For further information concerning this document please contact:

Martha Mims, MD, PhD
Co-Associate Director for Clinical Research
Dan L. Duncan Cancer Center
Baylor College of Medicine
One Baylor Plaza, BCM187
Houston, TX 77030
713-798-7535
mmims@bcm.edu

Helen Heslop, MD
Co-Associate Director for Clinical Research
Dan L. Duncan Cancer Center
Baylor College of Medicine
One Baylor Plaza, BCM505
Houston, TX 77030
832-824-4662
heheslop@bcm.edu
# Table of Contents

Abbreviations ......................................................................................................................................... 4

Overview .................................................................................................................................................. 5

Structure of Clinical Research Oversight ................................................................................................. 6

**Key Components of Data and Safety Monitoring**

Overview .................................................................................................................................................... 7

Principal Investigator ................................................................................................................................. 7

Conflict of Interest ..................................................................................................................................... 8

Institutional Review Board ........................................................................................................................... 8

Clinical Trials Support Unit ......................................................................................................................... 8

Clinical Research Leadership Committee .................................................................................................... 9

Patient Safety Officer ................................................................................................................................. 9

Protocol Review and Monitoring System ..................................................................................................... 9

Function ..................................................................................................................................................... 9

Structure ................................................................................................................................................... 10

Membership .............................................................................................................................................. 10

Protocol Review Procedures ...................................................................................................................... 11

Initial Protocol Review ............................................................................................................................... 11

Amendment Review ................................................................................................................................ 11

Ongoing/Continuing Review ....................................................................................................................... 12

Protocol Specific Data and Safety Monitoring Plans .................................................................................. 12

**Data and Safety Monitoring Mechanisms for Protocols** ...................................................................... 13

External Data and Safety Monitoring .......................................................................................................... 13

Internal Data and Safety Monitoring .......................................................................................................... 13

DLGCC Data Review Committee ............................................................................................................... 13

DRC Data Review .................................................................................................................................... 14

DRC Data Review Frequency .................................................................................................................... 14

DRC Meeting Review Process .................................................................................................................. 15

DRC Meeting Reports ................................................................................................................................ 15

DRC Appeal Process ................................................................................................................................ 15

DRC Confidentiality .................................................................................................................................. 16

**Data and Safety Monitoring Boards** ..................................................................................................... 16

DSMB Membership ................................................................................................................................... 16

DSMB Responsibilities ............................................................................................................................... 16

DSMB Charter ......................................................................................................................................... 16

DSMB Meeting Frequency ......................................................................................................................... 17

DSMB Recommendations .......................................................................................................................... 17

DSMB Appeal Process ............................................................................................................................... 17

DSMB Confidentiality ............................................................................................................................... 17
Guidelines for Data and Safety Monitoring Implementation

Phase I Trials .......................................................................................................................... 18
Phase I/II and Phase II Trials .................................................................................................. 18
Phase III Trials & Randomized Phase II Studies with a Placebo Control ......................... 18
Phase I-III Behavioral and Nutritional Trials ................................................................. 18
Training Grant Trials ........................................................................................................... 18

Review and Oversight Requirements

Adverse Event Reporting ........................................................................................................ 19
Study Progress ....................................................................................................................... 19
IRB Review ............................................................................................................................. 19

Data Quality Assurance and Protocol Compliance

Audit Types ............................................................................................................................. 20
Audit Process .......................................................................................................................... 20
Audit Findings ......................................................................................................................... 20
Audit Response Review .......................................................................................................... 21
Notification of NCI Regarding Suspension of a Funded Trial .............................................. 21
ABBREVIATIONS

AE           Adverse Event
BCM          Baylor College of Medicine
CAGT         Cell and Gene Therapy
CTCAE        Common Toxicity Criteria for Adverse Events
CTEP         Cancer Therapy and Evaluation Program
CTSU         Clinical Trial Support Unit
DLDCC        Dan L. Duncan Cancer Center
DCTD         Division of Cancer Treatment and Diagnosis
DRC          Data Review Committee
DSMB         Data and Safety Monitoring Board
DSMP         Data and Safety Monitoring Plan
FDA          Food and Drug Administration
CRC          Clinical Research Center
IRB          Investigational Review Board
NCI          National Cancer Institute
NCTN         NCI National Clinical Trials Network
NIH          National Institutes of Health
NHLBI        National Heart, Lung and Blood Institute
PI           Principal Investigator
PRMC         Protocol Review and Monitoring Committee
PSO          Patient Safety Officer
QA           Quality Assurance
RAC          Recombinant DNA Advisory Committee
SAE          Serious Adverse Event
SOPs         Standard Operating Procedures
DATA AND SAFETY MONITORING PLAN

OVERVIEW

As an NCI-designated cancer center, the Dan L. Duncan Cancer Center (DLDCC) at Baylor College of Medicine (BCM) places the highest priority on ensuring the safety of patients participating in clinical trials. The ability to safely conduct high-priority clinical research is a mission-critical activity of the DLDCC. All protocols are rigorously reviewed and monitored to ensure that all regulatory guidelines are met. Oversight for this process begins with the Principal Investigator (PI), but as outlined in this plan, is reinforced through integrated scientific, technical and ethical review coupled with ongoing quality assurance monitoring.

A broad spectrum of therapeutic clinical research studies, ranging from single center phase I clinical trials through participation in multi-institutional phase III studies, are conducted at the DLDCC. In addition, there are clinical research studies in other areas such as cancer prevention, epidemiology, behavioral research, quality of life and late effects.

This document details the DLDCC’s Data and Safety Monitoring Plan. This plan outlines the general process for data and safety monitoring, including institutional oversight and review procedures important to ensure and document compliance. This plan is designed to ensure the safety of participants, the validity of data, and the appropriate termination of studies in the event that undue risks have been uncovered, or it appears that trials cannot be conducted successfully. The institutional plan covers all cancer-related clinical trials within DLDCC. Particular attention is paid to monitoring investigator-initiated clinical trials, especially those for which there is no independent outside monitoring program.

The extent of safety monitoring for trials is based on an assessment of the degree of risk encountered by patients on the study. The type of agent or agents involved and the phase of the clinical trial are all taken into consideration when a risk level is assigned to a study. Sponsorship for DLDCC clinical trials includes NCI-funded NCTN trials, investigator-initiated trials, externally peer-reviewed trials, and pharmaceutical industry-sponsored trials.

Currently, the initiation, monitoring and termination of clinical research conducted at DLDCC is overseen by (1) the Protocol Review and Monitoring Committee (PRMC), (2) Data Review Committee (DRC); and (3) a Patient Safety Officer (PSO). The structure and scope of responsibility for these committees as well as the role and responsibilities of the PSO are described below. The committees and the PSO report to the Clinical Research Leadership Committee (CRLC) within the DLDCC and ultimately to the Cancer Center Director.
Figure 1. Structure of DLDCC Clinical Research Oversight

DLDCC Director
Dr. Kent Osborne

Co-Associate Directors for Clinical Research
Dr. Helen Heslop, Dr. Martha Mims

Clinical Research Leadership Committee (CRLC)

Quality Assurance and Quality Control

Patient Safety Officer (PSO)

Data and Safety Monitoring

Protocol Review and Monitoring Committee (PRMC)

Executive Committee

CAGT Working Group
Pediatric Working Group
Adult Working Group

DRC: Data Review Committee
DSMBs: Data and Safety Monitoring Boards
The DLDCC Data and Safety Monitoring Plan has been developed to coordinate data and safety monitoring oversight for all cancer clinical trials consistent with the following policy statements:

- National Institutes of Health Policy for Data and Safety Monitoring
  (05-Jun-00) http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html
- National Cancer Institute policy for data and safety monitoring of clinical trials
- Cancer Therapy Evaluation Program (CTEP) guidelines for monitoring of clinical trials for Cooperative Groups, CCOP Research Bases, and the Cancer Trials Support Unit (CTSU)
  http://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring_coop_ccop_ctsu.htm
- Handbook for Clinical Investigators Conducting Therapeutic Clinical Trials Supported by CTEP, DCTD, NCI
  http://ctep.cancer.gov/handbook/
- CTEP NCI Guidelines: Adverse Event Reporting Requirements
- Code Of Federal Regulations Title 45 Public Welfare Department Of Health And Human Services National Institutes Of Health Office For Protection From Research Risks, Part 46, Protection Of Human Subjects
  http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html
- FDA Guidance for Data and Safety Monitoring

**KEY COMPONENTS OF DATA AND SAFETY MONITORING**

**OVERVIEW OF DATA AND SAFETY MONITORING AT THE DLDCC**

The institution must promote an environment that facilitates detailed ongoing review and safe conduct of clinical research studies. Therefore, truly effective data and safety monitoring is not the result of a single committee or individual, but is a shared responsibility within the DLDCC protocol management infrastructure. Key elements and processes at the DLDCC that contribute to data and safety monitoring are summarized in this section.

**PRINCIPAL INVESTIGATOR**

Every study submitted for review at the DLDCC, regardless of the type of sponsor, must have a designated local Principal Investigator (PI) who is responsible for the safe conduct of the study at our Center. The PI must be a member of the Baylor College of Medicine (BCM) faculty. All PIs, co-investigators and key study personnel must have certification in human subjects research protection and participate in research educational sessions, based on current NIH and local IRB guidelines.
CONFLICT OF INTEREST

The DLDCC adheres to BCM’s Conflict of Interest Policy, which serves to protect the objectivity of persons who are engaged in research, and to preserve the integrity of the College and all of its employees. The BCM Conflict of Interest Committee administers and interprets the BCM Conflict of Interest Policy. In order to track the potential conflicts of interest and the management plans, an electronic conflict of interest disclosure must be submitted by faculty and selected staff as described in the BCM Conflict of Interest Policy. The activities outlined in the Conflict of Interest disclosure must be submitted to the College as they arise and at least annually, and must be evaluated and managed to avoid actual conflicts.

CONFIDENTIALITY

Information related to any study under DLDCC review, including study data, reports, correspondence, and appeals, will be maintained as confidential and disclosed only as required for review, unless additional disclosure is required by BCM policy or pertinent laws or regulations. All members of the review committees are subject to BCM and federal confidentiality requirements. Members will be reminded upon their appointment to committees and regularly throughout their committee service.

INSTITUTIONAL REVIEW BOARD

All activities involving human subjects must be reviewed and approved by the BCM institutional review board (IRB) prior to patient enrollment. The IRB functions as the human subjects review committee for all DLDCC affiliated institutions. The requirement for initial and ongoing IRB review of a protocol involving human subjects is applicable regardless of the source of support. Furthermore, IRB approval is required whether the research is performed on the premises of one the DLDCC affiliated hospitals or clinics or elsewhere, including collaborating sites.

CLINICAL TRIAL SUPPORT UNIT

The DLDCC Clinical Trial Support Unit (CTSU) and affiliated offices in Pediatrics and Cell and Gene Therapy (CAGT) serve as central resources to coordinate and assist with all cancer-related clinical research within the DLDCC and its affiliated hospitals and ambulatory care centers. The CTSU facilitates liaison with external investigators, NCTN cooperative groups, federal agencies, and the pharmaceutical industry, and coordinates the majority of clinical research studies in the DLDCC. There are comprehensive standard operating procedures (SOPs) that govern all aspects of clinical research within the DLDCC to ensure that its clinical research is of the highest quality.

This provides enhanced professional training and staff support, adherence to standardized procedures and improved oversight of regulatory compliance. In addition to oversight of regulatory coordinators, clinical research coordinators, and research nurses, the CTSU also oversees the Quality Assurance / Quality Control Program within the DLDCC.
CLINICAL RESEARCH LEADERSHIP COMMITTEE

The Clinical Research Leadership Committee (CRLC), composed of DLDCC senior leadership, reviews reports from Data Review Committees (DRCs), Data and Safety Monitoring Boards (DSMB) and Quality Assurance / Quality Control audits, which are independently submitted to this committee. This committee is comprised of the DLDCC Director, the Associate Directors for Clinical Research, the Director of the CTSU, the Chair and Vice-Chairs of the PRMC Executive Committee, and the Director of the Biostatistics Shared Resource.

PATIENT SAFETY OFFICER

The clinical research infrastructure of the DLDCC includes a Patient Safety Officer (PSO) who ensures that all data monitoring for Cancer Center trials is conducted in accordance with the approved monitoring plan. The PSO reports to the Associate Directors of Clinical Research.

Responsibilities of the PSO include the following:

- Maintenance of a database that tracks protocol reviews and approvals
- Monitoring adherence to the study’s approved DSMP
- Notification of the Associate Directors for Clinical Research and the CLRC if a plan is not being followed appropriately
- Advising clinical trial investigators regarding the optimal data and safety monitoring plan during development of investigator-initiated trials
- Coordinating the DLDCC DRC (including maintaining member roster, coordinating meetings, sending/receiving correspondence, etc.)
- Facilitating the development of independent DLDCC-coordinated Data and Safety Monitoring Boards (including constituting the DSMB, coordinating meetings, sending/receiving correspondence), as required.

PROTOCOL REVIEW AND MONITORING SYSTEM

FUNCTION

The purpose of the Protocol Review and Monitoring System is to provide internal, centralized oversight of cancer clinical research within the DLDCC. The Protocol Review and Monitoring Committee (PRMC) reviews interventional clinical trials whose primary aim is cancer related, including therapeutic, preventative, and supportive care.

STRUCTURE

The PRMC is comprised of an Executive Committee and three working groups. The working groups, described in detail below, meet every two weeks and the Executive Committee meets monthly. The working group reviews and recommendations are forwarded to the Executive Committee. The PRMC Executive Committee provides rigorous oversight of the
working groups. The working groups conduct complete review of each protocol according to Cancer Center Guidelines. When this review is completed, the Executive Committee reviews the protocol along with all actions of the working group in order to assure rigor of review and consistency among the working groups, and provides additional high level evaluation of issues related to protocol prioritization and resource utilization.

The PRMC Executive Committee consists of the PRMC Chair, Chairs of each working group, the Director of the Clinical Trial Support Unit (CTSU), a biostatistician, the administrative coordinators of each working group, the Cancer Center’s Associate Directors for Clinical Research, and at large members who may be appointed from time to time.

The three working groups are:

- **Cell and Gene Therapy (CAGT) Working Group**, which is responsible for reviewing all DLDCC protocols that involve the infusion of whole cells or vectors designed to modify the existing genetic structure of cells in subjects; target hematopoietic stem cell transplant patients; are ancillary to cell or gene therapy studies; or require RAC review. The committee consists of medical oncologists, pediatric oncologists, transplant physicians, pathologists, pharmacy staff, regulatory coordinators, nurses, laboratory scientists, a patient advocate, and a statistician.

- **Pediatric Working Group**, which is responsible for all protocols that target patients under 21 years of age that are not reviewed by the CAGT working group. The committee consists of pediatric oncologists, transplant physicians, pharmacy staff, regulatory coordinators, nurses, a patient advocate, and a statistician.

- **Adult Working Group**, which is responsible for reviewing all protocols that target patients 21 years of age and older that are not reviewed by the CAGT working group. The committee consists of medical oncologists, pediatric oncologists, transplant physicians, surgical oncologists, radiation oncologists, pathologists, regulatory coordinators, a patient advocate and statisticians.

In the event additional expertise is necessary to conduct a thorough scientific review, an *ad hoc* reviewer may be solicited from another working group, the wider DLDCC membership or another Cancer Center.

**PRMC MEMBERSHIP**

PRMC membership comprises a broad range of both clinical and basic scientists, with expertise in adult oncology, pediatric oncology, cell and gene therapy, biostatistics, pharmacology, pathology, radiotherapy, surgical oncology, oncology nursing, and regulatory affairs. Initial appointments to the PRMC are for 3 years with the possibility of re-appointment. Overlap in membership of each of the working groups, standard review tools, and standard operating procedures ensure consistent review and processes between working group committees.

The PRMC Chair is appointed by the Cancer Center Director. The PRMC Chair, in consultation with the Associate Directors for Clinical Research, subsequently appoints a Chair for each of the working groups, who also serve as Executive Committee Vice Chairs. Working group members are appointed by the Chair of each working group. Figure 1 includes the PRMC organizational structure.
PRMC Protocol Review Procedures

The PRMC review process is designed to ensure the highest quality research. All interventional DLDCC clinical trials involving cancer patients or with cancer-related primary endpoints must receive scientific review and approval by the PRMC before subject accrual may begin.

Initial Protocol Review

Clinical research studies in the DLDCC are developed within the programs or departments and receive review at that level prior to submission to the PRMC.

For each protocol submitted, the PRMC reviews the following:

1. Scientific Merit
   a) Importance of the problem
   b) Novelty of the approach
   c) Potential impact of the research
   d) Study priority for DLDCC

2. Study Rationale and Design
   a) Are study objectives clearly delineated?
   b) Is there sound scientific rationale?
   c) Is design appropriate for goals?
   d) Does the plan ensure adequate accrual to meet study goals?

3. Statistical Plan
   a) Is the statistical section including study endpoints consistent with study objectives?
   b) Is sample size calculation correct?
   c) Do the statistical analysis plans adequately address the study aims?
   d) Are there adequate stopping rules for safety/toxicity assessments if appropriate?
   e) Is there an adequate plan for interim analysis of efficacy or futility if appropriate?

4. Accrual and Implementation
   a) Are accrual estimations well justified and feasible?
   b) Can the protocol be logistically implemented?

5. Data and Safety Monitoring
   a) Is there an appropriate DSM plan including type of review and frequency?

Amendment Review

The PRMC is responsible for reviewing all protocol amendments that involve a significant change in the protocol including changes in the DLDCC PI; addition of a scientific objective; change in a BCM initiated study to become multicenter or BCM becomes the coordinating center; addition or deletion of an arm of the study; addition or deletion of a therapeutic or supportive agent or major change in schedule of administration for scientific or safety reasons; major change in eligibility criteria; changes in the number of patients to be accrued to the study; suspension of accrual due to concerns of an IRB or DSMC.

Amendments for CTEP-reviewed studies (such as NCTN trials) are not reviewed by the PRMC.
ONGOING/CONTINUING REVIEW
At the time of each protocol’s annual IRB review, the PRMC Executive Committee conducts a full review of each open protocol to ensure that reasonable progress is being made; however, review may be conducted more frequently at the discretion of the Committee.

Further details about the PRMC process can be found in the PRMC Standard Operating Procedures (SOP), which are available to Investigators and PRMC members on the DLDCC website (http://www.bcm.edu/cancercenter/?PMID=8890).

PROTOCOL SPECIFIC DATA AND SAFETY MONITORING PLANS

REQUIREMENT FOR MONITORING
All clinical trials conducted at the DLDCC must have a satisfactory data and safety monitoring plan (DSMP) that is described in detail in the protocol. The DSMP is reviewed during the PRMC review to ensure that the type and frequency of data and safety monitoring for individual studies will be commensurate with the size, complexity and risks of the trial.

Acceptable DSM Plans include, but are not limited to:
- Review coordinated and managed by an external sponsor (DSMB, DSMC, Medical Monitor, etc.)
- Review by a DLDCC-coordinated, study-specific independent DSMB
- Review by the DLDCC DRC
- Review by the local study PI

DSMP REQUIRED ELEMENTS
An acceptable DSMP must include:
- Adverse event grading and attribution scale
- Plan for unanticipated problem and serious adverse event reporting
- A plan for safety review and monitoring (by whom, at what frequency, and which elements)
- Plan for annual and interim (if required) reporting of adverse events
- For multi-center trials, an adequate communication plan among sites.

A template is available to DLDCC investigators to assist them with developing a suitable DSMP for investigator-initiated trials.

DATA AND SAFETY MONITORING MECHANISM FOR PROTOCOLS
Each DLDCC protocol must have a data and safety monitoring plan that is reviewed and approved by the PRMC prior to subject enrollment. Protocol monitoring for DLDCC protocols may be accomplished by several mechanisms including: NCI Cooperative Group data and safety review committees, medical monitors or committees established by a pharmaceutical or
academic sponsor, DLDCC standing Data Review Committee (DRC) when a full independent DSMB is not required, or by individual, protocol-specific DSMB when a full, independent DSMB is required for a DLDCC study. Data Review Committee and Data Safety Monitoring Boards for DLDCC investigator-initiated protocols report to the CRLC.

Local SAEs are reported to the BCM IRB according to IRB guidelines; the PSO reviews all local SAEs that are reported to the IRB, regardless of study sponsor or DSMP. These reports will be reviewed by the CRLC on a monthly basis.

**EXTERNAL DATA AND SAFETY MONITORING**

When a protocol has an outside sponsor, including NCI NCTN, a pharmaceutical company or another academic institution, the sponsor and/or coordinating center is responsible for creating the study’s DSMP. The PRMC reviews that plan for adequacy as part of the PRMC approval process. The PSO reviews all DSM reports from the study sponsor to ensure compliance with the protocol’s DSMP. Local AEs/SAEs are reported to the study sponsor according to the protocol.

All NCTN cooperative groups in which the DLDCC participates have an NCI-approved data and safety monitoring mechanism. Current copies of each cooperative group’s DSM charter are maintained centrally by the PSO, and updated as revised charters become available.

**INTERNAL DATA AND SAFETY MONITORING**

For studies that are initiated by a DLDCC investigator and DLDCC is the responsible coordinating center, data and safety monitoring will be coordinated by the DLDCC. DSM may be conducted by the DLDCC Data Review Committee, or a Data Safety Monitoring Board, depending on the risk and complexity of the trial. Low risk studies may be monitored solely by the study PI, as appropriate. As with all studies, the PRMC will review and approve each study’s data and safety monitoring plan for adequacy.

**DLDCC Data Review Committee**

The DLDCC has an established Data Review Committee (DRC) that performs data and safety monitoring activities for all DLDCC investigator-initiated trials that do not require full independent DSMBs. The DRC has a broad membership which covers a range of expertise and specialties. The DRC convenes at least once per month.

The DRC Chair is appointed by the DLDCC Director, in consultation with the Associate Directors for Clinical Research. The DRC Chair(s) appoint(s) members to the committee. Membership duration is two year terms, with unlimited number of terms. In the event additional expertise is necessary to conduct a thorough data and safety review for a particular study, membership may be augmented with an ad hoc reviewer selected from the wider DLDCC membership or another Cancer Center.

**DRC Data Review**

The DLDCC Data Review Committee provides oversight of study progress. Information reviewed by the committee includes:

- Overall protocol accrual and expected number of patients to be treated
- Patient registrations with regard to eligibility and evaluability
- All adverse events and their relationship to the protocol therapy (e.g., by dose level, treatment arm, etc.), in order to determine if participants are being exposed to unanticipated or excessive toxicity
- All serious adverse events or unanticipated problems requiring expedited reporting as defined in the protocol
- Results of any planned interim analyses
- Response evaluations, if relevant
- Any issues with protocol conduct or compliance
- Status of participation rate in correlative biology and/or imaging studies, if applicable
- Study amendments or modifications that may have occurred since last review
- Date of next planned review

**DRC Review Frequency**

The frequency of data review by the DRC is determined by the PRMC at the time of initial review and will be based on the level of risk to the study subjects. The risk level is defined by the type of trial in which participants are enrolled.

- **High risk studies** include DLDCC investigator-initiated trials, and all IND trials where a DLDCC investigator is the sponsor.
- **Standard risk studies** include all other DLDCC interventional investigator-initiated trials utilizing FDA-approved, commercially available compounds.

The study is assigned a monitoring milestone or a review date, depending on the level of risk determined as above and projected accrual rate. The milestone may also be based upon a specific accrual target.

High risk studies may also be assigned a first-enrollment audit to be conducted by the QA program.

The minimum level of monitoring required for investigator-initiated trials is a full DRC review on an annual basis. More frequent review may be required as determined by the PRMC based on risk of the intervention. Also, additional monitoring may be required based on the findings of the initial review.

For investigator-initiated non-IND studies, DRC review should continue until all subjects have completed study-related interventions, unless determined otherwise by the DRC. For investigator-initiated studies under an internal IND, DRC review should continue until the IND is closed, or until the DRC determines that review is no longer needed.

If the DRC finds a study report to be unsatisfactory, the report may be returned for revision while the study continues or the study may be paused until all questions are answered to the committee’s satisfaction. The DRC may require more frequent reports from the study team or request an audit of the study. The DRC may also recommend protocol closure if there are safety concerns or if a study fails to accrue in a manner which will allow the scientific question to be addressed.

Cooperative group and industry sponsored trials are not reviewed by the DLDCC DRC because they have independent data monitoring mechanisms in place.
DRC Meeting Review Process
Review of studies by the DRC includes two parts. The first part is an open session in which members of the study team may be present to answer questions posed by the DRC. Following the open session, there is a closed session in which members of the study team, as well as any DRC member who has an indirect or direct relationship with the study under review, are recused from the discussion in order to eliminate any conflict of interest. During the closed discussion, the DRC discusses interim outcome results, decides what actions are to be taken, and votes.

The DRC may recommend continuation, modification, or halting of a trial (either temporarily or permanently). If the DRC decides that the study should be halted, the PI can appeal the decision, as described below. If a study is halted, the PI must notify the IRB, FDA, NCI, and/or any other required regulatory agencies.

At a minimum, each study should be reviewed by a DRC biostatistician, a DRC medical reviewer, and a DRC Chair.

DRC Meeting Reports
A statement that the protocol has been reviewed by the DRC will be submitted to the PI for submission to the IRB and Federal funding/oversight agencies (as applicable). If study changes are recommended by the DRC, it is the responsibility of the PI to implement these changes (through the IRB and other appropriate regulatory agencies) and notify the DRC after the changes have been made. Failure to implement modifications recommended by the DRC prior to timeframe required by the DRC can result in the study being halted by the DLDCC Director. The DLDCC CRLC will be informed of DRC reviews and determinations.

DRC Appeal Process
In the unlikely situation that the trial PI does not concur with a DRC recommendation for modifying or halting a study, he/she may formally appeal the DRC’s decision. The PI must inform the DRC in writing of the reason(s) for disagreement and any alternate proposal. The DRC will meet to review the appeal. The DRC may vote to accept or reject the appeal. If the appeal is rejected, the PI may request a meeting with the DRC Chair, Cancer Center Director, and/or Associate Directors of Clinical Research. If these individuals reach a mutually acceptable decision about the study that differs from the DRC recommendations, the decision must be communicated in writing by the Cancer Center Director to the DRC and will become part of the DRC files for the protocol.

DRC Confidentiality
DRC information related to the study under review, including any appeals, will be maintained as confidential and disclosed only as outlined above, unless additional disclosure is required by BCM policy or pertinent laws or regulations.

Data and Safety Monitoring Boards
Per NCI recommendations, phase III randomized studies (except low risk behavioral and nutritional trials) will require a DSMB.
Certain other studies, including randomized phase II studies with a placebo control, may also require a DSMB. In certain cases, the PRMC may also feel that a study that is not a phase III or randomized phase II trial merits a DSMB. This decision will be made based on factors such as risk of the intervention and enrollment of vulnerable subjects.

Many protocols that require a DSMB will have originated in the NCI NCTN, or will have been initiated by a pharmaceutical company. The Cancer Center will not require a locally coordinated DSMB for these protocols but will rely on the sponsor’s DSM plan, which should be included in the initial protocol submission to the PRMC. The plan will be reviewed by the PRMC. If the sponsor’s plan is deemed inadequate, the PRMC may vote not to approve the study.

**DSMB Membership**

For investigator-initiated trials that require a DSMB, a study-specific DSMB will be constituted and coordinated by the DLDCC. Each DSMB will have at least 5 members, including a statistician who is not associated with the study. The study PI will suggest external members with appropriate expertise to interpret the data and ensure patient safety. Investigators directly involved with the conceptual design, conduct or analysis of the particular trial are not eligible to serve on the DSMB. The Patient Safety Officer, with support from the Cancer Center Administrative offices, will coordinate the establishment and operational aspects of the DSMB.

**DSMB Responsibilities**

The DSMB’s responsibilities include issues related to patient safety (specifically adverse events and the risk/benefit ratio of the trial), and interim analyses and study conduct necessary to accomplish the primary protocol objectives (including patient accrual, adherence to the study design, outcome measures, and release of protocol-related primary outcome data). The DSMB is expected to explicitly recommend closure, revision or continuation each time the protocol is reviewed.

The DSMB is charged with providing oversight of study progress, and will review the same information reviewed by the DRC (see page 14). The DSMB may choose to review other aspects of the study, and those aspects will be outlined in the DSMB’s charter.

**DSMB Charter**

Each DSMB will create its own charter, which will include the standard operating procedures such as membership composition, frequency of meetings, schedule for AE/SAE reporting, format of reports, and the type of data to be submitted and reviewed. After constitution, the DSMB will meet in person or by teleconference prior to protocol initiation. At this meeting they will elect a chair and establish standard operating procedures for inclusion in the charter. A DSMB Charter template is available to DLDCC investigators.

**DSMB Meeting Frequency**

The DSMB will determine the schedule for review of the data based on the study’s risk level, size, and complexity. The DSMB may elect to meet at regular time periods (e.g., every 6 months) or after a certain number of patients are enrolled. The DSMB must meet at least annually. For internally initiated, non-IND studies, DSM should continue
until all subjects have completed protocol procedures. For internally initiated, IND studies, DSM of open studies should continue until the IND is closed, or until the DSMB determines that review is no longer needed. At time of study closure, a final report and notice of the closure should be sent to the CRLC.

**DSMB Recommendations and Reports**
A statement that the protocol has been reviewed by the DSMB will be submitted to the PI for submission to the IRB and Federal funding/oversight agencies (as applicable). If study changes are recommended by the DSMB, it is the responsibility of the PI to implement these changes (through the IRB and other appropriate regulatory agencies) and notify the DSMB after the changes have been made. Failure to implement modifications recommended by the DSMB prior to timeframe required by the DSMB can result in the study being halted by the DLDCC Director.

The DLDCC CRLC will be informed of DRC reviews and determinations.

**DSMB Appeal Process**
In the unlikely situation that the trial PI does not concur with a DSMB determination for modifying or halting a study, he/she may formally appeal the DSMB’s decision. The PI must inform the DSMB in writing of the reason(s) for disagreement and any alternate proposal. The DSMB will meet to review the appeal. The DSMB may vote to accept or reject the appeal. If the appeal is rejected, the PI may request a meeting with the DSMB Chair, Cancer Center Director, and/or Associate Directors of Clinical Research. If these individuals reach a mutually acceptable decision about the study that differs from the DRC recommendations, the decision must be communicated in writing by the Cancer Center Director to the DSMB and will become part of the DSMB files for the protocol.

**DSMB Confidentiality**
It is expected that DSMB will adhere to the strictest criteria for maintaining confidentiality of the data and for managing conflicts of interest. Participants in the review of “masked”, unblinded or confidential data must not have a conflict of interest with or financial stake in the research outcome. BCM-affiliated members are covered under BCM confidentiality and conflict of interest policies. All DSMB members from outside BCM (voting and non-voting) will sign Confidentiality and Conflict of Interest agreements. DSMB members are required to disclose any potential conflicts of interest that may arise from their participation in Board activities. If a conflict is disclosed, the CRLC will review the conflict and determine the appropriate action to be taken, including recusal of members from voting if a conflict exists.

In general, outcome data for masked or blinded studies should not be made available to individuals outside of the DSMB until accrual has been completed and all patients have completed their treatment. At this time, the DSMB may approve the release of outcome data on a confidential basis to the trial PI.

**GUIDELINES FOR DATA AND SAFETY MONITORING IMPLEMENTATION**
General monitoring requirements for DLDCC investigator initiated trials are outlined below. All trials must have a data and safety monitoring plan commensurate with the level of risk to the participants and approved by the PRMC.
**PHASE I TRIALS**
Investigators will conduct continuous review of data and patient safety at their Phase I/Disease Group meetings where the results of each subject’s treatment are discussed. The discussion will include for each dose level: the number of subjects, significant adverse events that have occurred, requirements for dose modifications, and response assessment at protocol defined intervals. Reports will be submitted to the DRC at the frequency outlined in the protocol’s approved DSMP.

**PHASE I/II AND PHASE II TRIALS**
Data related to these trials are discussed at regularly scheduled Disease Group or Program meetings where the results of each subject’s treatment are discussed. For each arm, dose level, or stratum, the discussion will include: the number of subjects, significant adverse events as described in the protocol, dose adjustments, and response assessment at protocol defined intervals. Reports will be submitted to the DRC at the frequency outlined in the protocol’s approved DSMP.

**PHASE III TRIALS AND RANDOMIZED PHASE II STUDIES WITH A PLACEBO CONTROL**
All phase III trials and some phase II trials with a placebo control will have a DSMB constituted and functioning as described above.

**PHASE I – III BEHAVIORAL AND NUTRITIONAL TRIALS**
These trials are usually low risk, and pose no more than minimal risk to the participant. Monitoring will be commensurate with risk, and must be outlined in the protocol’s DSMP.

**TRAINING GRANT TRIALS**
Studies developed by an investigator in training who is supported on a training grant or mentored by a DLDCC investigator will be subject to the guidelines described above.

**REVIEW AND OVERSIGHT REQUIREMENTS**

**ADVERSE EVENT REPORTING**
The PI is responsible for the accurate, appropriate, and timely reporting of all necessary adverse events (AEs) to the BCM IRB, the sponsor, regulatory agencies, participating institutions, and co-investigators as outlined in the protocol.

The current BCM IRB guidelines require that investigators report to the IRB within 5 working days any event (including but not limited to on-site and off-site adverse event reports, injuries, side effects, breaches of confidentiality, deaths, or other problems) that occurs at any time during or after the research study, which in the opinion of the principal investigator meets all of the elements listed below:

- a) Suggests that the research places one or more participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized; and
- b) Is unexpected (an event is “unexpected” when its specificity and severity are not
accurately reflected in the informed consent document); and

c) Is related or possibly related to the research procedures (an event is “related to the research procedures” if in the opinion of the principal investigator it was more likely than not to be caused by the research procedures or if it is more likely than not that the event affects the rights and welfare of current participants).

For DLDCC investigator-initiated trials being conducted under an IND, adverse event reporting regulations from the Food and Drug Administration are to be followed.

http://www.fda.gov/medwatch/report/mfg.htm

For DLDCC investigator-initiated gene therapy studies, adverse event reporting regulations from the Recombinant DNA Advisory Committee (RAC) are to be followed.


For DLDCC investigator-initiated multi-center trials in which a DLDCC site is the coordinating center, the DLDCC requires all participating institutions to submit unexpected, research-related AE reports to the DLDCC PI, as well as their local IRB according to protocol and local IRB guidelines, and within the protocol specified timeframe. The DLDCC PI will be responsible for reporting the event to the BCM IRB according to IRB guidelines. The PI will also be responsible for faxing or emailing a memo outlining the AE and any resulting action to the PIs in all participating institutions according to protocol guidelines, and within the protocol specified timeframe, or within 15 days, whichever is more stringent. The DLDCC will be responsible for all data and safety monitoring for these trials.

Local SAEs are report to the BCM IRB according to IRB guidelines; the PSO reviews all local SAEs that are reported to the IRB. Reports must also be forwarded to the DRC or DSMB as required.

STUDY PROGRESS
Study progress assessments are conducted by the DLDCC PRMC at least annually, during PRMC Continuing Review.

IRB REVIEW
IRB continuing review is conducted at least annually according to IRB policies and procedures.

DATA QUALITY ASSURANCE AND PROTOCOL COMPLIANCE

All Cancer Center treatment studies conducted at BCM-affiliated institutions are subject to a formal, comprehensive source document review. The primary purpose of Quality Assurance (QA) activity is to evaluate and ensure that the conduct of clinical trials complies with all federal regulations and International Conference on Harmonization Good Clinical Practices. A secondary purpose of QA activity is to ensure that standard operating procedures (SOPs) establishing the processes used for conduct of clinical trials, and data collection and management related to clinical trials are appropriately defined, implemented, and being followed, and to improve and refine the processes established in the SOPs when necessary.

Audit priority is given to studies that are not audited by an external agency or sponsor. For studies that are conducted within Cancer Center Programs that have an existing internal auditing program, the audit responsibility may be delegated to that specific program as
determined by DLDCC Clinical Research Leadership Committee.

**AUDIT TYPES**

1. **Routine:** Routine audits of DLDCC investigator-initiated trials occur at least once every 24 months. A minimum of ten percent, but no less than 3, of randomly selected subject charts are audited. The selected subject charts undergo complete data review.

2. **First Enrollment:** Audits are conducted for newly initiated studies, with an emphasis on investigator-initiated trials and other high-risk trials. These audits are scheduled within six weeks of first subject enrollment.

3. **Investigator Requested:** Audits may be conducted at the request of the study PI, contingent upon the availability of the QA/QC program staff and the approval of the Clinical Research Leadership Committee.

4. **For Cause:** Audits may also be conducted at the discretion or suggestion of the Clinical Research Leadership Committee and the Data Review Committee.

**AUDIT PROCESS**

Approximately two weeks before the start of the audit, the QA/QC Project Manager or designee will send an audit notification email to the study PI and coordinator. The audit will begin on an agreed-upon date not to exceed 14 calendar days following the notification. The PI will supply a list of subjects enrolled on a study to the auditor. The auditor will notify the study PI and/or staff of the subjects to be audited.

The auditor must be given access to all IRB documentation for the study prior to starting the audit. For verification of study evaluations, the auditor may request that source documents be printed from the subject’s electronic medical record.

Audit forms addressing compliance in all areas under review are utilized.

**AUDIT FINDINGS**

An audit report is generated that describes trial deficiencies as Major or Minor. The QA/QC Project Manager conducts an exit interview with the PI to review the audit report. A written copy of the audit report is provided to the PI. The CRLC Committee is notified of audit activities on an ongoing basis. A formal written response is required by the PI for Routine or For Cause audits. If an audit is deemed “unacceptable” due to multiple major deficiencies, then the Clinical Research Leadership Committee with the approval of the Cancer Center Director, may suspend further accrual to the trial until the audit findings are addressed and a satisfactory corrective action plan is developed and implemented.

**AUDIT RESPONSE REVIEW**

Review of the audit report response is performed by the DLDCC Clinical Research Leadership Committee. QA/QC program staff also review and confirm that findings have been appropriately addressed. If the audit response and any corrective action plans are deemed “acceptable” then a Certificate of Completion is prepared by the QA/QC Project Manager to and sent to the PI as notification of completion of the audit.

If a PI fails to provide an audit response in a timely manner or if an audit response is
assessed as unacceptable, then CRLC with the approval of the Director may place the study on hold until the PI takes corrective action.

**NOTIFICATION OF NCI REGARDING SUSPENSION OF A FUNDED CLINICAL TRIAL**

When accrual is suspended or terminated for reasons outside the planned study design (e.g., unanticipated toxicities, inadequacies in protocol compliance or conduct resulting in suspension by the DLDCC or the IRB) or when administrative reasons require study suspension, the study PI should notify any granting agencies as outlined in the Notice of Grant Award letter. The PI is also responsible for notifying the study sponsor, regulatory agencies, Clinical Research Leadership Committee, and PSO as may be required. As the PI of the NCI CCSG award, the DLDCC Director will notify the NCI and NCI program directors of study suspensions.