Medical College of Wisconsin Cancer Center

Data and Safety Monitoring Plan

Ensuring Patient Safety and Clinical Research Integrity

AUTHORIZED BY:

JAMES THOMAS, MD, PHD

ROY L. SILVERSTEIN, MD

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Overview

The Medical College of Wisconsin Cancer Center (MCWCC) places the highest priority on ensuring the safety of patients participating in clinical trials. Every cancer trial conducted at MCW must include a data and safety monitoring plan (DSMP) commensurate with the degree of risk involved and the size and complexity of the trial. The MCW Associate Director for Clinical Research is responsible for data and safety monitoring, relying on the independent Scientific Review Committee to ensure that every new protocol has an appropriate DSMP and the Data and Safety Monitoring Committee (DSMC) to monitor active interventional investigator-initiated trials.

Externally-initiated clinical trials (e.g., cooperative group trials, industry trials, and consortium or institutional trials) must have DSMPs that are approved by the SRC and an Institutional Review Board (IRB), either local or central. The MCW principal investigator and coordination staff are responsible for adhering to sponsor, institutional, and governmental requirements for trial management and data reporting. Data (including reportable events) must be submitted to the sponsor and regulatory bodies via the designated system and in a timely fashion. All reportable safety events must also be submitted to the IRB according to its policy. Quality assurance monitoring of these trials is the responsibility of the sponsor primarily. The DSMC may review audit or safety reports for these trials, but it does not routinely perform data and safety monitoring for them.

MCW investigator-initiated trials (IITs) are required to have specific data and safety monitoring plans based on trial phase and potential risk to patients, and these plans are approved by the SRC, DSMC, and local IRB. The study team is responsible for reporting safety events to the IRB, FDA, sponsor, and DSMC as appropriate.

Non-interventional IITs are low risk and not routinely monitored by the DSMC. These protocols should have a DSMP that at a minimum describes how study data will be collected, managed, and stored to protect patient privacy.

Phase I and II interventional IITs are monitored by the DSMC at a frequency dependent on risk (e.g., monthly, semi-annually). The DSMC reviews safety and efficacy data (e.g., adverse events, deviations, best responses, survival) submitted via OnCore®, MCWCC's Clinical Trial Management System, or requested directly from the PI. DSMC decision reports are shared with the PI as well as the IRB. For multisite trials coordinated by MCWCC, the DSMC reviews data for all subjects and DSMC reports are shared with the external sites for submission to their IRBs. In the event that data and safety monitoring results in the suspension or termination of enrollment and/or treatment of patients, the principal investigator, the MCWCC Director, the MCWCC Associate Director for Clinical Research, the IRB, and the study sponsor will be notified within 24 hours of such action.

Large Phase III investigator-initiated trials with an accrual goal of more than 300 subjects must be monitored by a protocol-specific data and safety monitoring board (DSMB). Formal DSMBs consist of clinical investigators, biostatisticians, clinical trial experts, and lay patient advocates independent of investigators involved in the design and conduct of the trial. Following protocol review and monitoring, all DSMB recommendations and reports will be forwarded to the IRB, DSMC, and principal investigator.

The MCWCC Clinical Trials Office performs internal quality assurance review of active trials. MCW IITs are prioritized as these are not typically monitored by an external auditing mechanism. For routine review, IITs are categorized to a risk level (low, intermediate, high, or special status) at the discretion of the SRC. A portion of subject files are reviewed, including consent/eligibility, objective-based data, and regulatory documents. At the conclusion, Quality Assurance staff meets with study team members to discuss key findings, make

recommendations for improvement, and present deficiencies to which the PI must respond. The DSMC reviews these internal reports, as well as external audit reports for all trial types.

Abbreviations

ADCR	MCW Cancer Center Associate Director for Clinical Research
AdEERS	Adverse Event Expedited Reporting System
AE	Adverse Event
CDUS	Clinical Data Update System
CHW	Children's Hospital of Wisconsin
CTEP	Clinical Trial Evaluation Program
CTO	MCW Cancer Center Clinical Trials Office
CREC	MCW Cancer Center Clinical Research Executive Committee
DOT	Disease-Oriented Team
DSM	Data and safety monitoring
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
FDA	U.S. Food and Drug Administration
IDE	Investigational Device
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
PI	Principal Investigator
PRMS	Protocol Review and Monitoring System
SAE	Serious Adverse Event
SRC	Scientific Review Committee
QA	Quality Assurance
UPIRSO	Unanticipated Problem Involving Risk to Subjects or Others

1.0 Introduction

The Medical College of Wisconsin Cancer Center (MCWCC) has a diverse research program, which includes a broad portfolio of trials: Phase I dose-finding studies, Phase II studies, and large-scale, multi-institutional, randomized Phase III studies. These trials consist of national cooperative group trials, National Cancer Institute (NCI)/Clinical Trial Evaluation Program (CTEP)-sponsored local trials, limited multicenter trials, institutional investigator-initiated trials, and pharmaceutical industry trials that pose varying degrees of risk to study participants.

The MCWCC places the highest priority on ensuring the safety of patients participating in clinical trials. Every interventional cancer trial conducted at MCW must include a plan for data and safety monitoring (DSM). The extent of monitoring varies by the degree of risk encountered by patients on the study, the study sponsor, the type of agent or agents involved, the phase of the clinical trial, and the complexity of the study.

The MCWCC Data and Safety Monitoring Plan (DSMP) has been developed to coordinate and provide oversight for data and safety monitoring for interventional trials consistent with the following: the *National Institutes of Health Policy for Data and Safety Monitoring* dated June 10, 1998; *Policy of the NCI for Data and Safety Monitoring of Clinical Trials* dated June 22, 1999; *Further Guidance on a Data and Safety Monitoring Plan for Phase I and II Trials* from NIH dated June 5, 2000; and *Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by the National Cancer Institute* updated August 9, 2010. This DSMP describes the MCW Cancer Center's policies and procedures related to data and safety monitoring activities.

2.0 Background

2.1 Definition of a Clinical Trial

A clinical trial is operationally defined by the NCI Data and Safety Monitoring Guidelines (last updated 8/9/2010) 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 DSM policy, unless performing the diagnostic test itself imposes some risk on study subjects.
- *Behavioral clinical trials* include interventions whose goals are to increase behaviors (e.g. cancer screening, physical activity, fruits and vegetable intake), eliminate or reduce behaviors (e.g., smoking, sun exposure) and/or improve coping and quality of life (e.g., among cancer survivors) and reduce the negative sequelae of treatment. Interventions may pertain to cancer prevention, early detection, treatment, and survivorship. Observational studies and those that do not test interventions are not

clinical trials.

2.2 Applicability

This plan applies to MCW faculty and staff conducting cancer-related clinical research at the MCW Cancer Center at Froedtert Hospital, Children's Hospital of Wisconsin (CHW), and BloodCenter of Wisconsin, as well as at Froedtert's community sites and the Clement J. Zablocki VA Medical Center.

2.3 Conflict of Interest

All MCW faculty and staff are required to follow MCW policies regarding standards of conduct. All clinical investigators are required to disclose any potential conflicts of interest resulting from their involvement in a clinical trial. A conflict of interest is defined as professional interest, proprietary interest, and miscellaneous interest as described in the NIH Grants Policy Statement, Phase II-12, and 45 CFR Part 94. Decisions concerning whether individuals with potential conflicts of interest or the appearance of conflicts of interest may participate in protocol monitoring will be made in accordance with institutional policies.

MCW has a "Financial Conflicts of Interest in Research" policy that is applicable throughout the MCW organization and requires disclosure of significant financial interest. Significant financial interests may include publicly and non-publicly traded entities if the aggregated amount of income or interest from the entity exceeds $5000 in the 12 months prior to the person's disclosure; intellectual property rights and interests with an entity; travel reimbursed or sponsored by non-academic or non-governmental institutions. This policy is located online at http://www.mcw.edu/Office-of-Research/Financial-Conflicts-of-Interest-in-Research-FCOIR.htm. MCW prohibits any arrangement where the amount of compensation, or potential compensation, will be directly affected by the outcome of the research (e.g., an arrangement has been made where the value of the compensation will change depending on the outcome of the research).

The MCWCC research oversight committees abide by the above policies. Faculty members serving on the committees must disclose any potential conflict of interest, whether real or perceived, to the appropriate institutional officials. The Cancer Center has also established the following specific committee rules that govern the activity of members who have a conflict:

- A committee member may not vote on a protocol on which he or she serves as a Principal Investigator (PI) or sub-investigator. When a committee member is an investigator on a trial being reviewed, he or she is required to leave the meeting room for the committee's discussion, unless the other committee members have questions they would like to pose to the investigator. The investigator may not be present in the room for the committee's vote. Also, an investigator may not serve as an auditor for his or her own trial.
- Any committee member who is not an investigator on a trial, but who has another identified conflict may or may not be allowed to vote on actions related to the protocol. This will be determined by the committee chair and/or co-chair. Those individuals found by the chair and/or co-chair to have a significant conflict related to a trial will not be allowed to vote on items related to that trial.

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 on a committee or in a particular meeting will be made by the committee chair and/or co-chair.

2.4 Confidentiality

All discussions that occur within any of the MCWCC research oversight committees are confidential and are not disclosed except as outlined in this plan. Committee decisions are conveyed to the respective principal investigator on behalf of the entire committee via the meeting coordinator, but no specifics are given regarding

the reviewers or other committee members involved or details of the discussion that occurred. Further, the confidentiality of data presented during committee meetings is maintained. All data are strictly confidential and are not discussed or made available outside the meetings. Any outcome results or treatment assignments are not disclosed. 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. Paper materials distributed during committee meetings are collected and destroyed after each meeting.

3.0 Organization and Administration

The Associate Director for Clinical Research (ADCR) has the overall responsibility for data and safety monitoring of clinical trials conducted under the auspices of the MCWCC. In this role, the ADCR has the authority to suspend or terminate the enrollment and/or treatment of patients on any clinical trial conducted at the MCWCC to protect the safety of participating patients and scientific integrity of the trial.

The MCWCC research oversight system is comprised of several committees that play distinct roles in overseeing all aspects of clinical research conducted at the MCWCC (Appendix A, B). The Protocol Review and Monitoring System (PRMS) is made up of the disease-specific Disease-Oriented Teams (DOTs) and the Scientific Review Committee (SRC). The Data and Safety Monitoring Committee (DSMC) reviews the safety and integrity of active MCW investigator-initiated trials. These committees are independent and report to the ADCR. Lastly, the Clinical Research Executive Committee (CREC), chaired by the ADCR, provides oversight and direction for the other committees. The ADCR, in turn, reports to the Director of the MCWCC. External to the MCWCC, the protocols are reviewed by Institutional Review Boards (IRBs), which also evaluate patient safety. Committee responsibilities are described below.

3.1 Disease-Oriented Teams

The 14 Disease-Oriented Teams (DOTs) are disease-specific, multidisciplinary committees made up of physicians and scientists encompassing all relevant modalities (hematology/oncology, radiation oncology, surgery, pathology, radiology, and basic science). The DOTs are responsible for the disease-specific aspects of the cancer service line and maintaining a comprehensive clinical trial portfolio. Each committee has a Chair who is selected jointly by the ADCR and the Cancer Center Associate Director of Clinical Operations (Service Line Director). The Chair reports to the ADCR regarding activities related to clinical research. Goals and deliverables for each research program are determined by the DOT Chairs in conjunction with the Cancer Center Director, ADCR, and the Associate Director for Translational Research. Goals include, but are not limited to, accrual to interventional trials, accrual to investigator-initiated trials, cooperative group participation, publications and multidisciplinary grant submissions. Each committee meets at least monthly to review the progress of active trials, including accrual, deviations, and toxicities. The DOTs also identify new trials that are of clinical interest, complement their existing portfolio, and are a good fit for their patient populations. Trials approved by the DOTs are then sent to the Scientific Review Committee.

3.2 Scientific Review Committee

The MCWCC Scientific Review Committee (SRC) plays a vital role in protocol review and monitoring to ensure that clinical trials are scientifically sound and that approved trials maintain patient accrual goals and scientific progress. It reviews all cancer-related trials that have not received peer review by NIH-approved bodies, including local, investigator-initiated studies, industry-sponsored studies, limited multi-institutional studies, and

cooperative group studies (administrative review). The specific functions of the SRC include the following:

- Establishing and maintaining a review committee of sufficient size and breadth of expertise to conduct a critical and fair scientific assessment of proposed cancer-related research involving human subjects
- Conducting a thorough scientific review using a standard format based on specific, pre-determined review criteria
- Assisting MCWCC investigators in the development of scientifically and clinically sound research through well-written protocols
- Considering protocol feasibility with regard to budget, resources, and competing trials
- Establishing clear criteria for determining whether ongoing clinical trials are making sufficient progress, including adequate patient accrual rates, and terminating protocols not meeting expectations

SRC members are appointed by the ADCR. At least 14 members serve on the SRC with representative members from each of the following: Pediatric Hematology/Oncology, Adult Hematology/Oncology, Obstetrics and Gynecology, Radiation Oncology, Surgery, Basic Laboratory, Nursing, Pharmacy, Biostatistics, and an external community representative. Members are invited to participate based on disciplinary expertise as well as expertise in the design, conduct and analysis of specific trials.

The SRC reviews and approves protocol-specific DSMPs as part of the scientific review process prior to protocol review by the IRB. The SRC ensures that the trial includes an appropriately detailed plan tailored to the protocol's level of risk and that sufficient resources are available for its implementation. No interventional study will receive SRC approval without a DSMP.

3.3 Data and Safety Monitoring Committee

The MCWCC Data and Safety Monitoring Committee (DSMC) reviews trials for data quality and patient safety. Unlike the other committees, the DSMC focuses solely on MCW investigator-initiated interventional trials. The DSMC reviews protocols for stopping rules and DSM language, and unlike the SRC, also reviews patient consent forms to ensure that potential risks are adequately conveyed to participants. Additionally, the DSMC reviews the results of internal and external quality assurance audits of other trial types, including cooperative group trials. If the DSMC has a concern regarding patient safety or data quality, it may recommend changes to the protocol or consent form that must then be reviewed and approved by the SRC and/or IRB. Please see Section 5.0 below for more details about the DSMC.

3.4 Institutional Review Boards

All clinical trials opened at MCWCC are reviewed by the MCW IRB (adult trials), CHW IRB (pediatric trials), or a designated central IRB to which the local IRB deferred. The IRB review process is complementary to and independent of the MCWCC PRMS and DSMC. A key point of emphasis during the development of the SRC and DSMC was to have clear lines of distinction between their roles and that of the IRB. IRB review focuses on the ethical and regulatory requirements for the conduct of research involving human subjects, paying particular attention to subject safety, while the SRC reviews scientific quality and progress as outlined above. For cancer-related protocols, SRC approval is required before a protocol can go to the IRB for review. Like the IRB, the DSMC monitors patient safety, but only for investigator-initiated trials. Because the DSMC is composed of oncology specialists, the committee is particularly familiar with safety issues confronting cancer patients. Additionally, the DSMC is concerned with data quality, trial efficacy, and the results of quality assurance reviews. According to NIH policy, the MCWCC Data and Safety Monitoring Plan and individual protocol data

and safety monitoring plans require IRB review and approval.

3.5 Clinical Research Executive Committee

Oversight of committee activities is provided by the MCWCC Clinical Research Executive Committee (CREC), which meets quarterly and ad hoc for urgent matters. The committee oversees and directs clinical research at the MCWCC and its affiliates. CREC establishes priorities for the MCWCC Clinical Trials Office (CTO) and the CTO Medical Director, reviews general accrual and resource allocation issues, facilitates integration of research into the multidisciplinary clinics, and sets policy for the DOTs, SRC, and DSMC. The committee reviews minority recruitment efforts and assists in the development of future plans to enhance patient accrual. CREC is chaired by the ADCR, and other members include the Associate Director of Translational Research/CTO Medical Director, Associate Director of Clinical Operations, SRC Chair, DSMC Chair, and a subset of DOT Chairs and investigators representing different disease groups and modalities.

3.6 Clinical Trials Office

The MCWCC Clinical Trials Office (CTO) provides clinical, regulatory, budget, and administrative support to investigators and to the above Cancer Center committees. Specific functions include the following:

- Disease team research managers usher each protocol through the activation approval process and manage a protocol throughout its life cycle.
- Clinical and regulatory coordinators assist investigators with enrolling subjects onto clinical trials, managing subjects on trial, collecting and entering data, and reporting events (serious adverse events, deviations) to oversight bodies, including the DSMC.
- CTO Quality Assurance staff audit MCW investigator-initiated trials and report findings to the DSMC.
- Research managers and their clinical research assistants coordinate DOT meetings, prepare agendas, distribute review materials, and record minutes.
- The SRC/DSMC/CREC coordinator organizes committee meetings, prepares agendas, distributes review materials, records minutes, and maintains records of committee decisions.
- The CTO facilitates communication among the faculty committees and between the MCWCC and the IRB.

4.0 Investigator Responsibilities

The principal investigator of each study is ultimately responsible for every aspect of the design, conduct, and final analysis of their protocol. The investigator must ensure the following:

- All protocols must include a protocol-specific DSMP and procedures for its implementation. The DSMP will describe the procedure that will be utilized to ensure data integrity and protocol adherence. This can range from scheduled meetings between the PI and data manager(s) to formal audits by external agencies or the DSMC.
- There should be a procedure for monitoring of trial safety commensurate with the study's level of risk. Studies must have a structured adverse event determination, monitoring and reporting system, including standardized forms and procedures for referring and/or treating subjects experiencing adverse events. The proposed schedule for reporting adverse events to the Data and Safety Monitoring Board (DSMB; if one is established), the DSMC, the IRB (or IRBs in the case of multi-site studies),

and/or the NIH/FDA must be described. The PI is responsible for ensuring that all data required for oversight are accurately reported to the internal or external monitoring committee as required and that all adverse events are reported according to protocol guidelines and institutional requirements. If the proposed protocol has additional clinical sites besides that of the MCWCC, the protocol should describe procedures by which the PI will notify sites of any problems as identified by DSM, and they in turn will notify their IRBs. In cases where an outside agency (e.g., industry sponsor) is the sponsor of the test agent (i.e., holder of the Investigational New Drug [IND] application), PIs must submit individual adverse event reports to the funding agency (as sponsor) in accordance with agency and FDA regulations.

- An independent data and safety monitoring board (DSMB) is established if (1) the proposed study is a randomized Phase III trial or the trial proposes to include over 300 participants or (2) the PI feels that an independent DSMB would be useful for their study. A DSMB may also be formed if requested by the SRC or DSMC Chair.
- All blinded studies should describe a randomization scheme and specific criteria and procedures for unblinding. If a DSMB is not proposed, the protocol should also designate individuals with access to unblinded data.
- All changes to protocols must be approved by the IRB before trial activities are altered. Amendments to local investigator-initiated and external trials (except cooperative group trials) must be reviewed and approved by the SRC before submission to the IRB.
- Issues raised by the SRC, DSMC, CREC, or IRB are addressed appropriately and in a timely fashion.
- The MCWCC CTO and DSMC are informed of any actions taken by the IRB as a result of continuing review or other IRB submission.
- Trials are conducted in accordance with federal, state, and institutional regulations. All data are recorded and reported accurately and in a timely fashion. All study-related regulatory documents are maintained and kept up to date.

Investigators should also 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, April, 2001.

5.0 Data and Safety Monitoring Committee

The Data and Safety Monitoring Committee (DSMC) plays a vital role in protecting subjects participating in cancer-related MCW investigator-initiated trials (IITs) from unnecessary risks. The committee assists the ADCR by reviewing protocol DSM reports and providing recommendations on trial continuation, amendment, suspension, or termination. The DSMC reviews all interventional, investigator-initiated pilot and Phase I or II clinical trials. See Section 6.0 for more detailed discussion of how different types of trials are monitored.

Specific aims of the DSMC are to:

- review DSM reports as required for local, investigator-initiated, interventional cancer clinical trials involving human subjects

- establish clear criteria for determining whether ongoing clinical trials are safe in terms of the risks to participating subjects
- monitor ongoing trials and make recommendations regarding trial continuation, amendment, suspension, or termination based on safety criteria
- recommend informed consent form modification related to the risks of adverse events to the study's principal investigator(s)
- review internal and external quality assurance reports to identify potential systemic issues that need to be rectified
- recommend DSM policies related to clinical trial data and safety monitoring to the MCWCC leadership

5.1 Committee Composition and Roles

The MCWCC DSMC is composed of at least 6 members with a range of expertise, all appointed by the ADCR. The criteria for membership include expertise in the design and conduct of clinical trials in cancer prevention, diagnosis, or treatment and willingness to participate actively in the review of safety information. The Chair must be a clinical oncologist. There must be at least one biostatistician member. The other members must be experienced clinical trialists and may include clinicians, pharmacists, research coordinators/nurses, regulatory staff, and/or patient advocates. Members may be either internal MCWCC members or external members. 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 the DSMC, assigning protocols to DSMC members for review, corresponding with PIs with regard to protocol review and committee actions, and reporting DSMC activities to the MCWCC leadership. The Co-Chair performs the responsibilities of the Chair in the absence of, or as delegated by, the latter. 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 ADCR will appoint a replacement. All DSMC members serve at the pleasure of the ADCR, who may replace any member prior to completion of their term with the concordance of the MCWCC Director.

The DSMC is supported by the DSMC Coordinator, who is a CTO staff member. 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 (protocols, reviews, letters to PIs, etc.), and meeting minutes and attendance sheets documented in the DSMC binder. For protocols under review, the Coordinator runs the DSMC summary report in OnCore and sends it to the committee for review prior to the meeting. The Coordinator also assists PIs in preparing materials requested by the DSMC, ensuring all documentation is complete. Lastly, the Coordinator provides any other administrative support as required by the DSMC Chair or committee.

5.2 DSMC Review Process

The DSMC meets on the third Tuesday of every month from 4:00-5:00 pm in Clinical Cancer Center Conference Room 5318. A meeting quorum requires the presence of at least 50% of voting members. Each DSMC member has one vote. The Coordinator is present at the meeting to record the minutes.

The DSMC reviews new protocols, protocols due for scheduled monitoring, and serious adverse events (SAEs). Once a new interventional, investigator-initiated protocol is approved by the SRC, the DSMC Coordinator adds it to the next available meeting agenda and the Chair assigns a primary and secondary reviewer. At a protocol's initial review, the DSMC evaluates the protocol's DSM plan and stopping rules to

ensure they are appropriate. When the informed consent form becomes available, the committee reviews it to ensure that study-associated risks are adequately conveyed to potential participants. Once the protocol is open to accrual, the DSMC Coordinator puts it into the scheduled monitoring rotation for review. The committee then primarily reviews the protocol's OnCore-generated DSM reports and SAEs, but the committee may also request additional information from the study team for review.

While all committee members have a responsibility to read and be prepared to discuss all DSM reports, the Chair will assign two members as primary and secondary reviewers to lead the review and discussion of each protocol. Primary reviewers are always medical doctors. After a full discussion of the trial's DSM report, the committee conducts an open vote on the protocol. A simple majority is required for passage. In the event of a tie vote on a recommendation, the tie will be referred to the Associate Director for Clinical Research who will cast the deciding vote.

Protocols continue to be reviewed for safety monitoring until the final subject goes off treatment. At that point, the committee may cease review 30 days after the last treatment administrations, or when the committee feels comfortable that new AEs attributable to the study intervention are unlikely to occur.

Committee members are required to identify potential conflicts of interest prior to discussion of a protocol. Decisions concerning whether individuals with potential conflicts of interest or the appearance of conflicts of interest may participate in DSM for a specific protocol will be made in accordance with institutional policies (see Section 2.3). For protocols where a DSMC member is a PI or sub-investigator, the member may be present for discussion but not for the vote.

Trial features Monitored by DSMC

The Data and Safety Monitoring Summary Report generated by OnCore includes the following information:

- Protocol administration: PI; Title; DSMC, IRB and SRC review history; accrual goal/history; expected completion date; arms with agents and modality
- Demographics: number of patients accrued by gender, race, ethnicity, age, number on each arm, number on study/on treatment/off treatment/on follow-up/off study/expired
- SAEs, adverse events
- Subject deviations
- Best responses
- Survival

For Phase I dose escalation trials, the DSMC also reviews dose limiting toxicities and maximum tolerated doses. The DSMC reviews cohort data before the study moves to the next dose level.

Additionally, the DSMC may review external safety reports issued by sponsors, internal quality assurance reports, and external audit results.

No HIPAA-defined protected health information is included. Subjects are identified by initials and sequential numbers reflecting the sequence of their enrollment.

5.3 Committee Actions

After reviewing a protocol, the committee votes to recommend one of the following actions:

- Continue as designed – no changes required

- Continue as designed with stipulations to be formally addressed by the PI and approved by the DSMC Chair and reviewers
- Study suspension with stipulations to be formally addressed and approved by the full DSMC prior to study resumption
- Study termination recommended to the ADCR for final decision

Following the DSMC meeting, the recommendations of the committee are communicated in writing to the principal investigator within one week. The DSMC decision letters are also copied to regulatory personnel to be filed and forwarded to the IRB. If the review decision includes stipulations or requests for additional data or information, the PI must provide a written response addressing the committee's concerns within four weeks (by the next DSMC meeting). PIs can amend their protocol or provide justification for not modifying the study in response to a stipulation. The DSMC Chair and committee evaluate the PI's response and vote a final action on the trial.

The DSMC may feel that a trial is not making timely progress in meeting its accrual goal and that patients may be unnecessarily undergoing higher risk treatments on trials that are unlikely to be meaningful. In this situation, the DSMC notifies the SRC, which is the primary entity responsible for monitoring trial accrual. The SRC will then review the trial and take the appropriate action.

Trials with responses delinquent by more than one month from the requested submission date may be suspended until the PI submits a response and the DSMC votes to continue the trial as designed.

In the event that a conflict of interest exists with the ADCR, i.e., the ADCR serves as PI or co-PI of a reviewed clinical trial, the decision on action taken for that protocol will be made by the MCWCC Director.

If a protocol has been suspended or terminated, the ADCR will notify the principal investigator, the IRB, and the trial sponsor, including the NIH/NCI Project Officer if applicable. If the PI desires to re-open the trial, the DSMC Chair and the CTO will assist the PI with re-formulating the protocol to address safety concerns. The DSMC will then review the amended protocol and provide a recommendation to the ADCR. If approval is granted, the ADCR will notify the IRB and the trial sponsor of the decision to authorize trial resumption.

6.0 Monitoring Required by Trial Type

All clinical trials (as operationally defined by the NCI above) require data and safety monitoring. The extent of the monitoring varies by the degree of risk encountered by patients on the study, the study sponsor, the type of agent or agents involved, the phase of the clinical trial, and the complexity of the study (Appendix C). Given the great diversity of clinical trials performed at the MCWCC, trial data and safety monitoring, by necessity, reflects that diversity. MCWCC's Data and Safety Monitoring Plan 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. The individual trial sponsor or sponsoring group may dictate the specific nature and format of data and safety monitoring and reporting.

6.1 Cooperative Group Trials

Trials conducted under the sponsorship of the NCI's National Clinical Trials Network (NCTN) have well-defined DSMPs and functional DSMBs to provide appropriate DSM; thus, they are not routinely monitored by the MCWCC DSMC. Likewise, other NCI/CTEP-sponsored trials with mandated reporting through either the NCI's

Clinical Data Update System (CDUS) or the Clinical Trials Monitoring System (CTMS) operated by Theradex, Inc. are considered to undergo adequate DSM and do not require local DSM by the DSMC. Study staff must adhere to the DSM requirements and reporting mechanisms specific to each study.

Nevertheless, all SAEs from all trials are required to be reported to the IRB. The IRB has the authority to close any active study to further accrual and require more detailed reporting of SAEs and steps taken to minimize patient risk and maximize the safety of participating patients.

The DSMC does review the results of external audits of MCWCC performed by the cooperative groups.

6.2 Industry Trials

Trials sponsored by the pharmaceutical industry with little or no local investigator involvement in study design will be evaluated by the SRC and the IRB to ensure that an appropriate DSMP is in place for the trial. These protocol-specific plans should adhere to industry and FDA-specified guidelines and at a minimum clearly specify reporting for SAEs and unexpected adverse events. If an adequate DSMP exists, no monitoring will be conducted by the DSMC. If a DSMP does not exist, it must be developed by the sponsor and approved prior to study initiation. In no case will a trial lacking a DSMP be allowed to be conducted.

Local reporting for data and safety monitoring for industry-sponsored trials will require SAEs to be reported to the CTO and IRB using either industry-specified report formats or the FDA MEDWATCH SAE reporting form.

Local, investigator-initiated clinical trials with full or partial support by pharmaceutical sponsors are required to meet the data and safety monitoring requirements of local investigator-initiated trials as detailed below.

6.3 Consortium or External Institutional Trials

Investigator-initiated trials from other institutions will be evaluated by the SRC and the IRB to ensure that an appropriate DSMP is in place. Generally, the coordinating site will be the DSMB of record and the MCW DSMC will not be responsible for monitoring the trial; however, the DSMC may monitor the study at the request of the coordinating institution.

6.4 MCW Investigator-Initiated Trials

6.4.1 Phase I and Phase II Interventional Trials

Local investigator-initiated, cancer-related Phase I or II clinical trials approved for conduct at the MCWCC by the SRC and IRB must undergo DSM by the DSMC. These protocols include:

- trials with no external support relying on MCW support only
- trials with partial or full support by industry sponsors (i.e., supply of agent[s] only to full funding)
- trials receiving external funding through the NIH or other accepted peer review agency without NIH-mandated DSM (i.e., the NIH is not the IND holder)
- Phase I and II trials conducted in a limited multi-institutional setting with a MCW investigator as the principal investigator of the study and MCW serving as lead institution.

These studies receive no routine external monitoring, so they require particular attention and receive the highest priority for local oversight. Unless the DSMC approves a trial-specific waiver, the PI of a local IIT is required to include the following wording in the protocol:

“This study will be reviewed by the Medical College of Wisconsin Cancer Center Data and Safety Monitoring

Committee (MCWCC DSMC). A summary of the MCWCC DSMC activities are as follows:

- Review the clinical trial for data integrity and safety.
- Review all unexpected grade 3, and all grade 4 and 5 adverse events, as well as any others requiring expedited reporting as defined in this protocol. (Grades 4 and 5 events must be reported to the DSMC within 5 calendar days of study staff's knowledge.)
- Review all DSM reports.
- Submit a summary of any recommendations related to study conduct.
- Terminate the study if deemed unsafe for patients.

A copy of the MCWCC Data and Safety Monitoring Plan and membership roster will be maintained in the study research file and updated as membership changes. The committee will review reports from the study PI twice annually (or more frequently if needed) and provide recommendations on trial continuation, suspension or termination as necessary.

Any available DSMC letters will be submitted to the IRB of record as required."

Hematological studies where a large number of grade 4 hematological events are expected may report these at scheduled monitoring rather than expedited. The frequency of trial review by the DSMC is commensurate with patient risk. Most interventional treatment trials are reviewed every 6 months; however, lower risk trials may be reviewed annually, and higher risk trials may be reviewed more frequently (e.g., monthly or after every patient). Phase I dose escalation trials are also reviewed at the completion of each cohort to determine whether it is safe to move to the next dose level or if a cohort expansion is necessary. Data and safety monitoring activities for each study will continue until all patients have completed their treatment and all patients are beyond the time point at which study-related adverse events would likely be encountered.

6.4.2 Gene Therapy Trials

For IITs that are especially high risk to subjects, such as immunotherapy trials involving genetically modified T cells, extra precautions may be taken. External reviewers will be identified as ad hoc members of the DSMC for these protocols. This will provide the committee with additional expertise and support from physicians experienced with these agents. The ad hoc external reviewers will phone in to full committee meetings when the relevant study is on the agenda or send their written reviews via email. Due to the unpredictable nature of the timing and severity of patient reactions to treatment (e.g., cytokine-release syndrome), both external and internal DSMC members will be available to do ad hoc reviews of adverse events as they arise. Emergency contact information will be shared among the DSMC members and the Coordinator. The PI may also choose to identify a local medical monitor to help evaluate events in real time.

6.4.3 Phase III Interventional Trials

Commensurate with risk, all local Phase III clinical trials with an accrual goal of 300 or more subjects require the establishment of an independent Data and Safety Monitoring Board (DSMB) that will report to the DSMC and IRB. Other non-Phase III trials may require the establishment of a DSMB based on the number of patients/subjects to be enrolled, level of patient risk, use of gene therapy, conduct in a multi-institutional setting, or at the investigator's request.

Please see Appendix D for more information on establishing an independent DSMB.

Exception: Large Phase III behavioral or nutrition trials posing minimal risk to participants are required to have a DSMP but are not required to establish a DSMB, though they may do so at the investigator's discretion. A

DSMB may be particularly appropriate when investigators anticipate the possibility of early stopping based on differences in either risk or benefit.

For non-cooperative group, limited-institution Phase III studies without NCI/NIH monitoring, the PI at the lead institution will be responsible for monitoring the study and establishing the DSMB. The SRC is required to review data and safety monitoring plans and verify the existence of an appropriate DSMB prior to approving the study at MCW.

The following policies describe MCW requirements for local, investigator-initiated Phase III trials. They do not replace existing regulations on protection of human subjects, policies and guidelines for conduct of clinical research, inclusion of women and minorities, research project administration, reporting, and financial management, or requirements of local IRBs. The Department of Health and Human Service (DHHS) regulations for the protection of human subjects are described in 45 CFR46.

This policy document describes further steps to be taken to ensure the protection of human subjects when the study involves a potentially harmful intervention, and for other Phase III studies to ensure that participants receive an appropriate share of the benefits. In individual cases, the MCWCC may find it beneficial to have additional levels of involvement or oversight beyond those described in these policies.

The MCWCC SRC will review the risks of the intervention. If the proposal for a study with a potentially hazardous intervention does not include the required information for such studies (described below), the SRC will not activate the protocol until this information is received, reviewed, and approved. The SRC may obtain additional consultation from MCW staff or external advisors.

Protocols for any interventional study should clearly state whether the proposed study meets NIH's criteria for a NIH-defined Phase III trial and the basis for that opinion.

Phase III protocols must include:

- Plans for establishment of an independent DSMB.
- Plans for securing support, resources, and funding appropriate for the DSMB to meet its requirements.
- A data processing and analysis unit administered by a designated individual other than the PI(s) of the trial. This individual may report to the PI. In all cases, all data from this unit must be directly available to the SRC Chair and the DSMB upon request.
- Procedures for quality assurance/quality control, data management, and analysis.
- Plans for notifying subjects of trial results after the conclusion of the trial and providing the subjects' health providers with the appropriate information from the trial, as needed, concerning the individual subject (e.g., cessation of drugs, changes in dosage, etc.).

Though a detailed Manual of Procedures is not required in the protocol submitted to the SRC, the PI should prepare a manual of procedures for review and approval by the DSMB and SRC Chair, prior to implementation of the trial.

6.4.4 Cancer Prevention and Control Trials

Cancer prevention and control trials are defined as prospective studies to evaluate a biomedical or behavioral intervention designed to prevent or reduce the risk of cancer or to ameliorate the effects of the disease and/or its treatment or to improve quality of life. These trials may evaluate agents, drugs, treatments, devices, or behavioral or nutritional strategies in patients with cancer or in people without a diagnosis of cancer but at risk

for it.

As noted in the NCI definition, behavioral clinical trials include interventions whose goals are to increase behaviors (e.g. cancer screening, physical activity, fruits and vegetable intake), eliminate or reduce behaviors (e.g., smoking, sun exposure) and/or improve coping and quality of life (e.g., among cancer survivors) and reduce the negative sequelae of treatment. Interventions may pertain to cancer prevention, early detection, treatment, and survivorship.

The DSMP shall then identify the relevant data parameters and the format of the information to be regularly reported.

6.4.5 Non-Interventional Studies

Observational studies and those that do not test interventions are not clinical trials according to the NCI definition. These studies are considered low risk and are not routinely monitored by the DSMC. The protocols should still have a DSMP that at a minimum describes how study data will be collected, managed, and securely stored for patient privacy. The SRC checks for the inclusion of a DSMP during initial protocol review.

7.0 Adverse Event Reporting Requirements

It is the responsibility of the study PI, treating physician, and clinical team to identify events as they occur and report them according to protocol and regulatory guidelines (Appendix E).

Adverse events (AEs) are any unfavorable medical occurrences (such as abnormal exams, symptoms, or disease) temporally associated with a subject's participation on a clinical trial. They may be attributable to the intervention or not, they may be considered expected or not, and they vary in degree of severity.

Serious adverse events (SAEs) are defined as resulting in any of the following outcomes:

- Death of a subject
- A life-threatening condition
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability or incapacity that substantially interferes with the ability to conduct normal daily activities
- Congenital anomaly or birth defect
- Important medical events that are not life-threatening and do not result in hospitalization or death but are still considered serious and require medical or surgical intervention to prevent a serious outcome

All AEs/SAEs must be reported as required by the sponsor, institutional policy, and state and federal guidelines. The MCW and CHW IRBs require SAEs to be reported in two ways:

- Expedited reporting – SAEs that are unexpected AND possibly, probably, or definitely related to the intervention (or that meet the protocol's definition for expedited reporting) need to be reported within 5 calendar days of study staff's knowledge.
- Routine reporting – SAEs that are expected OR unrelated can be submitted for review at the time of the annual Continuing Progress Report.

Unanticipated problems involving risk to subjects or others (UPIRSOs) include research related incidents that may impact the rights, safety, or welfare of subjects. UPIRSOs may cause harm to a person's physical, financial, legal, social, emotional or psychological well-being, or affect their privacy or confidentiality. All UPIRSOs are reported to the IRB within 5 calendar days of study staff's knowledge.

All SAEs and UPIRSOs must be recorded in OnCore for internal tracking purposes.

Investigator-Initiated Trials
Interventional IITs are additionally monitored internally by the DSMC. The DSMC requires that studies submit all unexpected grade 3 and all grades 4 and 5 adverse events for review. These must be recorded in OnCore. Grade 4 and 5 events require expedited reporting within 5 calendar days of study staff's knowledge. Any other events requiring expedited reporting as defined in the protocol should also be reported within 5 days. Hematological studies where a large number of grade 4 hematological events are expected may report these at scheduled monitoring rather than expedited. Studies may request exceptions to this policy from the DSMC.

8.0 Quality Assurance Review

The MCWCC performs internal quality assurance reviews on active trials. Reviews are performed by the CTO's Quality Assurance (QA) Manager and Coordinator. These staff members do not perform any trial-related duties and are thus independent of all the study teams under review. MCW investigator-initiated protocols are prioritized as these are not typically monitored by an external auditing mechanism. Internal monitoring ensures that trials are conducted and data are collected in compliance with the protocol, Good Clinical Practice, and regulatory guidelines.

The QA staff selects trials for directed and routine review. Directed reviews (i.e., "for cause") may be initiated per the request of the DSMC, IRB, Research Manager, PI, or administrative personnel. For routine reviews, investigator-initiated trials are categorized by risk at the discretion of the SRC, using the below criteria as a guide. All studies will have the initial QA review within the first 3 months of the first patient enrolled.

Low Risk: Non-treatment trials (e.g., nutritional or behavioral interventional, observational, lab sample, QoL)
Intermediate Risk: Treatment phase II or III and non-IND or non-IDE, lower risk multisite trials
High Risk: Phase I, IND, IDE, most multisite trials
Special Status: IND, IDE, cellular/gene therapy, first-in-human

QA Review Schedule and Content

Low Risk	Intermediate Risk	High Risk	Special Status
• Reviewed **every 2 years** • **10%** of subject files will be selected randomly for review (max 5 subjects at each monitoring timepoint). • **Consent/eligibility** and **objective-based data** will be reviewed for those files selected • **Regulatory** documents	• Reviewed **every year** • **20%** of subject files will be selected randomly for review (max 5 subjects at each monitoring timepoint). • **Consent/eligibility** and **objective-based data** will be reviewed for those files selected • **Regulatory** documents	• Reviewed **every 6 months** • **30%** of subject files will be selected randomly for review (max 5 subjects at each monitoring timepoint). • **Consent/eligibility** and **objective-based data** will be reviewed for those files selected • **Regulatory** documents	• Reviewed **every 3 months (may be more often with PI discretion)**. The first subject will be reviewed shortly after dosing. • **30%** of subject files will be selected randomly for review (max 5 subjects at each monitoring timepoint). • **Consent/eligibility** and **objective-based data** will be reviewed for those files selected • **Regulatory** documents

At the conclusion, QA staff meet with study team members to review the findings. During this meeting, the QA staff discuss key findings and make recommendations for quality improvement and education. Formal written QA reports are prepared for the PI and copied to the study team and DSMC. In the event that a review uncovers deficiencies, the study team is given time to respond, in writing, with a corrective action plan. Severe deficiencies or failure to respond to QA recommendations can be grounds for formal sanctions, including closure of the protocol until the deficiencies have been corrected.

The QA staff will coordinate their study review schedule with the DSMC's review schedule, ending routine reviews at the time that the DSMC determines that future reviews can be deferred.

Auditing
Investigator-initiated trials are chosen randomly to be audited externally by MCW's Office of Research Human Research Protections Program or by MCW's Clinical & Translational Science Institute, according to their own policies. However, directed audits may be requested at any time by the MCWCC CTO QA staff, DSMC, MCWCC administrative staff, or study team.

DSMC Review
The DSMC reviews both the internal quality assurance reports generated by the CTO QA staff, as well as the results of any external audits performed by MCW staff. Additionally, the DSMC reviews the results from external audits conducted by national sponsors (e.g., NCTN) on non-IITs.

Quality assurance reviews are utilized in a continuous process of quality improvement, and operating procedures are reformulated to address issues that appear to be generalized concerns rather than protocol-specific.

9.0 Multisite Management

The MCWCC CTO has established procedures for the management of MCWCC investigator-initiated trials open at external participating sites. For a detailed description of the procedures, please see the MCWCC CTO Multisite Management Plan. The following is an overview of the key aspects.

Responsibilities
For multi-institutional clinical trials, where the MCWCC acts as the coordinating center, the MCW PI is ultimately responsible for overseeing the management of the trial at each of the participating sites. The MCWCC CTO has developed the Multisite Program to assist in this responsibility, with a dedicated coordinator serving as the primary point of contact for communication with participating sites.

The Multisite Coordinator facilitates all aspects of participating site study activity, in collaboration with MCW faculty and staff. The coordinator is responsible for notifying participating sites of amendments and safety events, ensuring sites are capturing data appropriately, and facilitating the reporting of AEs to central review bodies.

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

Site Qualification and Activation
Participating sites are evaluated for level of interest, adequacy of resources to execute protocol requirements, and potential for accrual. After the MCWCC SRC and the IRB grant initial approval to a protocol, the onboarding of external participating sites can be initiated. Study conduct must not occur at a participating site

until MCWCC study staff issue a formal activation letter. This occurs after all required documents have been received, budgets/contracts have been approved, and required trainings have been completed.

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 Coordinator and MCW PI. MCWCC staff will periodically update participating sites on study progress and any ongoing questions or logistical concerns.

MCWCC uses OnCore, a Clinical Trial Management System, for collection and management of data from participating sites. Additional software resources such as RedCap may be used as well. Study coordinators utilize OnCore to track subject data on electronic case report forms, as well as report AEs, SAEs, and deviations.

As the coordinating site, MCWCC is responsible for ongoing monitoring of the participating sites. Routine monitoring may be performed onsite or remotely, and additional monitoring may be scheduled at MCWCC's discretion. Frequency and extent of monitoring is based on the protocol's level of risk, as detailed in the Multisite Management Plan. Quality assurance reports are shared with the study staff and the DSMC, with corrective action or additional training requested as needed. MCWCC's DSMC is the DSMC of record for MCW multisite IITs and reviews safety data from all sites. The DSMC performs scheduled monitoring at a frequency commensurate with risk.

AE Reporting

Please see Appendix E for the 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 monitoring 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 MCW PI and the Multisite Coordinator in an expedited manner. The MCW PI then reports events to the MCW/CHW IRB and DSMC as applicable. If the MCW PI determines that an SAE or other event meets the FDA definition of requiring reporting (i.e., unanticipated problem, requiring action), then the MCW 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.

MCW will report DSMC letters to participating sites if they meet the FDA definition of requiring reporting (i.e., unanticipated problem), it is required by the DSMC, or results in a significant finding/recommendation/action (e.g., change in study conduct, study closure, study hold). All DSMC reports can be sent to participating sites upon request (e.g., at time of local IRB continuing progress report).

10.0 NCI Notification of Study Suspension or Closure

All temporary suspensions or permanent closures of NCI-sponsored clinical trials (non-cooperative group) 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 staff, and DOT Chair will also be notified. When possible, the DSMC, SRC, and CTO will assist the PI with re-formulating the protocol to address the concerns. 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.

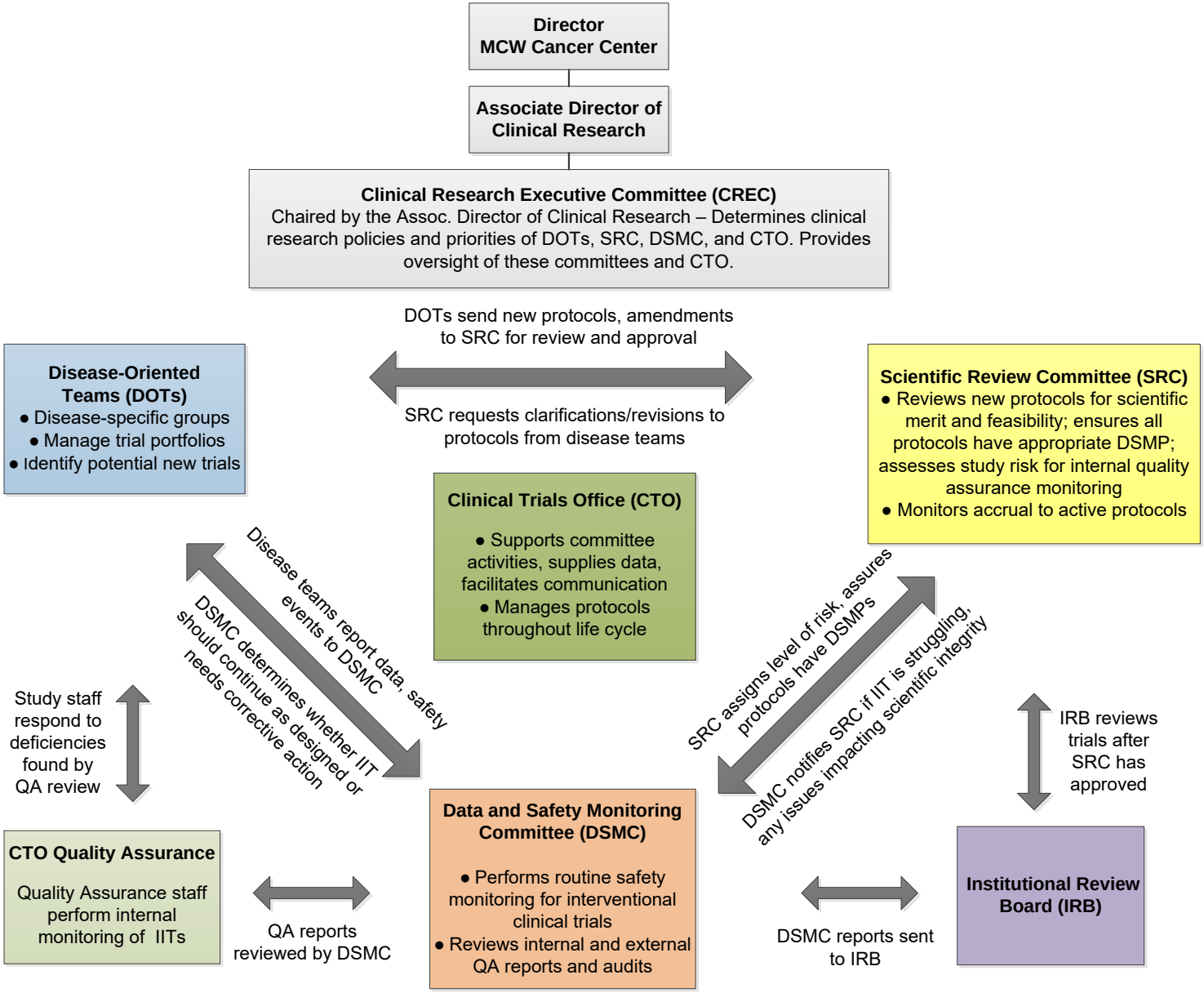
National Institutes of Health Policy for Data and Safety Monitoring dated June 10, 1998
http://grants.nih.gov/grants/guide/notice-files/not98-084.html
This is the basic NIH document that 1] states the policy that all clinical trials require data and safety monitoring, 2] spells out principles of monitoring 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
http://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 leaves much to one's imagination.

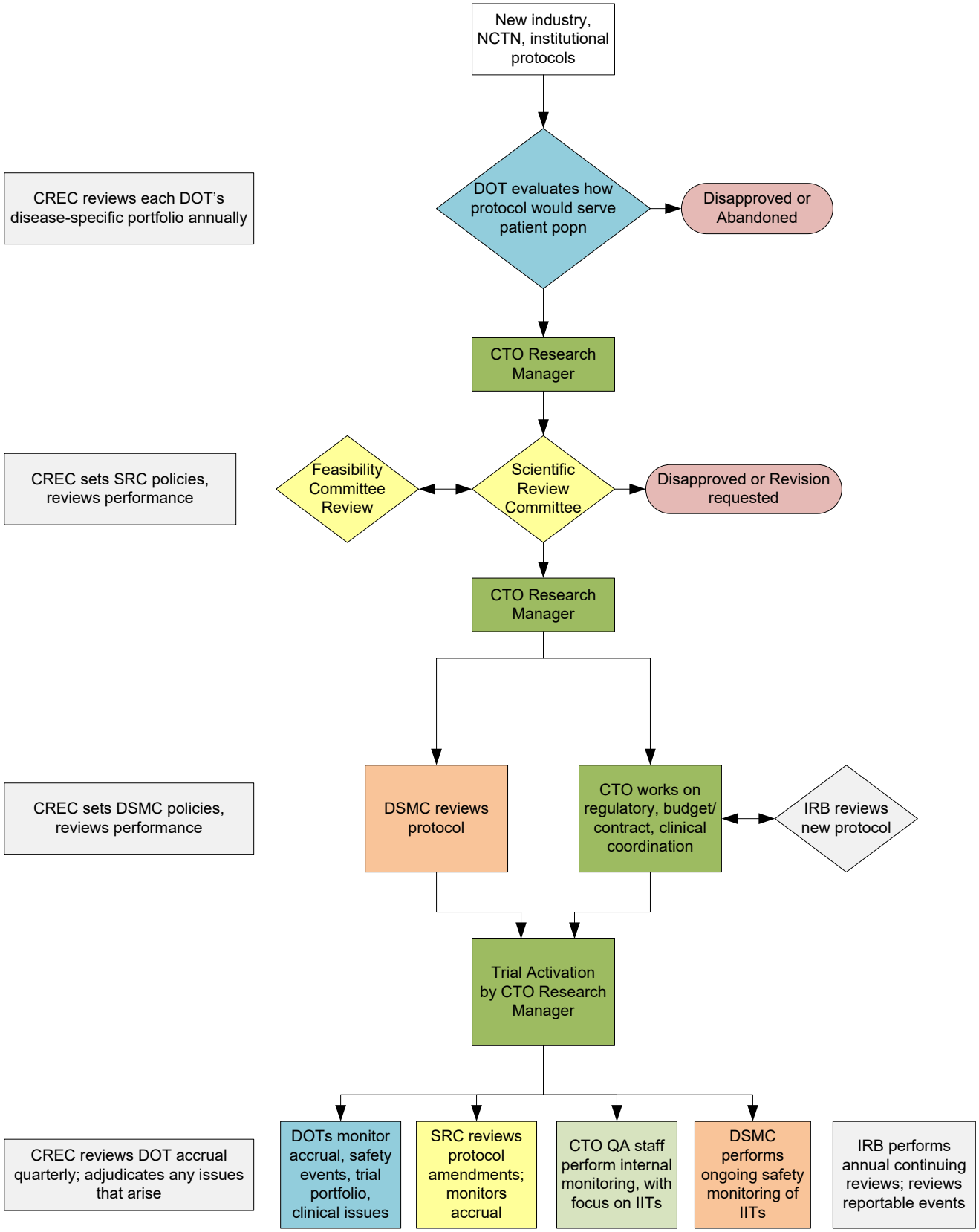
Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by the National Cancer Institute dated April 2001
http://cancertrials.nci.nih.gov/researchers/dsm/index.html
This document gives further guidance on the composition of institutional DSMPs and provides an operational definition of a clinical trial.

Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials dated June 11, 1999
http://grants.nih.gov/grants/guide/notice-files/NOT99-107.html

Appendix A. Committee relationships and responsibilities



Appendix B. Protocol Review Flow



Appendix C. Data and Safety Monitoring Plan by Trial Type

Trial Type	Monitoring
National Institutes of Health-Sponsored Trials	
National Clinical Trials Network	Monitored according to procedures specified by the particular cooperative group.
P01, R01, R21 grants	Identical to local, institutional trials
Industry-Sponsored Trials	
Industry-initiated	Require protocol-specific DSMPs that adhere to industry and FDA-specified guidelines
Investigator-initiated	Treated as local, institutional trial with additional reporting requirements as specified by sponsor and FDA
External Institution/Consortium Trials	
Independent external DSMB exists	Follow reporting requirements as outlined in protocol. May review external DSMB report.
No independent external DSMB exists	SRC may not approve trial to open at MCW if no external DSMB exists, depending on level of risk to patients. DSMC may review study as if it were a local IIT.
Local, Institution-Sponsored Trials	
Treatment, Phase I	DSMC monitors at least every 6 months and after completion of each cohort if dose-escalation component
Treatment, Phase II	DSMC monitors at least annually
Treatment, Phase III	Study-specific DSMB monitors at least every 6 months and reports summary to DSMC
Non-treatment Interventional	DSMC monitors at a frequency commensurate with level of risk to patients
Observational	SRC ensures protocol has appropriate DSMP. DSMC does not perform routine safety monitoring but does review any internal or external quality assurance reports.
Ancillary/Correlative	SRC ensures protocol has appropriate DSMP. DSMC does not perform routine safety monitoring but does review any internal or external quality assurance reports.
Multisite Trials – MCWCC is Coordinating Center	
DSMC reviews data and safety information for patients from all participating institutions. The Multisite Coordinator relays reportable events from all sites to the DSMC and communicates DSMC decisions to all participating institutions. The frequency of DSMC reviews is commensurate with level of risk to patients.	

Appendix D. 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 that will report to the MCWCC DSMC. Independent DSMBs are required for large, randomized Phase III trials, with an accrual goal of 300 or more patients, except for 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.

Establishing a DSMB

The DSMB must be set up prior to the activation of the trial. While DSMBs may vary in size and composition, at a minimum they require three clinicians experienced in the treatment modalities and disease under study, a clinical biostatistician, an individual with expertise in the regulatory aspects of clinical trials, and a layperson patient advocate. No members of a DSMB may be associated with the trial.

When a study needing a DSMB is reviewed by the SRC, the SRC must be sure a DSMB is established before approving. If the PI has not proposed a DSMB, the SRC Chair will determine whether or not a DSMB is required for adequate subject safety. If a DSMB is required, the SRC Chair will request the PI to indicate the proposed frequency of meetings for a DSMB; to submit a proposed list of data items to be provided to the DSMB; and to nominate a DSMB of no fewer than four persons [including such information on the nominated DSMB member as: CV, a list from each of the nominated DSMB members of their current affiliations with pharmaceutical and biotechnology companies including the name of the company and 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]. These nominations are submitted to the MCWCC ADCR, 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 to include scientific expertise in topic areas relevant to the trial such as biostatistics, ethics, or patient advocacy.

For studies with DSMBs, the SRC Chair will:

- Include in the protocol review process a condition stating that the PI cannot recruit participants until the SRC Chair approves the protocol based on recommendations of the DSMB.
- As needed, request that the DSMB provide advice to the study PI on trial protocol and safety issues arising over the course of the study, and continuation or termination of the study.
- Facilitate implementation of DSMB recommendations by the MCWCC

DSMB Responsibilities

Once a DSMB is established, its initial tasks are to review the entire study protocol, the study manual of procedures, and the informed consent form with regard to recruitment, randomization, intervention, subject safety, data management, plans for auditing 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 the need for modifications to the protocol, manual of procedures, consent form, etc., 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.

According to NIH policy, all protocol DSMPs must be reviewed and approved by an IRB.

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 the proposed research protocol, informed consent documents, plans for data management, and plans for data and safety monitoring prior to the initiation of the trial.
- 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. Inform 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 auditing system or other sources.
- Ensure confidentiality of data and results of analyses for monitoring purposes.
- Review manuscripts of trial results prior to submission for publication. (The ADCR may require that DSMB approval of the manuscript be obtained before submission.)

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).

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 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.

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 without modification, (2) to continue the trial following amendment, or (3) to terminate the trial based on safety or attainment of specified interim analysis goals. The recommendation should be made by formal majority vote. In the event of a split vote in favor of continuation, a minority report should be contained within the regular DSMB report. The report should not include unblinded data or a discussion of unblinded data.

A written copy of DSMB recommendations will be forwarded to the trial principal investigator, 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 principal investigator must act to implement the change as expeditiously as possible. In the unlikely situation that the trial principal investigator 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 Clinical Research Executive Committee 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 elects to temporarily suspend or permanently terminate enrollment of patients, the principal investigator of the trial, MCWCC ADCR, DSMC Chair, IRB, and the study sponsor will be notified within 24 hours of such action.

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 this time, the DSMB may approve the release of outcome data on a confidential basis to the trial principal investigator 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 DSMBs recommendation for general dissemination of results must be reviewed and approved by the DSMB.

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 are accepted and implemented. Each member of the DSMB, including non-voting members, must sign a statement of confidentiality.

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 principal investigator 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 as described in the NIH Grants Policy Statement, Page II-12, and 45 CFR Part 94. Potential conflicts which 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.

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 Principal Investigator, the Chair of the DSMB, the MCWCC ADCR, and the MCWCC 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 audit reports. Auditors so engaged will report directly to the DSMC Chair.

Appendix E. 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.