DAN L DUNCAN COMPREHENSIVE CANCER CENTER AT BAYLOR COLLEGE OF MEDICINE

DATA AND SAFETY MONITORING PLAN

MARCH 2019

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Table of Contents

Guidelines for Data and Safety Monitoring Implementation

Review and Oversight Requirements

Data Quality Assurance and Protocol Compliance

ABBREVIATIONS

AE	Adverse Event
BCM	Baylor College of Medicine
CAGT	Cell and Gene Therapy
CTEP	Cancer Therapy and Evaluation Program
CTSU	Clinical Trial Support Unit
DLDCCC	Dan L Duncan Comprehensive 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
IRB	Investigational Review Board
NCI	National Cancer Institute
NCTN	NCI National Clinical Trials Network
NIH	National Institutes of Health
PI	Principal Investigator
PRMC	Protocol Review and Monitoring Committee
PSO	Patient Safety Officer
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SOPs	Standard Operating Procedures

DATA AND SAFETY MONITORING PLAN

OVERVIEW

As an NCI-designated cancer center, the Dan L. Duncan Comprehensive Cancer Center (DLDCCC) 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 DLDCCC. 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.

For purposes of this document, the DLDCCC utilizes the following NIH definitions:

> Clinical Trial: A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral health-related outcomes.
>
> Intervention: Includes both physical procedures by which information or biospecimens are gathered (e.g., venipuncture) and manipulations of the subject or subject's environment that are performed for research purposes.
>
> Reference: https://humansubjects.nih.gov/glossary

A broad spectrum of treatment clinical trials, ranging from single-center phase I clinical trials through participation in multi-site phase III studies, are conducted at the DLDCCC. 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 DLDCCC'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 DLDCCC. Particular attention is paid to monitoring investigator-initiated trials (IITs), especially those for which there is no independent external monitoring program.

The extent of safety monitoring for trials is based on an assessment of the degree of risk encountered by study participants. 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 DLDCCC clinical trials includes NCI-funded NCTN trials, investigator-initiated trials, externally peer-reviewed trials, and pharmaceutical industry-sponsored trials.

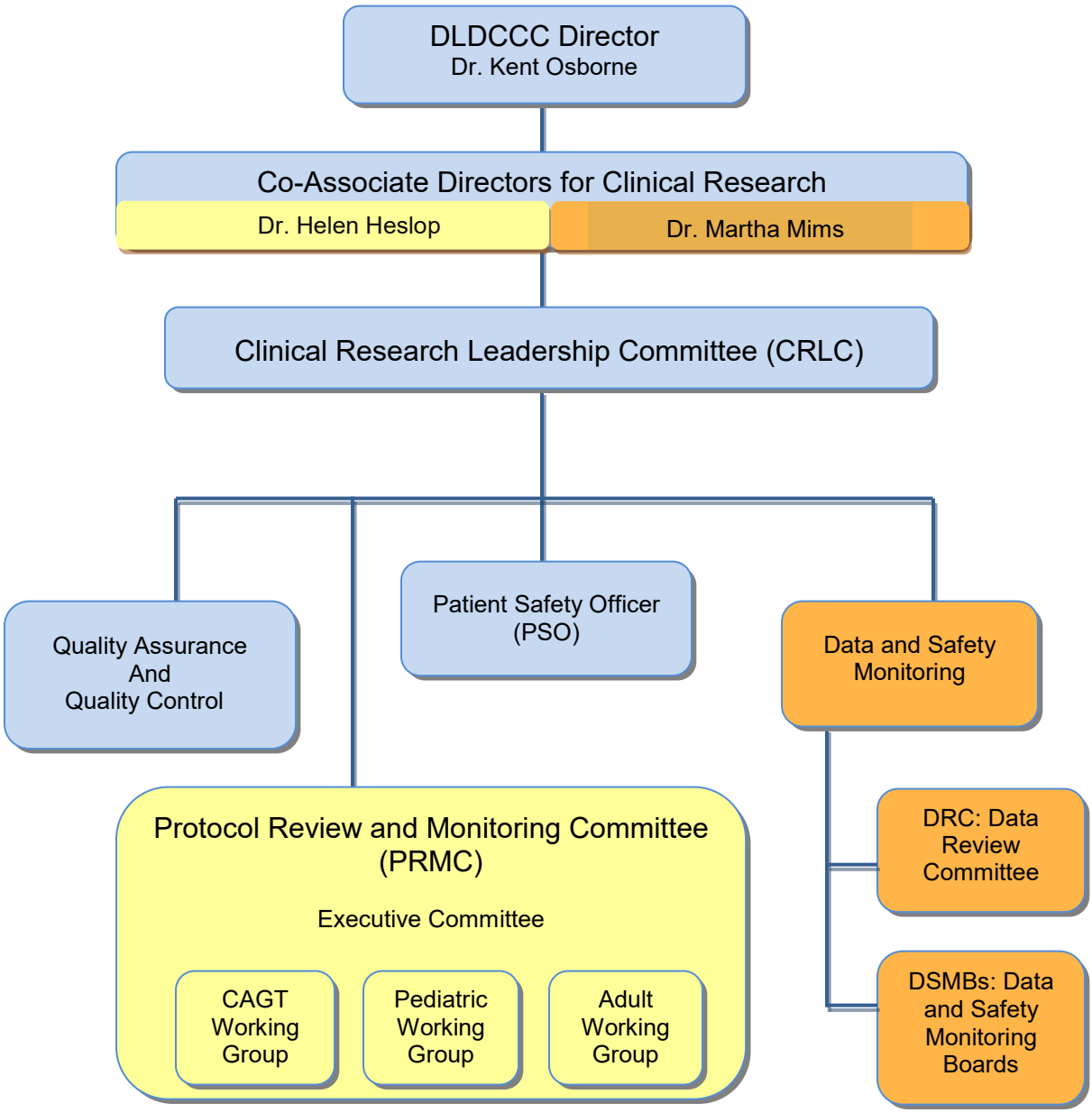
Currently, the initiation, monitoring, and termination of clinical trials conducted at DLDCCC is overseen by (1) the Protocol Review and Monitoring Committee (PRMC), (2) Data Review Committee (DRC) or Data and Safety Monitoring Board (DSMB); and (3) a Patient Safety

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 DLDCCC and ultimately to the Cancer Center Director. The oversight structure is outlined in Figure 1 below.

The DLDCCC 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
  (10-Jun-98) http://grants.nih.gov/grants/guide/notice-files/not98-084.html
  (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
  http://deainfo.nci.nih.gov/grantspolicies/datasafety.pdf
- 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
  https://ctep.cancer.gov/investigatorResources/docs/InvestigatorHandbook.pdf
- CTEP NCI Guidelines: Adverse Event Reporting Requirements
  http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/newadverse_2006.pdf
- 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
  http://www.fda.gov/downloads/Regulatoryinformation/Guidances/ucm127073.pdf

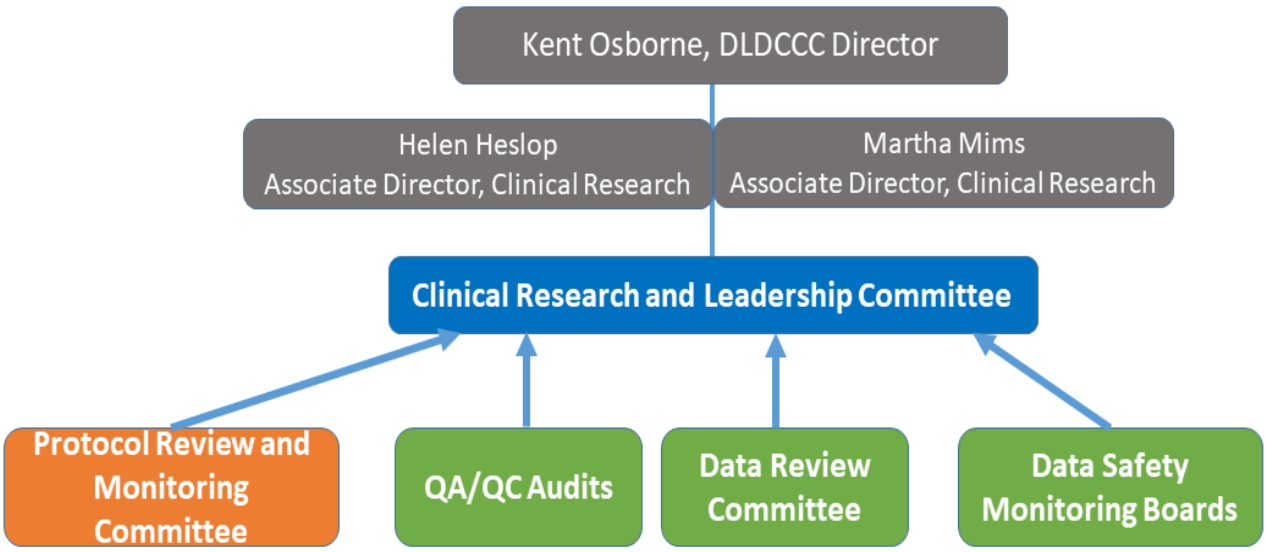
Figure 1. Structure of DLDCCC Clinical Research Oversight



The Clinical Research Leadership Committee (CRLC), composed of DLDCCC senior leadership, reviews reports from the Data Review Committee (DRC), Data and Safety Monitoring Boards (DSMBs), and QA/QC audits, which are independently submitted to this committee. This committee is comprised of the DLDCCC Director, the Associate Directors for Clinical Research, the Associate Directors of the CTSU, the Chair and Vice-Chairs of the PRMC Executive Committee, the Chair(s) of the DRC, and the Director of the Quantitative Sciences Shared Resource. The Data Review Committee and Data Safety Monitoring Boards for DLDCCC investigator-initiated protocols report to the CRLC. Membership of these committees is provided as an appendix to the DSM Plan. Reporting structure for the committees is illustrated in figure 2. The IRB is independent of the Data and Safety monitoring structure of

the DLDCCC. All activities involving human subjects must be reviewed and approved by the IRB of record prior to patient enrollment. Data Review Committee Reports and Data Safety Monitoring Reports are provided to the investigator who is responsible for providing these reports as required by the IRB.

Figure 2. Committee Reporting Structure



KEY COMPONENTS OF DATA AND SAFETY MONITORING

OVERVIEW OF DATA AND SAFETY MONITORING AT THE DLDCCC

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 DLDCCC protocol management infrastructure. Key elements and processes at the DLDCCC that contribute to data and safety monitoring are summarized in this section.

PRINCIPAL INVESTIGATOR

Every study submitted for review at the DLDCCC, 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 DLDCCC adheres to BCM's Disclosure of Outside Interests (DOI) 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. In order to track the potential conflicts of interest and the management plans, an electronic disclosure of outside interest document must be submitted by faculty staff, residents, clinical postdoctoral fellows, postdoctoral fellows and students as described in the BCM Disclosure of Outside Interests Policy. The activities outlined in the DOI disclosure must be submitted to the College as they arise and at least annually, and must be evaluated and managed to avoid actual conflicts

The President of the College appoints a Disclosure of Outside Interests Committee (DOIC), a subcommittee of the Executive Compliance Committee, which has the responsibility of administering and interpreting this policy, rendering advice about this policy and recommending changes as necessary. The DOIC and/or the President will approve any exceptions to this policy. The DOIC shall periodically report committee activities to the President, Executive Compliance Committee, and the Audit and Compliance Committee of the BCM Board of Trustees. In addition, the Research Conflict of Interest Committee (COIC) is an institutional committee formed to specifically oversee financial interests in research. It is appointed by and reports to the President and CEO through the Senior Vice President and Dean of Research. All significant financial interests as defined by the Public Health Service are reviewed by the RCOIC. If the RCOIC identifies a conflict of interest, it imposes an appropriate management plan to prevent bias in the design, conduct, or reporting of the research. Such plans may range from disclosure in presentations or publications through divestiture of the interest or recusal fro the reearch .

CONFIDENTIALITY

Information related to any study under DLDCCC 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 subject's review committee for all DLDCCC 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 DLDCCC affiliated hospitals or clinics or elsewhere, including collaborating sites.

CLINICAL TRIAL SUPPORT UNIT

The DLDCCC 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 DLDCCC 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 DLDCCC. There are comprehensive standard operating procedures (SOPs) that govern all aspects of clinical research within the DLDCCC 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 QA/QC Program within the DLDCCC.

CLINICAL RESEARCH LEADERSHIP COMMITTEE

The Clinical Research Leadership Committee (CRLC), composed of DLDCCC senior leadership, reviews reports from the Data Review Committee (DRC), Data and Safety Monitoring Boards (DSMBs), and QA/QC audits, which are independently submitted to this committee. This committee is comprised of the DLDCCC Director, the Associate Directors for Clinical Research, the Associate Directors of the CTSU, the Chair and Vice-Chairs of the PRMC Executive Committee, the Chair(s) of the DRC, and the Director of the Biostatistics Shared Resource.

PATIENT SAFETY OFFICER

The clinical research infrastructure of the DLDCCC 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 DLDCCC DRC (including maintaining member roster, coordinating meetings, sending/receiving correspondence, etc.)
- Facilitating the development of independent DLDCCC-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 DLDCCC. 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 groups conduct a complete review of each protocol according to Cancer Center Guidelines. The working group reviews and recommendations are forwarded to the Executive Committee, which 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 and Co-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 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; or are ancillary to cell or gene therapy studies.

- 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.

- 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.

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 DLDCCC 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; each working group Chair will also appoint a working group Vice Chair. 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 DLDCCC 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 DLDCCC are developed within the programs, disease working groups 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 DLDCCC
2. Study Rationale and Design
   a) Are study objectives are 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:

- change in the DLDCCC PI;
- change in or 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;
- major change in eligibility criteria;
- addition or deletion of a therapeutic or supportive agent, or major change in schedule of administration if the change is due to a change in scientific or safety design;
- change in the number of subjects to be accrued if it is due to a change, addition, or deletion of an objective, or due to the results of an interim analysis;
- change in the protocol in response to suspension of accrual due to concerns of an IRB or DSMC/DRC/DSMB.

Amendments for studies which undergo expedited review (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-to-accrual 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 DLDCCC website (https://www.bcm.edu/centers/cancer-center/research/clinical-research/protocol-review-and-monitoring-committee).

PROTOCOL SPECIFIC DATA AND SAFETY MONITORING PLANS

REQUIREMENT FOR MONITORING

All clinical trials conducted at the DLDCCC 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 an individual study is be commensurate with the size, complexity, and risks of the trial.

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 DLDCCC investigators to assist them with developing a suitable DSMP for investigator-initiated trials.

DATA AND SAFETY MONITORING MECHANISM FOR PROTOCOLS

Each DLDCCC protocol must have a data and safety monitoring plan that is reviewed and approved by the PRMC prior to subject enrollment. For each type of interventional study (including treatment, prevention, supportive care, diagnostic), the PRMC will determine if the DSM plan is adequate.

Acceptable DSM Plans are tailored to the risk of the study and may include, but are not limited to:

- Review coordinated and managed by an external sponsor (DSMB, DSMC, Medical Monitor, etc.), such as NCTN or an industry sponsor
- Review by a DLDCCC-coordinated, study-specific independent DSMB
- Review by the DLDCCC External DSMB, which is available for studies that require review by members that are external to DLDCCC
- Review by the DLDCCC DRC
- Review by the local study PI

The Data Review Committee and Data Safety Monitoring Boards for DLDCCC investigator-initiated protocols report to the CRLC.

EXTERNAL DATA AND SAFETY MONITORING

When a protocol has an external sponsor, such as 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.

All NCTN cooperative groups in which the DLDCCC 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.

Local AEs/SAEs are reported to the study sponsor according to the protocol.

INTERNAL DATA AND SAFETY MONITORING

For studies that are initiated by a DLDCCC investigator and DLDCCC is the responsible coordinating center, data and safety monitoring will be coordinated by the DLDCCC. DSM may be conducted by the DLDCCC 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.

For studies under DLDCCC DRC or DSMB review:

- Any local adverse event that is unexpected, serious, and possibly/probably/definitely

related to the study should be reported to the review committee (DRC or DSMB) within 15 calendar days of knowledge of event.
- For studies in which the IND is held by a DLDCCC investigator, any event that is reported to the FDA should also be reported to the DRC/DSMB at the same time.

DLDCCC Data Review Committee

The DLDCCC has an established Data Review Committee (DRC) that performs data and safety monitoring activities for all DLDCCC investigator-initiated clinical 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 DLDCCC Director, in consultation with the Associate Directors for Clinical Research. The DRC Chair(s) appoint(s) members to the committee, and the CRLC is informed of membership changes. 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 DLDCCC membership or another Cancer Center.

DRC Data Review

The DLDCCC 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 DLDCCC investigator-initiated IND trials.
- Standard risk studies include all other DLDCCC 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 DRC review on an annual basis. More frequent review may be required based on risk of the intervention. Also, additional monitoring may be required based on the findings of the initial review.

DRC review should continue until all subjects have completed study-related interventions, unless determined otherwise by the DRC.

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.

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.

Input from a DRC biostatistician, a DRC medical reviewer, and a DRC Chair is required for review of each study.

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, it is the responsibility of the PI to notify the IRB, FDA, NCI, and/or any other required regulatory agencies.

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 any funding or 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 DLDCCC Director.

The DLDCCC 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 clinical trials require a DSMB. (https://deainfo.nci.nih.gov/grantspolicies/datasafety.pdf)

Certain other studies, including randomized phase II studies with a placebo control, may also require a DSMB. In certain cases, the PRMC may determine 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.

For clinical trials that require a DSMB, there are two options:

1. A study-specific DSMB may be constituted, or
2. The standing DLDCCC External DSMB may review the study; the External DSMB is comprised entirely of members external to the DLDCCC.

The DLDCCC Patient Safety Officer will coordinate DSMB meetings and correspondence.

The following guidelines apply to DSMBs:

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 DLDCCC investigators.

DSMB Membership
Each DSMB will have at least 5 members, including a statistician who is not associated with the study.

- For study-specific DSMBs, 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.
- For the standing DLDCCC External DSMB, membership will be selected by DLDCCC Clinical Research Leadership; no member may have a current affiliation with the DLDCCC or BCM.

The Patient Safety Officer is a non-voting member and will coordinate the establishment and operational aspects of the DSMB.

DSMB Responsibilities
DSMB 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.

Each DSMB is charged with providing oversight of study progress and will review the same information reviewed by the DRC, as discussed above. The DSMB may choose to review other aspects of the study, and those aspects will be outlined in the DSMB charter.

DSMB Meeting Frequency
Each 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 conduct a review at regular time periods (e.g., every 6 months) or after a certain number of patients are enrolled. The DSMB must review the study at least annually. For internally initiated, non-IND studies, DSM should continue until all subjects have completed protocol interventions and procedures. For internally initiated, IND studies, DSM of 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 DLDCCC Director.

The DLDCCC CRLC will be informed of DSMB 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 DSMB 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 DLDCCC 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 or intervention 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.

In particular, the study PI must notify the DRC when a study transitions from Phase I to Phase II and must notify the DRC if additional cohorts are opened or added.

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.

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 IRB of record, the sponsor, regulatory agencies, participating institutions, and co-investigators as outlined in the protocol.

Per current BCM IRB guidelines, principal investigators must 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 here:

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/unanticipated (in terms of nature, severity, or frequency); and
c) Is related or possibly related to the participation in 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 DLDCCC 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 studies under DLDCCC DRC or DSMB review:

- Any adverse event that is unexpected, serious, and possibly/probably/definitely related to the study should be reported to the review committee (DRC or DSMB)

within 15 calendar days of knowledge of event.
- For studies in which the IND is held by a DLDCCC investigator, any event that is reported to the FDA should also be reported to the DRC/DSMB at the same time.

Adverse events that are reported should be sent the DLDCCC Patient Safety Officer (PSO) by the PI and study team. The PSO will review and distribute the report to the DRC/DSMB Chairs and members and send any correspondence back to the PI.

For DLDCCC investigator-initiated multi-center trials in which a DLDCCC site is the coordinating center, each participating institution must submit AEs to the DLDCCC PI per the protocol requirements, as well as to their local IRB according to protocol and local IRB guidelines. The DLDCCC PI will be responsible for reporting the event to the IRB of record according to IRB guidelines, and for reporting the event to the DRC/DSMB as stated above. The PI will also be responsible for distributing 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 DLDCCC will be responsible for all data and safety monitoring for these trials.

STUDY PROGRESS

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

IRB REVIEW

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

QUALITY ASSURANCE AND PROTOCOL COMPLIANCE

All Cancer Center clinical trials 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 DLDCCC Clinical Research Leadership Committee.

AUDIT TYPES

1. **Routine:** Routine audits of DLDCCC investigator-initiated trials occur at least once every 24 months. A minimum of 10%, 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. First enrollment audits may also be conducted on the first enrollment by a newly hired research coordinator, or for the first enrollment at a clinic site.

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.

5. Regulatory Audit: The regulatory files of newly activated trials may be audited, including a review of the IRB-approved consent forms.

6. Investigational Pharmacy Audits: The investigational pharmacies of all BCM-affiliates that conduct cancer-related treatment studies are subject to audit by the DLDCCC QA/QC program.

COMPONENTS OF AN AUDIT

Each protocol audit will have three major areas of review:

1. Regulatory documents
2. Subject records
3. Pharmacy records

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 study team. The audit will begin on an agreed-upon date within 14 calendar days following the notification. The auditor will review the list of enrolled subjects through OnCore The auditor will notify the study PI, Treating Investigator(s), and study team 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 findings in the audit report. A written copy of the audit report is provided to the PI. The CRLC is notified of audit activities on an ongoing basis. A formal written response is required for Major Findings, by the PI for Routine or For Cause audits. If an audit is deemed "unacceptable" due to multiple major deficiencies, then the CRLC, 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 PI's audit response is performed by the DLDCCC 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.

SUSPENSION OF A NCI-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 DRC/DSMB 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.