**	**Low Risk**
• CU Cancer Center investigator-initiated treatment trials without external data and safety monitoring. This includes: o IND is held by a CU Cancer Center investigator o Multi-site investigator-initiated trials where the CU Cancer Center is the coordinating center. o Institution is manufacturing the study agent o gene therapy protocols	• Interventional trials sponsored by industry or cooperative groups	• Intervention trials that are nutritional, behavioral or psychosocial • Intervention trials that are diagnostic in nature • Tissue banking only trials

The PI is responsible for developing and incorporating the DSMP for CU Cancer Center investigator-initiated protocols without external oversight (see Table 2 for requirements). The PI is responsible for ensuring that trial conduct is monitored for patient safety, data quality, as well as protocol and regulatory compliance through a trial specific monitoring plan. 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 needed. The PI is also encouraged to collaborate with clinical trial staff, as well as additional resources 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 PRMS and IRB-approved protocol. Therefore, all investigators and staff in the CU Cancer Center are required to participate 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. In addition, eligibility

checklists, the DSMC internal audit program, DSMPs in each protocol, and regular oversight by PIs assure data accuracy and protocol compliance.

The PI will ensure data required for appropriate oversight of subject safety are reported to the IRB, DSMC, DSMB (as appropriate), and that all reportable and/or serious adverse events (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 within 30 days of treatment. All reportable AEs, unanticipated problems (UAPs) and SAEs must be reported to the IRB and DSMC within 5 business days of receiving notification of the occurrence. Trials must stipulate at least an annual review of study data as long as subjects are undergoing study treatment or are being followed for study purposes. These annual Continuing Reviews are performed by the IRB.

Table 2: Potential Data and Safety Monitoring Plan (DSMP) requirements for CU Cancer Center investigator-initiated clinical trials without external oversight (high risk trials)

Trial Type	Potential DSMP Requirements
Phase I	• SAEs, UAPs and reportable AEs are reported to the DSMC and IRB • Number of subjects, significant toxicities, dose modifications, and treatment responses/outcomes discussed at weekly disease-oriented working group meetings • Submission of a DSM report, to include any monitoring report(s), to the CU Cancer Center DSMC on a six month basis • Auditing to be conducted by the CU Cancer Center DSMC
Phase I/II or II	• SAEs, UAPs and reportable AEs are reported to the DSMC and IRB • Number of subjects, significant toxicities, dose modifications, and treatment responses/outcomes discussed at regularly scheduled disease-oriented working group meetings • Submission of a DSM report, to include any monitoring report(s), to the CU Cancer Center DSMC on a six month basis • Auditing to be conducted by the CU Cancer Center DSMC
Phase III	• SAEs, UAPs and reportable AEs are reported to the DSMC and IRB • Safety monitoring by an external DSMB at least once every six months • Submission of a DSM report, including any monitoring report(s), to the CU Cancer Center DSMC on a six month basis • Auditing to be conducted by the CU Cancer Center DSMC
Tissue Bank	• Auditing to be conducted by the CU Cancer Center DSMC

Tissue Bank with Additional Risk Including Study-Related Biopsies	• SAEs, UAPs and reportable AEs are reported to the DSMC and IRB • Auditing to be conducted by the CU Cancer Center DSMC • Submission of a DSM report, including any monitoring report(s), to the CU Cancer Center DSMC on a six month basis

3.1.1 Multi-Center Trials

The lead institution/PI is responsible for the data and safety monitoring of the overall study. It is important to note that monitors must have access to data from all participating sites and that the results of the reviews are provided to all participating investigators to share with their local IRBs. If the CU Cancer Center is the lead institution, the PI will be responsible for the data and safety monitoring of the trial at all participating sites.

Each subject'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 patients, significant toxicities, dose modifications, and responses will be discussed and documented in meeting minutes.

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 events to the DSMC within 5 business days of receiving notification of the occurrence.

3.1.3 Trials Involving Vulnerable Subjects

High risk trials for vulnerable subjects such as children might consider a consent monitor or Certified Research Subject Advocate. Data and safety of all trial subjects 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 six month DSM report.

3.1.4 National or Regional Cooperative Group Trials

Cooperative group trials are generally monitored at the cooperative group level. Data and safety is monitored by set DSM committees at the cooperative group level. However, these trials are subject to routine DSMC internal auditing.

4. ADVERSE EVENT REPORTING COMPLIANCE

All reportable AEs, unanticipated problems (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 within 30 days of treatment. All unanticipated problems (UAPs) and SAEs must be reported to the IRB and DSMC within 5 business days of receiving notification of the occurrence.

The DSMC chair or an oncologist on the committee performs ongoing review of all study treatment related SAEs, reportable AEs and UAPs in real-time to identify safety-driven milestones within trials. The initial review by a DSMC oncologist serves as a triage and can trigger a full-board DSMC review for concerning toxicity or toxicity trends. The responsibility for reporting AEs rests with the PI; however, the DSMC ensures compliance with reporting. Cumulative reports of reportable AEs and SAEs will be discussed quarterly in order to provide consistency and "longevity" to AE analysis.

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

Per 21 CFR 312.32a definition of an 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.

Unanticipated Problems (UAPs) include adverse events which in the opinion of the principal investigator are both unexpected and probably or definitely related to the intervention/ drug or device, any unforeseen development that potentially increases the likelihood of harm to participants or others in the future, information that indicates a change to the risks or potential benefits of the research or an actual unforeseen harmful or unfavorable occurrence to participants or others that relates to the research protocol (injuries, psychological events, drug errors).

Other Reportable Adverse Events include death unrelated to study treatment if occurring within 30 days of the last study treatment, death at least possibly related to study treatment at any time point, secondary malignancy, pregnancy, fetal death, and neonatal death.

5. PERMANENT SUSPENSION OF NCI FUNDED CLINICAL TRIALS

All temporary or permanent closures of NCI-sponsored clinical trials (non-cooperative group) 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

CU and IRBs require all "covered individuals" to comply with the CU Administrative Policy Statement for Conflicts of Interest and Commitment (COIC), 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 faculty, individuals who are responsible for the design, conduct and reporting of basic or clinical research. This includes anyone who obtains informed consent, those who determine eligibility, those who review data or conduct data analysis, Research Committee Members (i.e. IRB members, DSMB Members and/or other research review committees), staff who negotiate or execute research agreements on behalf of CU Area/Program Administrators, and the staff of CU's Grants and Contracts and the Technology Transfer Offices. Covered individuals include non-CU employees that participate in human subject research protocols under the authority of IRBs. Covered individuals must include family members which are defined as spouse/domestic partner and dependent children when submitting disclosures. Where a non- CU employee is an employee of an affiliated hospital or research center that has a separate conflict of interest program, the CU Office of Regulatory Compliance will coordinate with the respective office at the affiliated hospital or research center. 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 Conflicts of Interest and Commitment's definition of significant financial interests) are reviewed in accordance with CU Procedure on Conflicts of interest and Commitment and receive management plans accordingly. Management plans are project specific and will be reviewed at a minimum on an annual basis by the CU Office of Regulatory Compliance.

The IRB's 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 subjects 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 CU 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 make a determination as to whether the conflict adversely affects the protection of human subjects. If the answer is yes and an approved conflict management plan exists, the IRB's 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's panel will forward the conflict information to the appropriate institutional office charged with overseeing and managing conflicts of interest for the institution (for UCDenver this office is the CU Office of Regulatory Compliance).

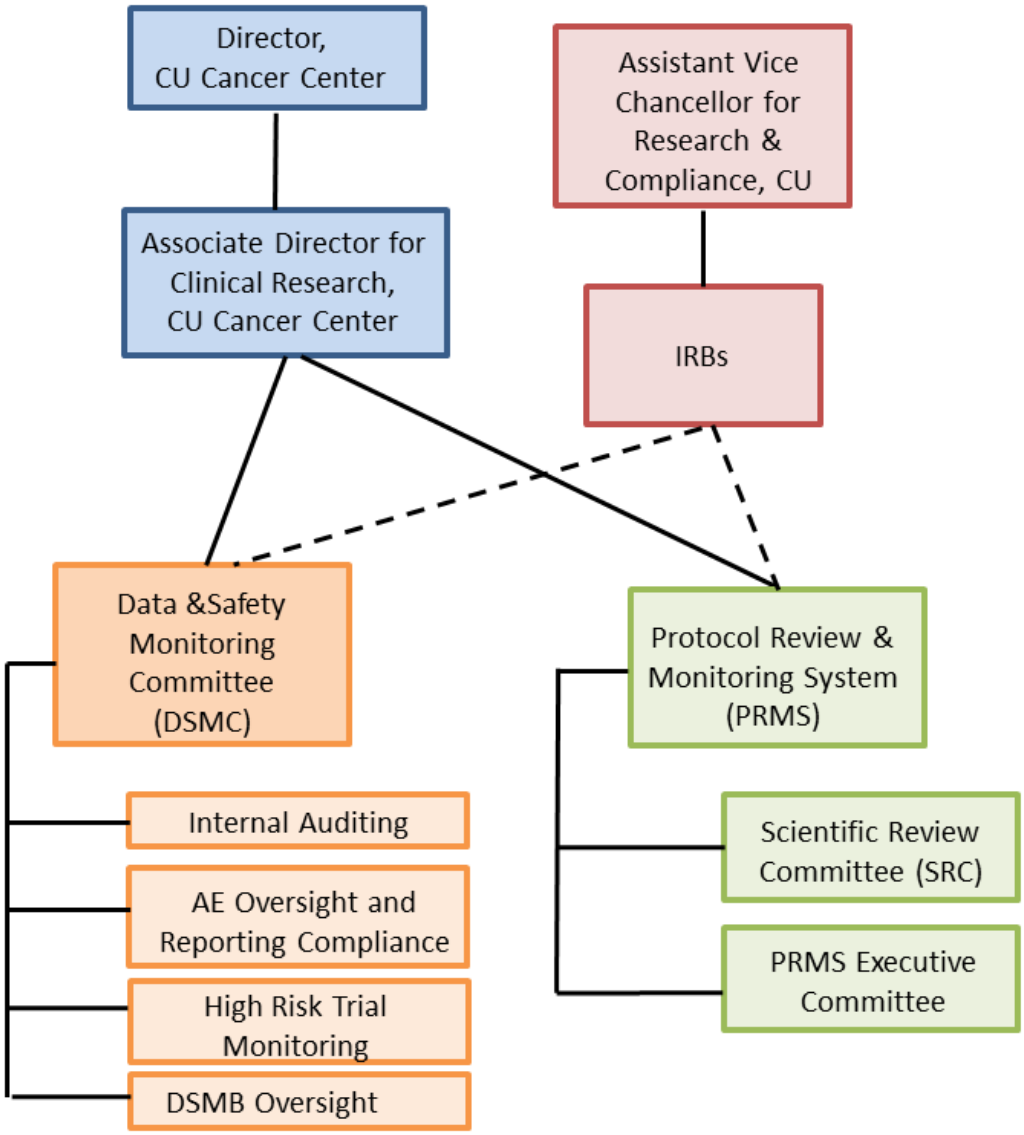
Review of conflict management plans are documented in the panel minutes for full board review and in the protocol file for expedited review. If a conflict of interest exists, final IRB approval cannot be given until an approved conflict management plan that adequately protects the human subjects is in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

If the conflict of interest status of an investigator or key personnel changes during the course of 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's panel will review the change as a modification to the protocol.

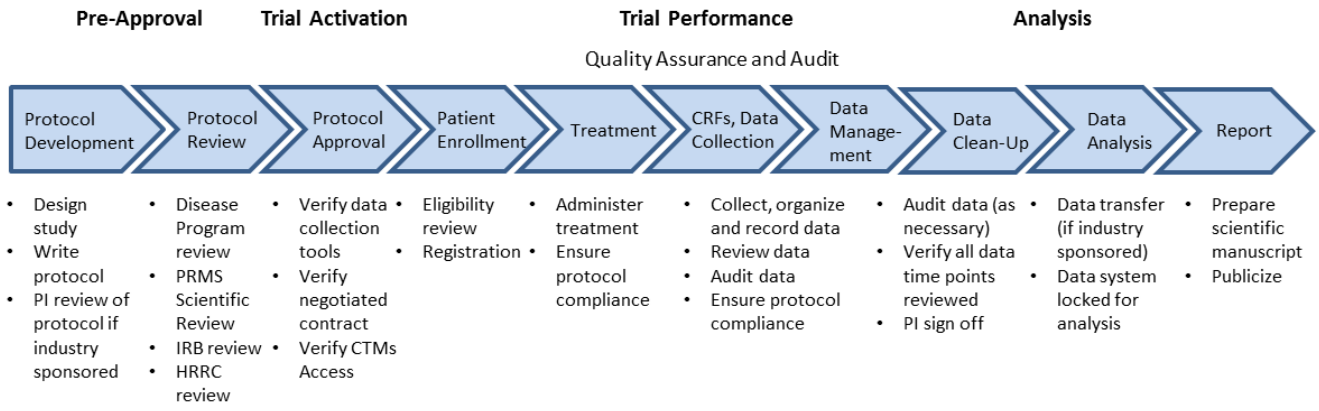
At the time of continuing review, the investigator and key personnel will be asked whether there has been any change in the conflict of interest status relating to the research. The IRB's panel will review conflict of interest as part of its continuing review.

Potential conflicts, which develop during a member's tenure on a DSMB, must also be disclosed 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: EXAMPLE DSMC COMMITTEE MEMBERSHIP

2014 - 2015
Jennifer R. Diamond, MD, Chair, Assistant Professor of Medical Oncology, University of Colorado Anschutz Medical Campus
Antonio Jimeno, MD, PhD, Medical Oncologist, Professor of Medical Oncology, University of Colorado Anschutz Medical Campus
Thomas Flaig, MD, Medical Oncologist, Associate Professor of Medical Oncology, University of Colorado Anschutz Medical Campus
Lia Gore, MD, Pediatric Medical Oncologist, Associate Professor of Pediatrics and Medical Oncology, University of Colorado Anschutz Medical Campus
Stephen Leong, MD, Medical Oncologist, Associate Professor of Medical Oncology, University of Colorado Anschutz Medical Campus
Christine Fisher, MD, Radiation Oncologist, Assistant Professor of Radiation Oncology, University of Colorado Anschutz Medical Campus
Elaine Lam, MD, Medical Oncologist, Assistant Professor of Medical Oncology, University of Colorado Anschutz Medical Campus
Patrick Blatchford, PhD, Biostatistician, Assistant Professor of Biostatistics and Informatics, University of Colorado Anschutz Medical Campus
Astrid Eder, PhD, Colorado Multiple Institutional Review Board (COMIRB) Senior Regulatory Analyst
Colleen Kellackey, RN, CU Cancer Center Cancer Clinical Trials Office Operations Manager
Adam Poust, PharmD, Investigational Pharmacist, University of Colorado Hospital
Lisa Haney, BS, CCRC, DSMC Manager
Jan Bullock, RN, BSN, DSMC Auditor
Kara Armstrong, DSMC Auditor
Andrew Wise, BA, DSMC Auditor

ATTACHMENT D: 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 insure subject 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 subjects and not that of the institution. 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 statistician. The summary will be submitted to DSMB members allowing sufficient 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 insure 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 to implement 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 subjects 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.

c) Any release of outcome data prior to 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 be 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.