Medical College of Wisconsin Cancer Center

Data and Safety Monitoring Plan

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List of Abbreviations

ADCR	Associate Director for Clinical Research
AE	Adverse Event
AESI	Adverse Event of Special Interest
CITI	Collaborative Institutional Training Initiative
CTO	Clinical Trials Office
CREC	Clinical Research Executive Committee
CRF	Case Report Form
DLT	Dose-limiting Toxicity
DSM	Data and safety monitoring
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
E/QA	Education/Quality Assurance
FDA	U.S. Food and Drug Administration
FC	Feasibility Committee
HRPP	Human Research Protection Program
iDOT	Integrated Disease-Oriented Team
IIT	Investigator-initiated trial
IND	Investigational New Drug
IRB	Institutional Review Board
MCW	Medical College of Wisconsin
MCWCC	Medical College of Wisconsin Cancer Center
NCI	National Cancer Institute
NCTN	National Clinical Trials Network
NIH	National Institutes of Health
PFC	Pediatric Feasibility Committee
PI	Principal investigator
PRMS	Protocol Review and Monitoring System
SAE	Serious Adverse Event
SRC	Scientific Review Committee
QA	Quality assurance
QI	Quality improvement

1.0 Introduction

The Medical College of Wisconsin Cancer Center (MCWCC) places the highest priority on ensuring the safety of individuals participating in clinical trials. MCWCC manages a diverse research portfolio comprising Medical College of Wisconsin (MCW) investigator-initiated trials (IITs, local, and multicenter), industry-initiated trials, National Cancer Trials Network (NCTN) trials, and other external institutional or consortium trials spanning all study phases. MCWCC developed this Data and Safety Monitoring Plan (DSMP) in accordance with the National Institutes of Health (NIH) guidelines (see references in Section 11.0) to ensure clinical trial participant safety, validity and integrity of research data, and protocol compliance.

This institutional DSMP describes MCWCC's policies and procedures for monitoring clinical trials based on their sponsor type and the degree of risk posed to participants. Individual protocols must have study-specific DSMPs consistent with the guidance in this institutional DSMP.

MCWCC's DSMP applies to all interventional, cancer-related, prospective, hypothesis-driven human subjects research conducted at our main hospital partners and their associated outpatient clinics: Froedtert Hospital, Froedtert Health network hospitals, and Children's Wisconsin. The DSMP also applies to cancer-related trials conducted by MCW faculty and staff in communities within MCWCC's Catchment Area.

1.1 Definition of a Clinical Trial

A clinical trial is operationally defined by the National Cancer Institute (NCI) Data and Safety Monitoring Guidelines as the following:

- A prospective study involving human subjects designed to answer specific questions about the effects or impact of particular biomedical or behavioral interventions; these may include drugs, treatments, devices, or behavioral or nutritional strategies. Participants in these trials may be patients with cancer or people without a diagnosis of cancer but at risk for it.
- In the area of molecular or imaging diagnostics, we consider a study to be a clinical trial if it uses the information from the diagnostic test in a manner that somehow affects medical decision-making for the study subject. In this way the information from the diagnostic may have an impact on some aspect of outcome, and assessment of this impact may be a key goal of the trial. By contrast, studies that do not use information from the diagnostic test in any manner that can affect the outcome of study subjects but whose objective is only the gathering of data on the characteristics of a new diagnostic approach are not clinical trials and are not covered by this DSMP, unless performing the diagnostic test itself imposes some risk on study subjects.
- Observational studies and those that do not test interventions are minimal risk and are not considered to be clinical trials for the purposes of this DSMP.

2.0 Administration and Oversight of MCWCC Clinical Trials

The responsibility for data and safety monitoring of MCWCC clinical trials ultimately resides with the Cancer Center Director. The Director is assisted in this by the MCWCC Deputy Director and the Associate Director for Clinical Research (ADCR), both of whom oversee the committees and staff responsible for activating and monitoring clinical trials (**Figure 1**). The Deputy Director has the authority to suspend or terminate enrollment and/or treatment of patients on any MCWCC clinical trial over concerns about subject safety or scientific integrity.

Research oversight is performed by several committees that play distinct but complementary roles in overseeing all aspects of clinical research conducted at the MCWCC (Appendix A). The Protocol Review and Monitoring System (PRMS) is made up of the integrated Disease-Oriented Teams (iDOTs), the Feasibility Committee (FC), and the Scientific Review Committee (SRC), which review trials for patient population fit, feasibility, and scientific merit. The Data and Safety Monitoring Committee (DSMC) reviews the safety and data integrity of MCW IITs. These committees operate independently but communicate with each other. The SRC and DSMC report to the Deputy Director, while the iDOTs report to both the ADCR and the AD of Oncology Operations. Lastly, the Clinical Research Executive Committee (CREC), chaired by the ADCR, provides

oversight and policy direction for the iDOT, FC, SRC, and DSMC committees. External to the MCWCC, trials are reviewed by Institutional Review Boards (IRBs), which also evaluate patient safety. Committee responsibilities are summarized below, but additional details can be found in the iDOT, FC, SRC, DSMC, and CREC charters.

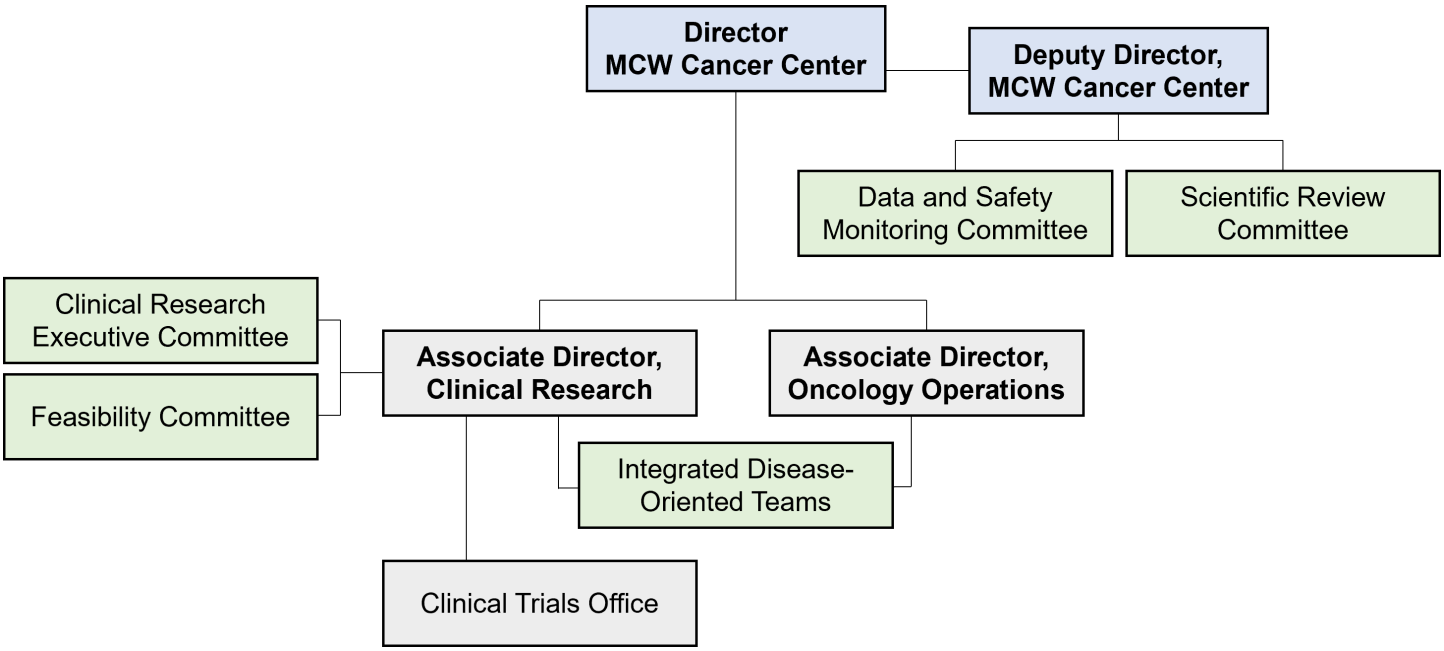


Figure 1. MCWCC clinical research organizational structure.

2.1 Integrated Disease-Oriented Teams

The iDOTs are disease- or discipline-specific committees made up of physicians encompassing all relevant treatment modalities, basic scientists, pharmacists, nurses, other allied health professionals, and Clinical Trials Office (CTO) staff, with responsibilities that include trial review and management, cancer care delivery and fostering translational research. The iDOTs are the first stage of PRMS review and are charged with maintaining comprehensive clinical trial portfolios for their patient populations. Each iDOT identifies new trials that are of clinical and scientific interest, that complement the existing trial portfolio, and that are a good fit for the iDOT's patient population. At their monthly meetings, iDOTs discuss the scientific merits and feasibility of new trials to either reject them or approve them to move forward in the approval and activation process. iDOTs also monitor their actively accruing trials, discuss trials that are struggling with low accrual or safety/logistical issues, and devise corrective action plans.

2.2 Feasibility Committees

After iDOT approval but prior to SRC submission, adult trials are reviewed by the MCWCC Feasibility Committee (FC), and pediatric trials are reviewed by the MCWCC Pediatric FC (PFC) to identify logistical, budgetary, or staffing issues that might impede implementation and completion of trials and ensure that adequate resources are available. The FC and PFC review the iDOT's projected accrual goal and the presence and management of competing trials. The FC is chaired by the ADCR; other members include the MCWCC CTO Medical Director and Assistant Medical Director, additional oncologists representing diverse diseases, and CTO administrative, operational, and business managers. The PFC consists of the PFC Chair (a senior pediatric oncologist, appointed by the Deputy Director), the pediatric hematology/oncology Section Chief, the MCWCC Pediatric Assistant CTO Medical Director, additional oncologists, and CTO administrative staff. The FC and PFC may query iDOTs for more information and may delay or decline submission to the SRC if substantive concerns are identified.

2.3 Scientific Review Committee

As the second stage of PRMS review, the MCWCC SRC plays a vital role in protocol review and monitoring to ensure that clinical trials are scientifically sound and that approved trials make acceptable progress toward their accrual goals and continue to be scientifically relevant. The SRC reviews all cancer-related studies, including industry-sponsored, external institutional, cooperative group, and investigator-initiated, though some studies are given administrative review only (e.g., NCTN studies). The specific functions of the SRC include the following:

- Conducting thorough scientific reviews of cancer-related research involving human subjects using a standardized format based on specific, pre-determined review criteria
- Monitoring active studies to ensure ongoing scientific relevance and value; reviewing amendments
- Monitoring active studies for adequate accrual progress based on pre-specified minimum annual accrual thresholds
- Monitoring accrual of underserved populations

SRC membership comprises representatives from each of the following: pediatric hematology/oncology, adult hematology/oncology, gynecologic oncology, radiation oncology, surgical oncology, biostatistics, and an external community representative. Members are appointed by the Deputy Director based on disciplinary expertise, as well as expertise in the design, conduct and analysis of clinical trials. The SRC communicates with the iDOTs via decision letters following new study, amendment, and accrual monitoring reviews.

The SRC reviews protocol-specific DSMPs as part of its initial review of each new trial. The SRC ensures that each trial includes an appropriately detailed plan tailored to the protocol's level of risk. No interventional study receives SRC approval without a risk appropriate DSMP. For interventional IITs, the SRC assigns a preliminary risk level and corresponding data and safety monitoring frequency, which the DSMC later confirms at its initial review.

2.4 Data and Safety Monitoring Committee

The MCWCC Data and Safety Monitoring Committee (DSMC) reviews trials for subject safety and data quality. Unlike the other committees, the DSMC focuses solely on MCWCC interventional IITs. The DSMC performs initial reviews of new protocols to confirm the risk level and required frequency of review, data reporting plan, and stopping rule language. Active studies are monitored for compliance, data integrity, safety, and progress toward endpoints on a frequency commensurate with their level of risk. If the DSMC has a concern regarding subject safety or data quality, it may suspend the trial or request changes to the protocol that must then be reviewed and approved by the SRC and IRB. For more details about the DSMC, please see the DSMC Charter (Appendix B).

2.5 Clinical Research Executive Committee

Oversight of the MCWCC clinical trial enterprise is provided by the MCWCC CREC, which meets quarterly. The committee oversees and directs clinical research at the MCWCC and its affiliates. CREC establishes priorities for the CTO, reviews general accrual and resource allocation issues, facilitates integration of research into the multidisciplinary clinics, and sets policy for the iDOTs, FC, SRC, and DSMC. The committee reviews minority recruitment efforts and assists in the development of strategies to enhance patient accrual. CREC is chaired by the ADCR, and participants include the MCWCC Director and Deputy Director, relevant Associate and Assistant Directors, CTO leadership, the SRC and DSMC chairs, and representative iDOT chairs. CREC reviews and approves changes to the institutional DSMP and the iDOT, FC, SRC and DSMC charters. This committee provides a forum for senior leadership to identify issues, trends, and opportunities for improving the cancer clinical research enterprise.

2.6 Institutional Review Board

In addition to the above MCWCC-specific entities, all research involving human subjects at MCWCC is independently reviewed by the MCW IRB or by a designated central IRB to which the local IRB has deferred. Prior to IRB review, studies must be reviewed and approved by applicable ancillary safety committees at the institution level: Magnetic Resonance Imaging Safety Committee, Radiation Safety Committee, and Institutional Biosafety Committee. Studies must receive IRB approval before they can open for enrollment.

The IRB review process is complementary to and independent of the MCWCC PRMS and DSMC. IRB review focuses on the ethical and regulatory requirements for the conduct of research involving human subjects, paying particular attention to the rights and welfare of subjects, while the SRC focuses on scientific quality and progress and the DSMC focuses on subject safety and data integrity for IITs as outlined above. IRB review includes evaluation of the informed consent form, the proposed process for recruiting subjects, and details of study-specific data and safety monitoring plans.

The IRB provides ongoing oversight of active studies. All amendments must be reviewed and approved by the IRB before implementation. Some events require immediate (within five calendar days) reporting to the IRB: unanticipated problems related to study participation, significant deviations, and non-compliance, serious adverse events (SAEs) that are unexpected and related to study intervention, and external safety or audit reports that describe new risks. The IRB also performs continuing reviews at frequencies based on level of risk. These reviews include cumulative summaries of reportable events, accrual/withdrawal rates, DSMC review letters, and changes to the risk assessment.

2.7 Clinical Trials Office

CTO staff provide centralized clinical, regulatory, budget, and administrative support to investigators and the above MCWCC committees. Specific functions include the following:

- Disease team research managers oversee their iDOT's protocols through all stages of a protocol's life cycle (pre-activation through study closure).
- Clinical and regulatory coordinators assist investigators with enrolling subjects onto clinical trials, managing subjects on trial, collecting and entering data, and reporting events to oversight bodies, including the sponsor, DSMC, IRB, and the Food and Drug Administration (FDA). Coordinators participate in quality assurance reviews and respond to findings.
- CTO staff support the operations of all MCWCC clinical research committees (iDOTs, FC, SRC, DSMC, CREC), organizing meetings, managing review materials, recording minutes, and maintaining records of committee decisions. Staff facilitate communication between committees and between the MCWCC and the IRB.
- Education/Quality Assurance (E/QA) staff onboard new staff, providing general oncology and research orientation, as well as role-specific education. E/QA staff monitor new staff and provide continuing education for all staff. All CTO staff are required to complete human subjects protection training through the Collaborative Institutional Training Initiative (CITI) program.

3.0 Investigator Responsibilities

The principal investigator (PI) is ultimately responsible for every aspect of the design, conduct, and final analysis of a trial. The PI ensures that the trial is conducted per the protocol and in compliance with federal, state, and institutional regulations and requirements. The PI may delegate authority to perform certain tasks to appropriate study team members, but the PI retains the responsibility for each of the tasks. The PI must ensure the following requirements are met:

- All clinical trial protocols must include a risk-based DSMP describing the procedures that will be utilized to ensure data integrity, protocol adherence, and safety monitoring.
- Studies must have a structured adverse event (AE) determination, monitoring, and reporting system. The protocol must describe how to document and report AEs to the appropriate oversight authorities

(e.g., IRB, DSMC, FDA, sponsor) per their requirements. For multisite studies, the protocol should describe procedures by which the overall PI will collect AEs from participating sites and keep participating sites informed of unanticipated AEs and any problems identified by the DSMC or IRB.

- The PI must maintain ongoing oversight of all trial aspects, including the status of active subjects, AEs and their attributions, adherence to the protocol, and data integrity. The PI is responsible for ongoing quality oversight of their study to ensure protocol compliance, proper regulatory and data documentation, data accuracy, and notification of oversight authorities of reportable events.
- All blinded studies should describe a randomization scheme and specific criteria and procedures for unblinding. The protocol should also designate individuals with access to unblinded data. The PI is responsible for establishing an independent Data and Safety Monitoring Board (DSMB) when one is called for (see Appendix C).
- The PI must submit regular reports to the DSMC and IRB per their guidelines. Concerns raised by any clinical research oversight body (FC, SRC, DSMC, CREC, IRB, or FDA) must be addressed appropriately and in a timely manner, and the PI must adhere to their decisions. The PI must inform the DSMC of any actions taken by the IRB as a result of its review. The PI is responsible for submitting the DSMC's routine decision letters to the IRB at the time of continuing review; however, the DSMC will notify the IRB and SRC directly when it recommends that an IIT should be suspended or terminated (see DSMC Charter in Appendix B).
- All changes to protocols must be approved by the IRB before trial activities are altered. Amendments to local investigator-initiated and externally sponsored trials (except cooperative group trials) must also be reviewed and approved by the SRC. It the SRC deems that the amendment involves a change in risk level, it refers the amendment to the DSMC for review prior to submission to the IRB.
- In accordance with federal policy, the PI is responsible for clinicaltrials.gov registration and reporting.
- Investigators must adhere to the IRB's requirements for human subjects research training.

It is recommended that investigators be aware of NIH policy "Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials" (NIH Guide for Grants and Contracts, June 11, 1999), "NIH Policy on Data and Safety Monitoring" (NIH Guide for Grants and Contracts, June 10, 1998), "Further Guidance on Data and Safety Monitoring for Phase I and Phase II Trials" (NIH Guide for Grants and Contracts, June 5, 2000), and "Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by the NCI" (NCI, September 2014).

4.0 Oversight of Externally Sponsored Trials

All clinical trials (as operationally defined above in Section 1.1) require data and safety monitoring. The extent of the monitoring varies by the degree of risk encountered by study participants, the study sponsor, the type of agent or agents involved, the phase of the clinical trial, and the complexity of the study. MCWCC's DSMP is tailored to 1) ensure monitoring of all clinical trials, 2) meet the reporting requirements of individual trial sponsors, and 3) eliminate redundant monitoring and reporting.

4.1 Network Trials

Trials conducted under the sponsorship of NCTN and the Blood & Marrow Transplant Clinical Trials Network have well-defined DSMPs, functional DSMBs, and auditing processes to provide appropriate safety oversight and central access to study events from all participating sites to identify trends. Thus, local toxicities, deviations, etc., are not routinely monitored by the MCWCC DSMC. Study staff must adhere to the DSM requirements and reporting mechanisms specific to each study. While the DSMC does not routinely monitor these trials, the CTO E/QA team performs QA reviews of patients enrolled onto NCTN studies.

4.2 Industry Trials

Industry sponsors are responsible for data and safety monitoring of trials they manage or for contracting with a third party to do so. Industry protocols must have a DSMP describing AE reporting requirements and logistics. The sponsor is responsible for providing the appropriate level of oversight. Phase III studies should have a DSMB. For phase I and II studies, the sponsor should utilize at least one of the following: medical monitor, regular calls with site PIs to discuss safety events/study progress, a committee that reviews phase I cohorts and determines whether to dose escalate, safety committee, data monitoring committee, or DSMB. Locally, at initial review, the SRC and IRB ensure that an appropriate DSMP is in place before approving the study for activation at MCW. If a DSMP does not exist, it must be developed by the sponsor and approved prior to study initiation.

Locally managed IITs with full or partial financial support from pharmaceutical sponsors are required to meet the data and safety monitoring requirements of institutionally funded IITs (Section 5.0).

4.3 Other Externally Sponsored Trials

Studies sponsored by other academic centers, foundations, consortiums, and other groups will be evaluated by the SRC and IRB to ensure that an appropriate DSMP is in place that defines the coordinating center and participating site roles, as well as the process for reporting safety events and study data. Generally, it is the responsibility of the sponsor to provide oversight.

5.0 Oversight of Internally Sponsored Trials

Internally sponsored, locally coordinated, interventional IITs are overseen by the DSMC. This applies to all IITs lacking routine external monitoring, including those funded by pharmaceutical companies and NIH. For a full description of the DSMC and its review processes, please see the DSMC Charter (Appendix B). A short overview is provided here.

The DSMC plays a vital role in ensuring the safety and data integrity of interventional MCWCC IITs that otherwise receive no external monitoring. DSMC responsibilities include the following:

- Review interventional IITs to confirm or modify the SRC-assigned risk level, safety reporting language, stopping rules, and data management language;
- Perform ongoing scheduled review of open trials, reviewing DSM progress reports summarizing accrual, safety, and endpoint data, and study conduct;
- Approve progression to the next dose level in dose-escalation trials and transition from dose escalation to dose expansion;
- Recommend changes to the study based on updated toxicity information;
- Review internal quality assurance monitoring findings and corrective action plans;
- Make recommendations to the PI and relevant oversight committees concerning the continuation, modification, suspension, or termination of clinical trials based on observed safety, efficacy, or QA outcomes.

5.1 Risk-based Monitoring

The frequency and extent of data and safety monitoring are risk-based. New trials are assigned an initial risk level by the SRC during its review based on the guidelines in **Table 1**. The risk level determines the approximate frequency of the DSMC's scheduled reviews (study progress reviews of cumulative toxicity data, outcome data, accrual, etc.), as well as the frequency and breadth of quality assurance monitoring. The extent of monitoring varies depending on factors such as trial phase, trial complexity, type of agent(s) involved, expected toxicity profile, and whether an Investigational New Drug (IND) application is held locally. At its discretion, the DSMC may choose to alter the overall risk level or the frequency of specific reviews either at

initial review or later while the trial is active based on factors such as accrual rate, new safety or efficacy information, or compliance issues.

Table 1. Data and Safety Monitoring by Risk Level (timeline starts at time first patient is consented)

Risk Level	Trial Description	DSMC Scheduled Review Frequency	QA Monitoring Frequency	QA Monitoring Content
Low	Non-treatment trials (e.g., behavioral or nutritional interventions)	Annual	Annual	10% subject files; 1 comprehensive review*; regulatory; pharmacy
Intermediate	Phase II treatment trials, no local IND	6 months	Annual	20% subject files; 1 comprehensive review*; regulatory; pharmacy
High	Phase I trials, local IND	6 months	6 months	30% subject files; 1 comprehensive review*; regulatory; pharmacy
Special Status	Cell/gene therapy, first-in-human	1-3 months	3 months	30% subject files; 1 comprehensive review*; regulatory; pharmacy

*If QA reviewer believes warranted, additional comprehensive reviews may be conducted.

5.2 Trials Requiring DSMBs

A subset of trials require the establishment of an independent DSMB that reports to the MCWCC DSMC. Independent DSMBs are required for randomized phase III interventional trials. Large behavioral or nutritional trials posing little risk to participants do not need DSMBs. Other, earlier phase treatment trials may require the establishment of a DSMB based on the number of subjects to be enrolled, level of patient risk, use of gene therapy, conduct in a multi-institutional setting, or at the investigator's request. The need for a DSMB will be at the discretion of the DSMC.

If a DSMB is required, it should be described in the protocol's DSMP section and must be approved by the DSMC and the IRB. The DSMC will review the DSMB monitoring reports while the trial is active. See Appendix C for more information regarding DSMB creation.

5.3 Noninterventional Studies

As noted earlier, noninterventional studies are not clinical trials. These studies are considered minimal risk and are not routinely reviewed by the DSMC. The protocols should still have a brief DSMP that describes how study data will be collected, managed, and securely stored for subject privacy. The PI is responsible for ensuring the study is conducted safely and compliantly, with reportable events submitted to the IRB per institutional guidelines, and for ensuring data accuracy and integrity.

6.0 Multisite Management

The MCWCC DSMC serves as the DSMC of record for multisite trials where MCW is the coordinating center; DSM reports must summarize data from all participating sites. All subjects enrolled at external sites must be registered in OnCore so that the DSMC can view subject status information. Reportable AEs, SAEs, and deviations from subjects at all participating sites must be communicated to the DSMC for review, and the protocol should clearly describe the process by which participating sites will report events to the coordinating center. Participating sites are also responsible for submitting documents and reportable events to their local IRBs per their institutional guidelines. The MCW PI is ultimately responsible for ensuring that data from the external participating sites are reported to the DSMC. The MCW PI is also responsible for communicating DSMC determination letters, amendments, and other study updates to the participating sites.

6.1 Multisite IITs Coordinated by Cancer Center CTO

The MCWCC CTO has established procedures for the management of MCW IITs open at external participating sites. The following is an overview of the key aspects.

In coordination with the MCW PI, the Multisite Team facilitates all aspects of participating site study activity. It is responsible for notifying participating sites of amendments and safety events, ensuring sites are capturing data appropriately, and facilitating AE reporting to central review bodies.

Participating site PIs serve as co-investigators and oversee the conduct of the trial at their respective sites. They notify MCWCC of significant changes at the site (e.g., study staff changes), follow protocol requirements, and report patient safety issues to the MCW PI.

6.1.1 Site Qualification and Activation

Participating sites are evaluated for level of interest, feasibility of implementation, adequacy of resources and experience to execute protocol requirements, and potential for accrual. After the MCWCC SRC and MCW IRB grant initial approval to a protocol, onboarding of external participating sites is initiated. Study conduct must not occur at a participating site until MCWCC study staff issues a formal activation letter. This occurs after receipt of all required documents, approval of budgets/contracts, completion of required training, and IRB approval.

6.1.2 Ongoing Study Management

Study staff at each participating site must conduct the trial according to the protocol, their local institutional policies, and the policies of the applicable regulatory bodies. Questions regarding study conduct are directed to the Multisite Team and MCWCC PI. MCWCC staff will periodically update participating sites on study progress and any ongoing questions or logistical concerns.

OnCore is used to collect and manage data from participating sites. Additional software resources such as REDCap may be used as well. Study coordinators utilize OnCore to track subject data.

As the coordinating site, MCWCC is responsible for ongoing monitoring of participating sites. Routine monitoring may be performed onsite or remotely. The frequency and extent of monitoring is based on the protocol's level of risk. Quality assurance reports are shared with the study staff and the DSMC, with corrective action or additional training requested as needed.

6.1.3 AE Reporting

Please see Appendix D for AE reporting flow. When a reportable event occurs at a participating site, the local PI must determine the event's CTCAE grade, attribution, and expectedness, and whether it meets expedited or routine reporting as defined in the protocol. Routine reported events are entered into OnCore for review at the next DSMC scheduled review and reported to the IRB at the time of annual review.

Events requiring expedited reporting must also be entered into OnCore. The local PI must notify the MCWCC PI and the Multisite Team in an expedited manner. The MCWCC PI then reports events to the MCW IRB and DSMC as applicable. If the MCWCC PI determines that an SAE or other event meets the FDA definition of requiring reporting (i.e., unanticipated problem, requiring action), then the MCWCC PI will report the event to all other participating sites for reporting to their local IRBs. The external site PIs must consider their local IRB reporting policies in all cases.

7.0 Adverse Event Reporting

All clinical trial protocols should include language describing procedures and time frame for collection and reporting of AEs/SAEs. Protocols involving investigational drugs, devices, or clinical procedures must define the criteria that will be used to grade events. Investigators are responsible for identifying and reporting events (either routine or expedited) to the trial sponsor, IRB, and FDA as applicable per protocol, institutional, and federal guidelines.

AE Reporting to the DSMC. Interventional IITs must report AEs/SAEs to the DSMC per the reporting requirements approved by the DSMC in the protocol. In general, the DSMC requires AEs/SAEs to be reported per **Table 2**, though non-treatment trials usually have reduced reporting requirements (e.g., only high-grade, related events). Some events are given routine review as part of the aggregated data at the trial's next scheduled review. Events requiring expedited reporting must be sent to the DSMC within 5 calendar days of staff knowledge. While **Table 2** describes typical DSMC reporting requirements, reporting may be tightened or relaxed on an individual trial basis, depending on the nature and associated risk of the intervention. The DSMC sets the minimum reporting requirements for safety monitoring, but PIs may choose to collect additional events for study purposes (e.g., grade 1 and 2 AEs on phase 1 trials). These events are also reviewed by the DSMC. PIs or the DSMC may also choose to collect AEs of Special Interest (AESIs). In that case, the DSMC will determine whether the AESIs should be reported in a routine or expedited manner.

Table 2. Adverse Event Reporting Requirements for DSMC

Grade 1-2 (SAEs only)	Grade 3		Grade 4-5 (AEs and SAEs)
	AEs	SAEs	
Routine Review	Routine Review	Expected or Unrelated: Routine Review Unexpected and At Least Possibly Related: Expedited Review	Expedited Review*

*For trials of hematologic malignancies, Grade 4 hematological AEs may be permitted routine review rather than expedited.

AEs/SAEs are reported to the DSMC in the following ways:

- Routine review
    - AEs: Study team enters the AE into the AE case report form (CRF); AEs are pulled in aggregate for review at the study's next DSMC scheduled review.
    - SAEs: Study team fills out an OnCore SAE report (or equivalent if not using OnCore) with AE details and narrative; study team also enters associated AEs into the AE CRF; SAE will be reviewed at the study's next DSMC scheduled review.
- Expedited review (must be submitted within 5 calendar days of staff knowledge)
    - AEs: Study team enters the AE into the AE CRF; study team sends email notification to the DSMC (DSMC_MCWCC@mcw.edu) noting subject number, AE toxicity code, onset date, grade, expectedness, and attribution.
    - SAEs: Study team fills out an OnCore SAE report (or equivalent if not using OnCore) with AE details and narrative and either emails a copy to the DSMC (DSMC_MCWCC@mcw.edu) or alerts the DSMC that it is saved in OnCore; study team also enters associated AEs into the AE CRF.

8.0 Quality Assurance

Quality assurance review is critical to ensuring that trials are conducted safely and compliantly and that trial data are collected consistently and accurately for publication. Internal monitoring is performed with the following goals:

- To ensure ongoing compliance with IRB, DSMC, FDA, good clinical practice, and MCWCC guidelines and regulations;
- To ensure adherence to the protocol and data accuracy;
- To educate clinical research faculty and staff regarding policies and regulations to encourage efficiency and consistency in the conduct of clinical trials;

- To identify and prevent recurring problems through corrective action plans or changes to MCWCC operational processes.

Clinical trial QA is carried out by the CTO E/QA team under the oversight of the CTO Administrative Director. The E/QA team performs internal QA monitoring as described below, and it also coordinates external audits by sponsors and the FDA. Final reports from internal and external QA reviews are provided to the CTO Medical Director, CTO Administrative Director, and CTO Assistant Directors so that leadership can keep abreast of trends and take action to correct issues.

8.1 Externally Sponsored Trials

As noted in Section 4.0, oversight of safety and data integrity on external trials is primarily the responsibility of the sponsor. However, MCWCC performs additional monitoring as described below.

8.1.1 NCTN Trials

For non-IND trials, the NCTN groups do not perform frequent monitoring of participating sites and instead perform audits, typically every three years. The E/QA team performs monitoring to catch issues earlier and to ensure studies are audit-ready. The NCTN groups perform routine monitoring of FDA Registration trials according to the monitoring plan outlined in the protocol.

For all NCTN trials, the E/QA team reviews the first subject enrolled to each treatment arm, as well as the trial's regulatory documents. Additional reviews may be added if concerns are identified.

8.1.2 External Institutional Trials

If self-review is a condition of our site's participation in a trial sponsored by another cancer center or consortium, then the E/QA team will monitor the trial per the risk-based guidelines followed for IITs.

8.2 Internally Sponsored Trials

IITs overseen by the DSMC are routinely monitored at a frequency commensurate with their risk level, as generally described in **Table 1**. The DSMC may adjust study-specific monitoring plans at its initial review of new protocols based on trial characteristics (e.g., expected accrual rate). As a trial progresses, the DSMC may also adjust the QA review frequency as needed based on emerging data, accrual rate, or findings from previous reviews. The DSMC may initiate for-cause audits at its discretion.

Dedicated CTO QA coordinators perform QA reviews. When a trial reviewed by the DSMC opens to accrual, the QA coordinators add it to the internal monitoring rotation. The initial QA review is scheduled after the first subject is consented. Subsequent reviews occur per the protocol-specific DSMP, but generally every 3, 6, or 12 months (per **Table 1**) with the intent that completed QA reports can be reviewed by the DSMC when the trial is due for DSMC scheduled monitoring. If the QA coordinators are unable to complete all routine monitoring due in a given month, they prioritize higher-risk trials for review. Internal monitoring continues until a trial is closed to further accrual and the final subject is off treatment. If the DSMC delays scheduled review of a trial for some reason (e.g., lack of new accruals), the QA review may be delayed as well.

Each routine QA review follows the process described below. All QA reviews are logged in OnCore, noting elements such as the date of review, type of review (routine vs. for-cause), and subject cases reviewed.

8.2.1 Scheduling the Review

Two weeks before a review, the QA coordinators send a notification to the study team: PI, primary clinical research coordinator, primary regulatory specialist, IND specialist, clinical research manager, and investigational pharmacy, as applicable. The notification informs the study team of the timing of the review, as well as which cases will be reviewed. Additionally, staff request access to the study's regulatory and subject files, including access to the electronic medical record. Study teams may provide access to files virtually via Florence eBinders, Box folders, REDCap, etc. or via paper binders. QA coordinators also have access to study

information and electronic CRFs in OnCore. For trials involving investigational drug, staff review drug management through Vestigo, the pharmacy's electronic management system. Reviews are conducted in a secure fashion to assure the confidentiality of data.

8.2.2 Subject Selection

Depending on the trial's risk level (**Table 1**) and protocol-specific language, 10-30% of subject cases are reviewed (max of 5 per review). Individual subjects are selected impartially but with an effort made to include a broad representation of time points (on treatment vs. in follow-up), treating investigators, and study sites (if multisite trial). Previously reviewed subjects are avoided in favor of new subjects.

8.2.3 Content Reviewed

During monitoring, the QA coordinators review the following trial aspects (not an exhaustive list):

- Regulatory documentation
    - IRB review documentation of amendments, reportable events, continuing progress reports
    - CVs, Delegation of Authority logs
    - 1572s, IND documentation
    - Training records
    - DSMC review documentation
- Pharmacy records
    - Drug accountability and inventory
    - Storage conditions/temperature logs
    - Training documentation
- Subject cases
    - Signed consents
    - Subject eligibility confirmation, documentation of all eligibility criteria
    - Appropriate training/delegation of subject's providers
    - Adherence to the study calendar/protocol
    - Treatment administration – per calendar, confirmation of subject self-administration via drug diary or progress notes, documentation of dose modifications/holds
    - Response assessment – tumor measurement forms, imaging, biomarkers, progress notes
    - AE/SAE documentation and timeliness of reporting
    - Documentation of subject follow-up visits, telephone/written communications
    - Source data verification on case report forms
- PI Oversight – For trials utilizing FDA-regulated drugs or devices, PIs are expected to meet with their primary clinical research coordinator at least monthly to review status of enrolled subjects, deviations, AEs/SAEs, potential amendments, and any other study business. During review, the QA coordinator confirms that documentation of these meetings is being kept.

8.2.4 Final Report

After the QA staff completes the review, their findings are summarized in a draft report. The QA staff meets with the study team to go over the findings, giving the study team and reviewer the opportunity to ask

questions and resolve or clarify findings. The QA staff may also make recommendations for quality improvement, suggested protocol revisions, and education.

Following the meeting, a final report is issued to the study team. The study team must provide written responses to findings within 30 days of receipt of the report. Extensions may be granted by QA staff on rare occasions when there are significant extenuating circumstances. QA staff review study team responses and confirm whether the actions described were completed.

QA staff share the final reports (with study team responses and QA confirmation of completion) with the PI and CTO study team, DSMC, CTO Medical Director, CTO Administrative Director, CTO Assistant Director of Research Compliance, and the CTO E/QA Manager for their review and awareness. The final report is also saved in the study's regulatory binder.

8.2.5 DSMC Review

A copy of the final report with study team responses is sent to the DSMC for review at the study's next scheduled review. The CTO Administrative Director attends DSMC meetings to explain unusual findings, answer reviewers' questions about the reviews, and serve as a resource in discussions regarding proper study conduct. After review, if the CTO Administrative Director and the DSMC feel that the study team's initial responses were not satisfactory, they may request further response or corrective action from the PI. If the DSMC has serious concerns about study conduct, it may suspend the trial to further accrual until the concerns are resolved.

8.2.6 Multisite Trials

External sites participating in IITs coordinated by MCWCC are subject to QA review. The MCW study team must facilitate the QA team's remote access to participating sites' regulatory and subject files, including source data, via direct connection to the site's electronic medical record and/or secure file sharing systems. Study teams may contract monitoring/auditing services from a third party; however, the QA plan must be approved by the DSMC, and the DSMC must receive the resulting reports. Multisite trials are reviewed by the QA team at the depth and frequency of their assigned risk level. The Multisite Program performs monitoring of trials it manages, and the resulting monitoring reports are provided to the DSMC in addition to the QA review results. Participating sites that fail to provide study records for QA review may be held from further enrollment to the trial by the DSMC.

8.3 HRPP QA Reviews

At the institutional level, MCW's Human Research Protection Program (HRPP) performs QA reviews of studies activated through the MCW IRB. HRPP Quality Assurance/Quality Improvement (QA/QI) staff conduct routine reviews of randomly selected studies, as well as for-cause audits, often at the IRB's request. During QA/QI reviews, HRPP staff interview members of the study team; review the conduct, documentation and reporting of study activities (including regulatory and subject files); and have a closeout meeting with the study team to discuss findings and answer questions. The final report is shared with the study team and the IRB, and a corrective action plan may be requested from the PI. When HRPP performs a review of an IIT overseen by the DSMC, the DSMC requires that the study team share the final report along with the corrective action plan, if applicable.

9.0 Investigator Conflict of Interest

All MCW faculty and staff are required to follow MCW policies regarding standards of conduct, and clinical investigators are required to disclose any potential conflicts of interest associated with their involvement in a clinical trial. MCW's policies (Conflicts of Interest, Outside Professional Activities and Consulting [AD.CR.030] and Financial Conflicts of Interest in Research [RS.GN.020]) mandate that MCW faculty and staff must report all conflicts of interest to the institution for review and determination at least annually. Potential conflicts are reviewed by MCW's Corporate Compliance Office and the Financial Conflicts of Interest in Research Committee. Additionally, the MCW IRB requires investigators to report all potential conflicts of interest at the

time of initial submission of a research project to the IRB, at the time of continuing review, and within 10 days of becoming aware of any previously undisclosed significant financial interest.

10.0 NCI Notification of Study Suspension or Closure

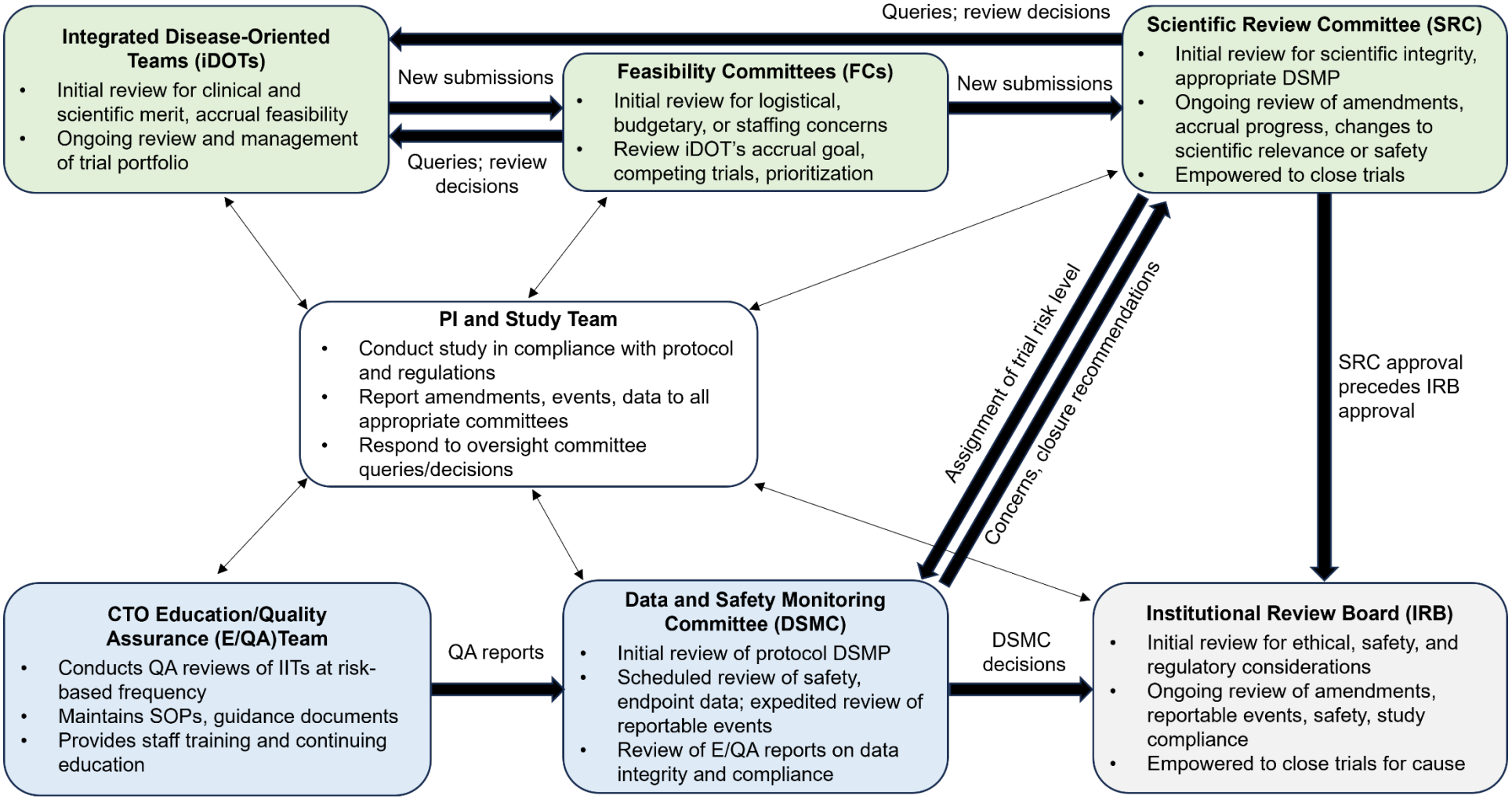
All temporary suspensions or permanent closures of NCI-sponsored clinical trials (non-NCTN studies) by the IRB or MCWCC due to non-compliance or safety concerns will be reported to the NCI Grant Program Director by the PI and regulatory staff within 5 working days of the determination. The ADCR, CTO Medical Director, CTO Administrative Director, CTO Assistant Directors, CTO disease team research manager, and iDOT Chair will also be notified. When necessary and possible, the DSMC, SRC, and CTO will assist the PI with revising the protocol to address the concerns. Operational issues that contributed in whole or in part to the suspension will be described and addressed in a Corrective Action Plan that is submitted to the DSMC, SRC, and IRB. Once DSMC, SRC, and IRB approval is granted, all parties will be notified, and the trial will be resumed.

11.0 References

The following annotated references to data and safety monitoring are electronic publications available over the Internet on government-sponsored websites.

- *National Institutes of Health Policy for Data and Safety Monitoring* dated June 10, 1998
  https://grants.nih.gov/grants/guide/notice-files/not98-084.html
  This is the basic NIH document that 1) states the policy that all clinical trials require data and safety monitoring, 2) spells out principles of monitoring and safety, and 3) addresses issues of implementation. This document is the starting point for developing an institutional plan.
- *Further Guidance on Data and Safety Monitoring for Phase I and Phase II Trials* dated June 5, 2000
  https://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html
  This policy presents further details for monitoring of Phase I and Phase II trials, which was not clearly covered in the 1998 document (above). While examples are presented, the structure and format of institutional plans and implementation still leave much to one's imagination.
- *Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by the National Cancer Institute* dated September 2014
  https://deainfo.nci.nih.gov/grantspolicies/datasafety.pdf
  This document gives further guidance on the composition of institutional DSMPs and provides an operational definition of a clinical trial.
- Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials dated June 11, 1999
  https://grants.nih.gov/grants/guide/notice-files/NOT99-107.html

Appendix A. Committee Relationships and Responsibilities



Appendix B. Data and Safety Monitoring Committee Charter

1.0 Data and Safety Monitoring Committee Overview

The Medical College of Wisconsin Cancer Center (MCWCC) Data and Safety Monitoring Committee (DSMC) reviews interventional, cancer-related, investigator-initiated trials (IITs) where MCWCC is the coordinating center. The primary mission of the DSMC is to ensure that IITs are conducted safely and compliantly and that trial results are based on sound data. The DSMC performs initial reviews of new protocols to confirm the risk level and review frequency, data reporting plan, and stopping rule language. Active studies are monitored for compliance, data integrity, safety, and progress toward endpoints on a frequency commensurate with their level of risk. If the DSMC has a concern regarding subject safety or data quality, it may suspend the trial or request changes to the protocol.

Specifically, the DSMC responsibilities include the following:

- Review interventional IITs to confirm or modify the SRC-assigned risk level, safety reporting language, stopping rules, and data management language;
- Perform ongoing scheduled review of open trials, reviewing DSM progress reports summarizing accrual, safety, and endpoint data, and study conduct;
- Approve progression to the next dose level in dose-escalation trials and transition from dose escalation to dose expansion;
- Recommend changes to the study based on updated toxicity information;
- Review internal quality assurance monitoring findings and corrective action plans;
- Make recommendations to the PI and relevant oversight committees concerning the continuation, modification, suspension, or termination of clinical trials based on observed safety, efficacy, or audit outcomes.

The DSMC reports to the MCWCC Deputy Director. Please see the MCWCC institutional Data and Safety Monitoring Plan (DSMP) for additional information about the DSMC's position and role within the MCWCC.

2.0 Committee Composition and Roles

The MCWCC DSMC is composed of at least 6 members with a range of clinical trial and disease expertise, all appointed by the MCWCC Deputy Director. Criteria for membership include expertise in the design and conduct of clinical trials in cancer prevention, diagnosis, or treatment. The Chair must be a clinical oncologist, and membership must include at least one biostatistician. Other members include clinicians from multiple disciplines and research nursing. Ad hoc reviewers/members may be identified for studies requiring additional expertise. The responsibilities of the Chair include the following: conducting monthly DSMC meetings, maintaining the integrity and quality of DSMC reviews, corresponding with PIs with regard to protocol review and committee actions, and reporting DSMC activities to MCWCC leadership. The Co-Chair performs the responsibilities of the Chair in the absence of, or as delegated by, the Chair. The Chair and all members of the DSMC are appointed to three-year terms with the option to renew. Should any member be unable to complete their term, the Deputy Director will appoint a replacement. All DSMC members serve at the pleasure of the Deputy Director, who may replace any member prior to completion of their term.

The DSMC is supported by the DSMC Coordinator. The Coordinator is responsible for maintaining the DSMC records: a log of appointment and term length of DSMC members, the OnCore database of protocols reviewed by the DSMC, files pertaining to reviewed protocols (DSMC reports, reviews, letters to PIs, etc.), and meeting minutes and attendance sheets. The Coordinator generates the monthly meeting agendas and assigns reviewers based on expertise in collaboration with the Chair. For protocols due for scheduled review, the Coordinator compiles a DSMC summary report from OnCore or obtains a summary from the study team. The Coordinator also facilitates expedited reviews of reportable events as they are received from the study teams. During meetings, the Coordinator records DSMC decisions and meeting minutes. Lastly, the Coordinator helps the Chair generate and distribute DSMC decision letters and provides any other administrative support as

required by the DSMC Chair or committee. The DSMC is also supported by CTO QA staff who perform quality assurance monitoring of trials overseen by the DSMC. The QA coordinators provide monitoring reports to the DSMC for review.

2.1 Conflict of Interest

DSMC members are required to disclose potential conflicts of interest, whether real or perceived, on individual trials and decline review responsibilities. Potential conflicts that develop during a member's tenure on a committee must also be disclosed. Decisions concerning whether individuals with potential conflicts of interest or the appearance of conflicts of interest may participate in a particular review will be made by the committee Chair and/or Co-Chair. When a DSMC member is a PI or sub-investigator on a trial (or has some other significant conflict of interest), they must leave the meeting for the general discussion of the trial and the vote on the trial's disposition. A reminder to disclose all potential conflicts of interest is made at the start of each meeting.

2.2 Confidentiality

All discussions that occur within the DSMC are confidential and are not disclosed except as outlined in this plan. Committee decisions are conveyed to the respective PI on behalf of the entire committee via the Coordinator, but no specifics are given regarding the reviewers or other committee members involved or details of the discussion that occurred. Further, all data presented during committee meetings are confidential and are not discussed or made available outside the meetings except to other oversight bodies (e.g., MCW IRB). In general, confidential outcome information will not be released while a trial is actively enrolling or patients are on study intervention. Any analysis of outcome data performed by the DSMC will not be released to the PI without approval from the DSMC Chair or Co-Chair. Blinded studies remain so until they are to be un-blinded as per study design, or in response to a safety issue that requires knowledge of treatment received by a study participant. DSMC members who are study team members may not see unblinded data unless the study is unblinded per study design.

3.0 Risk-Based Monitoring of Investigator-Initiated Trials

The DSMC is responsible for reviewing internally sponsored, locally coordinated, interventional investigator-initiated trials. This applies to all investigator-initiated trials lacking routine external monitoring, including those funded by pharmaceutical companies and NIH. Frequency and extent of monitoring is risk-based. New trials are assigned an initial risk level by the SRC during its review based on the guidelines in Table 1. The risk level determines the approximate frequency of the DSMC's scheduled review (study progress reviews of cumulative toxicity data, outcome data, accrual, etc.), as well as the frequency and breadth of quality assurance monitoring. The extent of monitoring varies depending on factors such as trial phase, trial complexity, type of agent(s) involved, expected toxicity profile, and whether an IND is held locally. Each protocol must have a study-specific DSMP approved by the DSMC. General guidelines are listed in **Table 1**; however, the DSMC may choose to adjust the frequency/extent of review on individual protocols based on factors such as accrual rate, new safety or efficacy information, or compliance issues.

3.1 Trials Requiring DSMBs

A subset of trials require the establishment of an independent DSMB that reports to the MCWCC DSMC. Independent DSMBs are required for randomized phase III interventional trials. Large behavioral or nutritional trials posing little risk to participants do not need DSMBs. Other, earlier phase treatment trials may require the establishment of a DSMB based on the number of subjects to be enrolled, level of patient risk, use of gene therapy, conduct in a multi-institutional setting, or at the investigator's request. The need for a DSMB will be at the discretion of the DSMC.

Table 1. Data and Safety Monitoring by Risk Level (timeline starts at time first patient is consented)

Risk Level	Trial Description	DSMC Scheduled Review Frequency	QA Monitoring Frequency	QA Monitoring Content
Low	Non-treatment trials (e.g., behavioral or nutritional interventions)	Annual	Annual	10% subject files; 1 comprehensive review*; regulatory; pharmacy
Intermediate	Phase II treatment trials, no local IND	6 months	Annual	20% subject files; 1 comprehensive review*; regulatory; pharmacy
High	Phase I trials, local IND	6 months	6 months	30% subject files; 1 comprehensive review*; regulatory; pharmacy
Special Status	Cell/gene therapy, first-in-human	1-3 months	3 months	30% subject files; 1 comprehensive review*; regulatory; pharmacy

*If QA reviewer believes warranted, additional comprehensive reviews may be conducted.

If a DSMB is required, it should be described in the protocol's DSMP section and must be approved by the DSMC and the IRB. The DSMC will review the DSMB monitoring reports while the trial is active. See the MCWCC DSMP for more information regarding DSMB creation.

Noninterventional Studies

Noninterventional studies are not clinical trials according to the NCI definition. These studies are considered minimal risk and are not routinely monitored by the DSMC. The protocols should still have a brief DSMP that describes how study data will be collected, managed, and securely stored for subject privacy. The PI is responsible for ensuring the study is conducted safely and compliantly, with reportable events submitted to the IRB per institutional guidelines, and for ensuring data accuracy and integrity.

4.0 DSMC Review Process

The DSMC meets monthly and ad hoc for urgent matters. A meeting quorum requires the presence of at least 50% + 1 voting members and must include at least two physicians and a biostatistician. Each DSMC member has one vote.

4.1 Initial Reviews

During or immediately following SRC initial review, interventional IITs are added to the next available DSMC agenda. The DSMC Coordinator assigns primary (must be a physician) and secondary reviewers. At the protocol's initial DSMC review, the committee members familiarize themselves with the study and verify the appropriateness of the study's risk level, AE reporting language, dose escalation criteria, dose-limiting toxicity definitions, stopping rules, and interim analyses. The committee may request modifications to the protocol. At the initial review of low-risk trials, the DSMC may determine that further review is unnecessary and exempt the protocol from DSMC monitoring.

4.2 Scheduled Review

Monitoring occurs at full committee meetings. At least a week before the meeting, the DSMC Coordinator provides the committee with the agenda, reviewer assignments, and review materials, including the DSMC data summary and quality assurance reports. Subject data are de-identified before being shared with the DSMC. At the meeting, the primary and secondary reviewers summarize the study for the committee and note any concerns. Reviewers who are unable to attend the meeting submit their reviews in advance so that they can be read out during the meeting. After discussion, the committee votes on a decision. A simple majority is required for passage. In the event of a tie vote, the issue is referred to the MCWCC Deputy Director, with a summary of the data and DSMC deliberations, to cast the deciding vote.

DSMC scheduled review begins following the consent of the first subject. Monitoring recurs at the frequency denoted in the protocol, commensurate with risk (e.g., Table 1). The committee may choose to increase or

decrease the frequency based on factors such as accrual rate and frequency or severity of safety events. Scheduled review ends 30 days after the final subject goes off treatment or continues until completion of follow-up of all patients to the point at which study-related adverse events are no longer likely to be encountered.

At scheduled review, the DSMC assesses these study aspects:

- Trial accrual rate and retention
- Cumulative summaries of all reportable AEs and SAEs, including those reported in an expedited fashion and those that only need to be reported at time of scheduled monitoring
- Cumulative summaries of all deviations, including those reported in an expedited fashion and minor deviations that are reported at time of scheduled review
- Endpoint data, interim analyses (if available)
- Application of stopping rules
- Internal quality assurance reports, completeness of data

These data are compiled into a progress report by the DSMC Coordinator and/or study team for review by the committee.

4.2.1 Adverse Event Reporting

Interventional IITs must report AEs/SAEs to the DSMC per the reporting requirements approved by the DSMC in the protocol. In general, the DSMC requires AEs/SAEs to be reported per Table 2. Some events are given routine review as part of the aggregated data at the trial's next scheduled review. Events requiring expedited reporting must be sent to the DSMC within 5 calendar days of staff knowledge. While Table 2 describes typical DSMC reporting requirements, reporting may be tightened or relaxed on an individual trial basis, depending on the nature and associated risk of the intervention. Also, the DSMC typically allows hematologic malignancy trials to report grade 4 hematological AEs in a routine rather than expedited fashion. The DSMC sets the minimum reporting requirements for safety monitoring, but PIs may choose to collect additional events for study purposes (e.g., grade 1 and 2 AEs on phase 1 trials). These events are also reviewed by the DSMC. PIs or the DSMC may also choose to collect AEs of Special Interest (AESIs). In that case, the DSMC will determine whether the AESIs should be reported in a routine or expedited manner.

Table 2. Adverse Event Reporting Requirements for the DSMC

Grade 1-2 (SAEs only)	Grade 3		Grade 4-5 (AEs and SAEs)
	AEs	SAEs	
Routine Review	Routine Review	Expected or Unrelated: Routine Review Unexpected and At Least Possibly Related: Expedited Review	Expedited Review*

*For trials of hematologic malignancies, Grade 4 hematological AEs may be permitted routine review rather than expedited.

4.2.2 Quality Assurance Monitoring

Quality assurance review is critical to ensuring that trials are conducted safely and compliantly and that trial data are collected consistently and accurately for publication.

QA reviews are performed by CTO QA coordinators as detailed in the MCWCC DSMP. For each QA review, a copy of the final report with study team responses is sent to the DSMC for review. The CTO Administrative Director attends DSMC meetings to discuss concerning findings and may recommend adjusting the frequency of the CTO's QA reviews (e.g., based on QA findings or study accrual rate) or corrective action on the study team's part if their initial responses were not satisfactory. The DSMC may include QA recommendations in its

decision letters, and if the DSMC has serious concerns about study conduct, it may suspend the trial to further accrual until the concerns are resolved.

4.2.3 Multisite Management

The MCWCC DSMC serves as the DSMC of record for multisite trials where MCW is the coordinating center, and DSM progress reports must summarize data from all participating sites. All subjects enrolled at external sites must be registered in OnCore, so that the DSMC can view subject status information. Reportable AEs, SAEs, and deviations from subjects at all participating sites must be communicated to the DSMC for review, and the protocol should clearly describe the process by which participating sites will report events to the coordinating center. External participating sites are also subject to QA review. The MCW PI is ultimately responsible for ensuring that data from the external participating sites are reported to the DSMC. The DSMC may suspend participating sites for failure to provide data or access to study records for QA review. The MCW PI is responsible for communicating DSMC determination letters as needed, amendments, and other study updates to the participating sites.

4.3 Other Review Types

In addition to initial reviews and scheduled review of trial progress, the DSMC also reviews the following events as they occur:

- Immediately reportable safety events – typically, SAEs (all grade 4s and 5s, unexpected and related lower grades), grade 4 AEs, and unexpected grade 3 AEs must be reported to the DSMC within five calendar days of study staff's knowledge (but see protocol-specific language).
- Dose-limiting toxicities (DLTs) – DLTs must be reported to the DSMC within five calendar days of study staff's knowledge.
- Phase I dose level cohorts, expansions – Studies with dose escalations will be reviewed by the DSMC at the completion of each cohort. Studies may not proceed to the next dose level or to the dose expansion phase without DSMC approval.
- Amendments – DSMC reviews changes to DLT definitions, toxicity reporting language, stopping rules, and interim analyses.

When one of the above events occurs, the study team notifies the DSMC Coordinator via email and provides a summary of the event. The DSMC Coordinator sends the summary of the event to the DSMC Chair and the study's primary and secondary DSMC reviewers via email. For expedited reviews, the DSMC may choose from among the same set of actions (see below) as for full committee reviews. Once a determination is reached, the DSMC Coordinator sends a decision letter. The DSMC Chair may elect to defer discussion of an event for discussion at the next full committee meeting.

5.0 Committee Actions

Following DSMC review, the recommendation of the committee is communicated in writing to the PI. The DSMC decision letters are also copied to regulatory personnel to be filed and forwarded to the IRB at time of continuing review, per IRB requirements.

After reviewing a protocol, the committee recommends one of the following actions:

- Acknowledged – The DSMC has reviewed a reportable event (e.g., SAE, DLT) and has no concerns.
- Continue as designed – After scheduled review, there are no outstanding subject safety or data integrity issues; accrual may continue. Non-binding recommendations or questions may be communicated.
- Continue as designed with stipulations or requests for additional information – After scheduled review, the DSMC has questions or concerns that require a response, but accrual may continue in the meantime.
- Study suspension – The DSMC has major concerns and accrual must be suspended until concerns are resolved.

- Study termination – The DSMC recommends to the SRC that a trial should be permanently closed due to major safety or study integrity concerns.

If the review decision includes stipulations or requests for additional data or information, the PI should provide a written response addressing the committee's concerns within four weeks (by the next DSMC meeting). Studies not responding within four weeks may be subject to suspension. PIs can amend their protocol or provide justification for not modifying the study in response to a stipulation.

The DSMC may vote to suspend a study for reasons including, but not limited to, triggering of an early stopping rule, safety concerns that alter the risk/benefit ratio, new data suggesting study objectives cannot be achieved, lack of response to DSMC queries, study compliance issues, major deficiencies in an internal or external monitoring or audit report, or data integrity concerns. The decision to suspend a study is communicated to the PI, CTO study team, SRC, IRB, CTO Medical Director, CTO Administrative Director, CTO Assistant Directors, ADCR, and MCWCC Deputy Director.

In the event that the DSMC's concerns cannot be rectified after discussion with the PI, the DSMC may recommend termination of the study. The DSMC will communicate its recommendation to the SRC, which will review and make a final determination regarding study closure. The SRC will communicate closure decisions to the DSMC, PI, CTO study team, IRB, CTO Medical Director, CTO Administrative Director, CTO Assistant Directors, ADCR, and MCWCC Deputy Director. The PI is responsible for notifying the FDA, NCI, and funding sponsor, as applicable.

Appendix C. Guidelines for Establishing and Running Data and Safety Monitoring Boards

A subset of studies will require the establishment of an independent Data and Safety Monitoring Board (DSMB) that will report to the MCWCC DSMC. Independent DSMBs are required for randomized Phase III trials, with the exception of behavioral or nutritional trials posing little to no risk to participants. Other, non-phase III trials may require the establishment of a DSMB based on the number of subjects to be enrolled, level of patient risk, use of gene therapy, conduct in a multi-institutional setting, or at the investigator's request.

A. Establishing a DSMB

The DSMB must be set up prior to the activation of the trial.

When a study needing a DSMB is reviewed by the SRC, the SRC must ensure a DSMB is established. If a DSMB is required, the SRC Chair will ask the PI to indicate the proposed frequency of meetings for a DSMB, submit a proposed list of data items to be provided to the DSMB, and nominate DSMB members. The PI should provide information on the nominated DSMB member, such as a CV, a list of current affiliations with pharmaceutical and biotechnology companies, including the type of affiliation [e.g., stockholder, consultant], as well as any other relationship that could be perceived as a conflict of interest related to the study and associated with commercial interests. Per NCI guidance, DSMBs should include physicians, a statistician, other scientists, and lay representatives based on experience, objectivity, and familiarity with clinical trial methodology. Members may be internal or external, but a majority should not be affiliated with the institution. Nominations are submitted to the MCWCC Deputy Director, who formally appoints each DSMB member. If appropriate, PIs should also submit a proposed budget for travel and administrative expenses for the DSMB. The SRC will reserve the right to recommend the appointment of additional members to the DSMB with relevant expertise. The PI cannot recruit patients until the DSMB has reviewed and approved the protocol.

B. DSMB Responsibilities

Once a DSMB is established, its initial task is to review the study protocol with regard to recruitment, randomization, intervention, subject safety, data management, plans for monitoring of primary subject records, quality control and analysis, and to identify needed modifications. The DSMB shall then identify the relevant data parameters and the format of the information to be regularly reported. If a need for modifications to the protocol or consent form is indicated by the DSMB and/or the IRB, the DSMB shall postpone its recommendation for the initiation of subject recruitment until after the receipt of a satisfactory revised protocol.

The DSMB must meet on a regular schedule at least twice a year (with additional meetings as needed) over the course of study to:

- Review data (including masked data) over the course of the trial relating to efficacy, recruitment, randomization, compliance, retention, protocol adherence, trial operating procedures, form completion, data quality and timeliness, intervention effects, gender and minority inclusion and subject safety.
- Identify problems relating to safety over the course of the study and inform the study PI via written report, who in turn will ensure that all clinical site PIs receive this report.
- Identify needs for additional data relevant to safety issues and request these data from the study investigators.
- Propose appropriate analyses and periodically review developing data on safety and endpoints related to outcome.
- At each meeting, consider the rationale for continuation of the study with respect to recruitment, progress of randomization, retention, protocol adherence and compliance, data management, safety issues, and outcome data, if relevant, and make a recommendation for or against continuation of the trial.
- Provide the PI, DSMC, and IRB written reports following each DSMB meeting. The PI will then forward the report to the study sponsor.
- Provide advice on issues regarding data discrepancies found by the data monitoring system or other sources.

- Ensure confidentiality of data and results of analyses for monitoring purposes.
- Approve release of study data to the PI for presentation or publication.

If there is more than one clinical site, the study PI is responsible for sending the reports to individual site PIs, who in turn are required to distribute the report to their local IRBs, as detailed in the NIH "Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials" (NIH Guide for Grants and Contracts, June 11, 1999).

C. DSMB Meetings

DSMB meetings will be divided into three parts. First, an open session in which members of the clinical trial team may be present, at the request of the DSMB, to review the conduct of the trial and to answer questions from members of the DSMB. Issues discussed may include accrual, protocol compliance, and general toxicity. Outcome results and any information which may unblind study team members must not be discussed during this session. Following the open session, a closed session involving the DSMB and study statistical staff will be held. The statistician(s) should present and discuss the outcome results with the DSMB. A final executive session involving only DSMB members should be held to allow the DSMB opportunity to discuss the general conduct of the trial and all outcome results, including toxicities and adverse events, develop recommendations, and take votes as necessary.

D. DSMB Recommendations

DSMB recommendations should be based on results for the trial being monitored as well as on data available to the DSMB from other studies. It is the responsibility of the PI to ensure that the DSMB is kept apprised of non-confidential results from other related studies that become available. It is the responsibility of the DSMB to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored. The DSMB recommendations include (1) to continue the trial as designed without modification, (2) to continue the trial with stipulations (e.g., request for additional information or protocol amendment), (3) to suspend the trial until DSMB concerns are addressed, or (4) to terminate the trial based on safety, futility, or data integrity concerns. The recommendation should be made by formal majority vote.

A written copy of DSMB recommendations will be forwarded to the trial PI, DSMC, and IRB. If the DSMB recommends a study change for patient safety or efficacy reasons, or that a study be closed early due to slow accrual, the trial PI must act to implement the change as expeditiously as possible. In the unlikely situation that the trial PI does not concur with the DSMB, then the DSMC Chair must be informed of the reason for disagreement. If a mutually acceptable decision cannot be reached, the matter may be escalated to the Deputy Director for resolution. Confidentiality must be maintained during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and staff to seek advice to assist in reaching a decision.

If a recommendation is made to change a trial for other than patient safety or efficacy reasons or for slow accrual, the DSMB will provide an adequate rationale for its decision.

In the event that the DSMB recommends temporary suspension or permanent termination of a trial, the DSMB will notify the SRC to review and act upon the recommendation. The PI of the trial, MCWCC Deputy Director, ADCR, DSMC Chair, IRB, and the study sponsor will be notified promptly of the action taken.

E. Release of Outcome Data

In general, outcome data should not be made available to individuals outside of the DSMB until accrual has been completed and all patients have completed their treatment. At that time, the DSMB may approve the release of outcome data on a confidential basis to the trial PI for planning the preparation of manuscripts and/or to a small number of other investigators for purposes of planning future trials. Any release of outcome data prior to the DSMB's recommendation for general dissemination of results must be reviewed and approved by the DSMB.

F. Confidentiality Procedures

No communication, either written or oral, of the deliberations or recommendations of the DSMB will be made outside of the DSMB except as provided for in this policy. Outcome results are strictly confidential and must not be divulged to any non-member of the DSMB, except as indicated above in the Recommendations section,

until the recommendation to release the results is accepted and implemented. Each member of the DSMB, including non-voting members, must sign a statement of confidentiality. A reminder that all proceedings are confidential will be made at the start of each DSMB meeting.

G. Conflict of Interest

DSMB members are subject to MCW policies regarding standards of conduct. Individuals invited to serve on the DSMB as either voting or non-voting members will disclose any potential conflicts of interest, whether real or perceived, to the trial PI and the appropriate MCW official(s), in accordance with the institution's policies. Conflict of interest can include professional interest, proprietary interest, and miscellaneous interest. Potential conflicts that develop during a member's tenure on a DSMB must also be disclosed. Decisions concerning whether individuals with potential conflicts of interest or the appearance of conflicts of interest may participate in a DSMB will be made in accordance with the institution's policies. A reminder to disclose potential conflicts of interest will be made at the start of each DSMB meeting.

H. DSMC Responsibilities

The DSMC will review all DSMB reports. The DSMC Chair may serve as a non-voting, ex officio member of the protocol DSMB.

The DSMC will additionally:

- Institute any reports needed or request additional data for subject safety, satisfactory data management, quality, and analysis; recruitment and protocol adherence (e.g., data reporting formats and schedules, restrictions on expenditure of funds pending completion of particular activities, etc.).
- As needed, request that the DSMB provide advice to the study PI on trial protocol and safety issues; data management, quality, and analysis; recruitment, retention, and protocol adherence issues arising over the course of the study and continuation or termination of the study.
- Acknowledge reports of serious data discrepancies found by the DSMB, or other sources within two weeks of the receipt of this information by the CTO. This acknowledgment should be in writing and should be sent to the PI, the Chair of the DSMB, the MCWCC ADCR, and the MCWCC Deputy Director.
- Assure preparation and dissemination of a clinical alert in the event of a clinically significant finding. This dissemination should also include informing the subjects of this clinical alert and providing them and their health provider with as complete information as possible that may affect the subjects' well-being.
- Reserve the option, at any point in the trial, to obtain an independent audit of a sample of primary subject records for comparison with the trial's regular monitoring reports. Auditors so engaged will report directly to the DSMC Chair.

Appendix D. Reporting Events

Safety and other events occurring at MCWCC or participating sites should be reported as specified in the protocol in accordance with institutional and federal requirements.