Medical College of Wisconsin
Cancer Center

Data and Safety Monitoring Plan

April 16, 2012
Data and Safety Monitoring Plan

Ensuring Patient Safety and Clinical Research Integrity

Summary

The Medical College of Wisconsin Cancer Center places the highest priority on ensuring the safety of patients participating in clinical trials. Every cancer interventional trial conducted at MCW must include a plan for safety and data monitoring. Specific plans may vary based on the degree of risk involved in participation and the size and complexity of the clinical trial. The development of protocol monitoring plans and reporting requirements are dependent upon the study sponsor, nature of the investigational agent, and phase of trial. By NIH definition, clinical trials are prospective studies involving human subjects designed to evaluate the effect of biomedical or behavioral interventions.

The MCW Associate Director for Clinical Research is responsible for the data and safety monitoring, relying on the independent Data and Safety Monitoring Committee (DSMC) to review data and safety monitoring reports.

Clinical trials sponsored by the NCI Cooperative Group Program [ECOG, CALGB, GOG, NSABP, CCG, ACOSOG, RTOG, and SWOG] will be monitored by long-standing and established systems for cooperative group data submission, reporting, review, and monitoring. Phase I/II studies sponsored by NCI/CTEP will be monitored by the principal investigator with required reporting to NCI/CTEP using the Clinical Trials Monitoring Service [CTMS], the Clinical Data Update System [CDUS], and/or the Adverse Event Expedited Reporting System [AdEERS].

All local, investigator-initiated clinical trials will be required to have specific data and safety monitoring plans based on the size and complexity of each trial and the potential risk to patients. Protocol specific DSM plans will be approved by both the DSMC and the MCW Institutional Review Board (IRB). Local, investigator-initiated trials will be required to be continuously monitored by the principal investigator of the study with biannual safety and progress reports submitted to the DSMC. The DSMC may require more frequent reporting for early Phase I studies of agents posing higher risks to patients. Local, investigator-initiated randomized Phase III clinical trials will be monitored in a manner and scheduled determined by protocol-specific data and safety monitoring boards [DSMB]. Formal DSMBs will 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.

All data and safety monitoring reports for local, investigator-initiated studies will include the number of patients entered, number of patients treated, dose level of agent[s] involved, summary of all adverse events reported to date using standardized grading, a specific list of all serious adverse events [SAEs]. Data safety and 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. All serious adverse events experienced by patients will be reported to the DSMC, Clinical Trials Office, the MCW IRB, and the study sponsor. 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 MCW CCC Director, the MCW Associate Director for Clinical
Research, the MCW IRB, and the study sponsor [to include the NIH project officer, the Department of the Army, pharmaceutical industry sponsors, and other external sponsors] will be notified within 24 hours of such action.

The MCW DSMC will additionally submit an annual report to the Associate Director for Clinical Research on activities of the past year and make recommendations to improve data and safety monitoring activities.
Abbreviations

The Data and Safety Monitoring Plan is littered with cryptic abbreviations for agencies, offices, committees, and reports. While initial references are provided, the following list may assist the reader.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ADCR</td>
<td>The MCW Cancer Center Associate Director for Clinical Research; has responsibility for coordinating all clinical research activities of the CCC and overseeing data and safety monitoring.</td>
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<td>AdEERS</td>
<td>Adverse Event Expedited Reporting System: NCI system designed for reporting and tracking of adverse events on trials incorporating NCI-supplied investigational agents.</td>
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<td>AE</td>
<td>Adverse Event.</td>
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<tr>
<td>CDUS</td>
<td>Clinical Data Update System: NCI-sponsored clinical data management system for late phase I and phase II protocols – collects summary data.</td>
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<td>CSRC</td>
<td>Clinical Scientific Review Committee: MCW CC committee with Protocol Review and Monitoring System responsibilities.</td>
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<td>CTCAE</td>
<td>Common Terminology Criteria for Adverse Events: the NIH/NCI standard system for grading the severity of adverse events – usually a version number is appended.</td>
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<td>CTC</td>
<td>Common Toxicity Criteria: the initial system developed by the NIH/NCI to grade adverse events – supplanted by CTCAE [above].</td>
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<td>CTEP</td>
<td>Clinical Trial Evaluation Program: NCI branch evaluating new investigational agents.</td>
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<td>CTO</td>
<td>Clinical Trials Office: a shared resource of the MCW Cancer Center.</td>
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<td>DSM</td>
<td>Data and safety monitoring.</td>
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<td>DSMB</td>
<td>Data and Safety Monitoring Board: An independent monitoring body established to oversee patient safety on clinical trials.</td>
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<td>DSMC</td>
<td>Data and Safety Monitoring Committee: The MCW Cancer Center committee with primary data and safety monitoring oversight responsibility for the Center.</td>
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<td>DSMP</td>
<td>Data and Safety Monitoring Plan: plans may be institutional or protocol-specific.</td>
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<tr>
<td>FMLH</td>
<td>Froedtert Memorial Lutheran Hospital.</td>
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<td>FDA</td>
<td>US Food and Drug Administration.</td>
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<td>IC</td>
<td>Institute Center: an NIH reference to a specific NIH institute clinical center.</td>
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<td>IDB</td>
<td>Investigational Drug Branch: an NCI unit within the Division of Cancer Treatment and Diagnosis.</td>
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<td>IND</td>
<td>Investigational New Drug.</td>
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<td>IRB</td>
<td>Institutional Review Board.</td>
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<td>MCW</td>
<td>Medical College of Wisconsin.</td>
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<td>NCI</td>
<td>National Cancer Institute.</td>
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<td>NIH</td>
<td>National Institutes of Health.</td>
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<td>Abbreviation</td>
<td>Description</td>
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<td>PI</td>
<td>Principal Investigator</td>
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<td>PRMS</td>
<td>Protocol Review and Monitoring System: NCI mandated system for scientific review of clinical trials and to oversee trial conduct</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
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MCW Cancer Center Data and Safety Monitoring Plan

1.0 Introduction

The Medical College of Wisconsin Cancer Center places the highest priority on ensuring the safety of patients participating in clinical trials. Every cancer interventional trial conducted at MCW must include a plan for safety and data monitoring. The extent of data and safety monitoring [DSM] 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 clinical research programs of the MCW Cancer Center form a mixture of trials ranging from early single agent phase I dose finding trials to large scale, multi-institutional randomized phase III studies. At any given time, over 100 active therapeutic interventional protocols are underway to include phase I trials, phase II studies, randomized phase III trials, trials of chemopreventive agents, and trials of behavioral interventions to reduce cancer risk. Studies consist of national cooperative group trials, NCI/CTEP-sponsored local trials, limited multicenter trials, institutional investigator-initiated trials, and pharmaceutical industry trials.


2.0 Definition of a Clinical Trial

This DSM Plan applies to the conduct of all MCW CC clinical trials in cancer encompassing a wide range of therapeutic modalities – all directed towards evaluating a form of intervention. The NCI operational definition of a clinical trial is “a prospective study involving human subjects designed to answer specific questions about the effects or impact of particular biomedical or behavioral interventions; these may include drugs, treatments, devices, or behavioral or nutritional strategies. Participants in these trials may be patients with cancer or people without a diagnosis of cancer but at risk for it.”

Some studies do not meet the operational definition of a clinical trial and, while DSM may be necessary, do not fall under the aegis of this plan. From the NCI’s April 2001 policy definition [see references]:

“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.”

The key concept in the definition of a clinical trial is that of an intervention affecting an outcome.

3.0 MCW Cancer Center Organization and Administration

The Associate Director for Clinical Research has the overall responsibility for data and safety monitoring of clinical trials conducted under the auspices of the MCW CC. 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 MCW CC to protect the safety of participating patients and scientific integrity of the trial.

The ADCR is assisted by a 6-8-member Data and Safety Monitoring Committee to provide advice on matters of DSM and, following review of protocol-specific DSM reports, to provide recommendations on trial continuation, suspension or termination. The ADCR appoints the Chair and all members of the Data and Safety Monitoring Committee [DSMC] to two-year terms of office. Should any DSMC member be unable to complete their term, the ASCR 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 CCC Director.

4.0 Data and Safety Monitoring Committee

Description

The Data and Safety Monitoring Committee [DSMC] plays a vital role in protecting patients participating in MCW CC local investigator-initiated trials from unnecessary risks. The DSMC was established in the summer of 2011 to provide DSM oversight for local MCW CC trials with policies specified in the revised Data and Safety Monitoring Plan. The new NCI guidelines state that data and safety monitoring functions “should not be the direct responsibility of the same Protocol Review and Monitoring System (PRMS) that oversees scientific aspects of cancer clinical trials”, calling for the
separation of these functions and the establishment of an independent committee to monitor the data and safety of patients on cancer clinical trials.

In 2012, the MCW CC appointed Bruce Camitta, M.D., as chair of the new committee. The DSMC operates in collaboration with and receives administrative support from the MCW CC Clinical Trials Office [CTO].

The DSMC meets monthly to review data and safety reports submitted for local, investigator-initiated cancer clinical trials conducted at the MCW CC.

**Specific Aims**

Specific aims of the DSMC in support of its goal of monitoring data and safety:

- to review all DSM reports required for local, investigator-initiated [institutional] cancer clinical trials involving human subjects,
- to establish clear criteria for determining whether ongoing clinical trials are safe in terms of the risks to participating patients and subjects,
- to monitor and make recommendations of trial continuation, suspension, or termination to the ADCR on all cancer-related institutional clinical trials at the MCW CC based on safety criteria,
- to recommend informed consent form modification related to the risks of adverse events to the study principal investigator[s], and
- to recommend DSM policies related to clinical trial data and safety monitoring to the MCW CC leadership.

**DSMC Membership**

The criteria for membership on the four-six member DSMC 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, research coordinators/nurses, regulatory staff, and/or patient advocates. Members may be either internal MCW CC members or external members. The chair and all members of the DSMC are appointed by the MCW CC Associate Director for Clinical Research to two-year terms with an optional two-year renewal.

**Clinical Trials Requiring Review by DSMC**

All clinical trials require data and safety monitoring [DSM]. The operational definition of a ‘clinical trial’ from the NCI and the MCW CC DSM Plan is “a prospective study involving human subjects designed to answer specific questions about the effects or impact of particular biomedical or...
behavioral interventions; these may include drugs, treatments, devices, or behavioral or nutritional strategies. Participants in these trials may be patients with cancer or people without a diagnosis of cancer but at risk for it.” 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. The key concept in the definition of a clinical trial requiring data and safety monitoring is that of an intervention affecting an outcome.

All local investigator-initiated, cancer-related pilot and phase I/II clinical trials approved for conduct at the MCW CC by the Clinical Scientific Review Committee [CSRC] and MCW Institutional Review Board [Cancer IRB] must undergo DSM by the DSMC. These protocols include trials with no external support relying on MCW support only, trials with limited industry support [i.e., supply of agent(s) only], trials receiving external funding through the NIH or other accepted peer review agency without specified DSM, and phase I/II trials conducted in a limited institution setting with a MCW investigator as the principal investigator of the study and the MCW serving as lead institution.

Trials conducted under the sponsorship of the NIH/NCI National Cooperative Groups Program have well-defined and functional DSMB’s to provide appropriate DSM and will not be locally monitored. Likewise, trials conducted as part of the MCW’s Phase II N01 contract (through University of Chicago) and other trials with NCI/CTEP-sponsorship 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.

Trials sponsored by the pharmaceutical industry with little or no local investigator involvement in study design will be evaluated by the CSRC and MCW IRB to insure that an appropriate DSM plan is in place for the trial. If such a plan exists, no monitoring will be conducted by the DSMC. If a DSM plan does not exist, it must be developed by the sponsor and approved prior to study initiation. In no case will any trial lacking a DSM plan be allowed to be conducted.

As specified in the MCW CC DSM Plan, local, investigator-initiated phase III trials require the establishment of an independent DSM Board. The DSMB has the responsibility for DSM for these trials rather than the DSMC. All reports generated by a separate DSMB must be submitted to the MCW CC DSMC as well as to the IRB.

The MCW CC ADCR acts on recommendations from the DSMC and issues a memo of concurrence or nonconcurrency with the DSMC. If the action is one of trial continuation, the notice of continuation will be sent to the trial investigator via email with a copy to the DSMC and CTO.
In the event that the ADCR concurs with the recommendation of the DSMC to suspend or terminate enrollment and/or treatment of patients on a clinical trial, the ADCR will communicate that action to the investigator, the IRB, and the sponsor of the study to include the NIH/NCI Project Officer should the trial be funded wholly or in part by an NIH grant or contract.

**MCW CC Clinical Scientific Review Committee**

The MCW CC Clinical Scientific Review Committee [CSRC] plays a vital role of protocol review and monitoring to assure that clinical trials are scientifically sound and that approved studies maintain adequate patient accrual and scientific progress. The CSRC is the body responsible for meeting the future NCI requirement for a Protocol Review and Monitoring System [PRMS]. The CSRC conducts a full scientific review of all studies that have not received peer review by NIH-supported review bodies [NCI/CTEP/cooperative group]. The CSRC fully reviews all 1] local, investigator-initiated studies, 2] pharmaceutical industry-sponsored trials, and 3] limited institutional trials that have not undergone NIH-recognized peer review.

The CSRC reviews and approves protocol-specific data and safety monitoring plans as part of the review process for cancer-related local investigator-initiated therapeutic interventional trials prior to protocol review by the MCW IRB. The CSRC insures that the trial includes an appropriately detailed plan and that sufficient resources are available for its implementation. The CSRC will rely on the assistance of the Clinical Trials Office in this task, particularly as related to resource review. No study will receive CSRC approval without a data and safety monitoring plan.

**MCW Cancer Clinical Trials Office**

The MCW CC Clinical Trials Office [CTO] provides administrative assistance and support to the DSMC. As part of this assistance, the CTO:

- assists investigators in providing for appropriate data and safety monitoring for clinical trials by supplying DSM language during protocol preparation,
- provides investigators with templates for required protocol-specific DSM reports,
- collects, distributes, and maintains required DSM reports from all studies requiring local DSM,
- organizes and coordinates monthly meetings of the DSMC,
- participates in all meetings of the DSMC to provide information, facilitate communication, and take minutes, and
- facilitates communication between the DSMC Chair, the ADCR, and the IRB.
• Audits investigators initiated trials and supplies the audit report to the DSMC.

The primary role of the CTO in DSM is that of collecting DSM reports from study principal investigators of local, investigator-initiated trials and distributing them to members of the DSMC. Templates for DSM reports are included as appendices to this plan.
Investigator Responsibilities and Requirements

The principal investigator [PI] of each study is ultimately responsible for every aspect of the design, conduct, and final analysis of their protocol. The study PI is responsible to insure that:

- All protocols include a data and safety monitoring plan [DSMP] and procedures for its implementation.

- A data and safety monitoring board [DSMB] is established if the proposed study meets any of the following criteria:
  a. The trial is a randomized, Phase III clinical trial.
  b. The trial is a multi-site clinical trial.
  c. The trial includes a high risk intervention.
  d. The trial employs gene therapy.
  e. The trial proposes to include over one hundred participants.

Note: PIs for studies that do not meet the above criteria for having a DSMB may still propose to have a DSMB if they feel it would be useful for their study.

- All studies 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 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 proposed schedule should include a system for sending DSMB reports regarding safety issues [see section "Requirements of Data and Safety Monitoring Boards"] to the study Principal Investigator [PI]. In multi-site studies, the study PI is responsible for sending these DSMB reports to individual site PIs, who in turn are required to distribute these reports to their local IRBs.

- The MCW CC CTO and DSMC are informed of actions, if any, taken by the IRB as a result of its continuing review.

- All masked studies should describe a randomization scheme, and specific criteria and procedures for unmasking. If a DSMB is not proposed, the application should also designate individuals with access to unmasked data.

- If the PI believes that an independent DSMB is required for adequate subject safety, the protocol should indicate the proposed frequency of meetings for the DSMB, and include a proposed list of data items to be provided to the DSMB and estimates for DSMB-related expenses in the proposed protocol budget. The PI should nominate prospective DSMB members, 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 forwarded to the MCW CC Associate Director for Clinical Research who formally appoints each DSMB member. [DSMB members should have no direct involvement with the study or conflict of interest with investigators conducting the study.] If the PI has not proposed a DSMB, but prior to activation of the proposed project the DSMC Chair believes an independent DSMB is required, the PI will make arrangements for a DSMB as described in the section pertaining to phase III trials.

- If the proposed protocol has additional clinical sites besides that of the MCW CC, the protocol should describe procedures by which the PI will notify sites of any problems as identified by the DSMB if one is established.

- In specific cases where an outside agency [i.e., National Institutes of Health, Department of the Army, pharmaceutical industry sponsors] 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.


**Clinical Trial Monitoring**

The extent of the monitoring and reporting period 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.

Given the great diversity of clinical trials underway at the MCW CC, trial data and safety monitoring, by necessity, reflects that diversity. Our Center’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. Trial sponsors include the National Institutes of Health, pharmaceutical industries, and local investigator-initiated trials with limited external funding.

**National Cooperative Oncology Group Contracts**

The MCW CC conducts clinical trials of the Eastern Cooperative Oncology Group ECOG), Cancer and Leukemia Group B [CALGB], the Gynecologic Oncology Group [GOG], the National Surgical Adjuvant Breast/Colorectal Program [NSABP], the American College of Surgeons Oncology Group
[ACOSOG], the Radiation Therapy Oncology Group [RTOG], the Southwest Oncology Group [SWOG], the AIDS Malignancy Consortium [AMC], and the Children’s Oncology Group [COG].

Each of these national groups conducts a range of therapeutic [phase I, II, and III] and non-therapeutic clinical trials. Each contract with the principal investigator [clearly specifies the data and safety monitoring requirements for each study. Since these trials are multi-institutional, specific data management systems using a variety of computer and communications technology allow safety and efficacy data to be closely monitored for each study by site and for the group as a whole often by a groupwide DSMB. We will not place additional reporting requirements on staff supporting these trials, but will rely on mandated reporting mechanisms to monitor patients on these studies.

Nevertheless, all SAEs from all trials are required to be reported to the CTO, DSMC and IRB. The MCW 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.

**Pharmaceutical Sponsored Trials**

All clinical trials conceived and initiated by pharmaceutical industry sponsors with subsequent MCW CC participation will require data and safety monitoring plans that have been reviewed and approved by both the CSRC and MCW IRB. These protocol-specific plans will adhere to industry and FDA-specified guidelines and as a minimum clearly specify reporting for serious adverse events [SAE] and unexpected adverse events. 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. No pharmaceutical industry sponsored trials will be activated without an approved data and safety monitoring plan.

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. Investigators are reminded that the administration and conduct of such trials requires appropriate support. Investigators should contact the CTO to insure that adequate funding is requested to support data and safety monitoring.

**Local, Investigator Initiated Trials**

All local investigator-initiated, cancer-related pilot and phase I/II clinical trials approved for conduct at the MCW CC by the Clinical Scientific Review Committee [CSRC] and IRB must undergo DSM by the DSMC. These protocols include:

- trials with no external support relying on MCW support only [often Protocol Specific Research Support],
• trials with limited industry support [i.e., supply of agent(s) only],
• 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], and
• phase I/II trials conducted in a limited institution setting with a MCW CC investigator as the principal investigator of the study and the MCW CC serving as lead institution.  
Since these trials have no external requirements for data and safety monitoring, they require particular attention for local monitoring. These studies receive the highest priority for local oversight. The study PI of a local, investigator-initiated trial will be required to develop a local data and safety monitoring plan that adheres to the following plans based on the phase of trial.

**Phase III Trials**

Commensurate with risk, all local phase III clinical trials require the establishment of an independent Data and Safety Monitoring Board [DSMB].

As previously noted, 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.

Exception: Large phase III behavioral or nutritional trials posing little or minimal risk to participants while required to have a DSM plan are not required to establish a DSMB, but 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.

Independent DSMBs must be established prior to the initiation 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.

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 CSRC is required to review and approve data and safety monitoring plans and verify the existence of an appropriate DSMB prior to activating 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 Institutional Review Boards (IRBs). DHHS regulations for the protection of human subjects are described in 45 CFR46. The implementation of these regulations for PHS research grants involving human subjects is found in the PHS 398 form (rev. 4/98), available on the NIH home page (http://www.nih.gov/grants/forms.htm).

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 MCW CC may find it beneficial to have additional levels of involvement or oversight beyond those described in these policies.

Therapeutic protocols should state (on the IRB submission form) whether the proposed study intervention could have harmful effects, and the basis for that opinion. After the MCW Institutional Review Board’s [IRB] review and approval, the MCW CC Clinical Scientific Review Committee [CSRC] 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 CSRC will not activate the protocol until this information is received, reviewed, and approved. The CSRC may obtain additional consultation from MCW staff or external advisors.

In addition to the reports generated as a result of DSMB analyses, to include formal interim analysis, the study PI is required to submit annual reports to the CSRC Executive Committee on the anniversary date of the original IRB approval of the trial. This annual report will include the number of patients entered on the trial, the number of patients treated, a summary of all adverse events reported to date using CTCAEv3 grading, a specific list of serious adverse events requiring immediate reporting, and significant literature reporting developments that may affect the safety of participants or the ethics of the study.

Protocols for any intervention 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. The CSRC Chair will review this information. If the protocol deemed by the CSRC to be a Phase III trial does not include the required information for such studies [described below], the protocol will not be approved and activated until this information is received and reviewed by the CSRC Chair.

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 as listed below.
- 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 CSRC 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 CSRC, the PI should prepare a manual of procedures for review and approval by the DSMB and CSRC Chair, prior to implementation of the trial.

If a study is approved by the CSRC on scientific grounds and the PI has not proposed a DSMB, the CSRC Chair will determine whether or not a DSMB is required for adequate subject safety.
DSMB is required, the CSRC 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 less 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 MCW CC Associate Director for Clinical Research, who formally appoints each DSMB member. If appropriate, PIs should also submit a proposed budget for travel and administrative expenses for the DSMB. The CSRC 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.

5.4.5  **Phase III CSRC and DSMC Responsibilities**

For phase III studies with DSMBs, the CSRC Chair will:

- Include in the protocol review process a condition stating that the PI cannot recruit participants until the CSRC 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 MCW CC

For phase III studies with DSMBs, 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 MCW CC Associate Director for Clinical Research, and the MCW CC 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.

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. Observational studies and those that do not test interventions are not clinical trials.

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 CSRC Chair, the DSMB shall postpone its recommendation for the initiation of subject recruitment until after the receipt of a satisfactory revised protocol.
Data and Safety Monitoring Operations

After a clinical trial and its association DSM plan is approved by both the MCW CC CSRC and MCW IRB and opened for patient enrollment, data and safety monitoring is initiated. The frequency of monitoring and report submission is based on the nature of the trial and the potential risks to participants as noted in section 5.

The DSMC Chair conducts a preliminary review of each DSM report to ensure that it adheres to the specified report format and that data are complete. If major deficiencies are noted, the DSMC Chair will defer review and notify the investigator with specific report deficiencies that are required to be addressed before the DSMC will review the report. Delay in submitting and amending a deficient report may serve as the basis for the DSMC recommending trial suspension or closure to the MCW Associate Director for Clinical Research.

DSMC Meetings and Recommendations

Monthly DSMC meetings may be held either in person, face-to-face format or by teleconference following receipt of DSM reports by committee members. Four members must be present to attain a quorum. In either meeting or teleconference format, the Office Administrative Associate or CTO staff member will be present to take official minutes and record committee deliberations and formal motions on each trial reviewed.

While all committee members have a responsibility to read and be able to discuss all submitted DSM reports, two members will be assigned as primary reviewers for each protocol and will lead the discussion of that trial. After a full discussion of the trial 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 for a recommendation with an even number of members voting, the tie will be referred to the Associate Director for Clinical Research who will cast the deciding vote. Potential motions include recommendations for:

1. Study continuation; no changes required
2. Study continuation with stipulations to be formally addressed and approved by the DSMC Chair
3. Study suspension with stipulations to be formally addressed and approved by the full DSMC prior to study resumption
4. Study termination

Committee members are required to identify potential conflicts of interest prior to voting. If a conflict of interest exists, either actual or by appearance, the DSMC member is required to abstain from voting. Obvious conflicts include participation in the trial under review as principal or co-investigator or serving as a principal investigator of a grant supporting a given 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 DSM for a specific protocol will be made in accordance with institutional policies.

Following the DSMC meeting, recommendations on each trial report reviewed are forwarded within two days to the MCW CC Associate Director for Clinical Research [ADCR]. Based on the DSMC recommendations, the ADCR either concurs or does not concur with the DSMC. If the ADCR concurs with the DSMC, the decision will be communicated in writing and by email to the principal investigator within one week. A copy of the decision will be filed in the CTO protocol file. If the ADCR does not concur with the DSMC recommendation, they will attempt to resolve the issue with the DSMC Chair. Should the DSMC and the ADCR fail to reach concurrence within one month of the original DSMC review date, a final decision will be made by the MCW CC Director.

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 MCW CC Director. In the event of a conflict of interest between the ADCR and the Chair of the IRB, i.e., they serve as co-investigators of a study or the same person fills both roles, Cancer IRB decisions will be made by the Senior Associate Dean for Research.

If the report review decision includes stipulations, the PI must provide a written response within two weeks addressing all stipulations. Stipulations may be addressed by protocol modification or by providing evidence to justify not modifying the study in response to the stipulation. The ADCR, with the assistance of the DSMC Chair, evaluates the PI’s response to stipulations and votes a final action on the trial.

The accrual and treatment of patients on trials with DSM reports delinquent by more than one month from the required submission date will be suspended until the report is submitted and receives a recommendation of continuation from the DSMC.

If a protocol has been suspended or terminated, the ADCR will notify the principal investigator, the IRB, and the trial sponsor to include the NIH/NCI Project Officer. The DSMC Chair and the CTO will assist the PI with re-formulating the protocol addressing the safety concerns for subsequent review by the DSMC with a recommendation to the ADCR for approval of trial continuation. At the time such approval is granted, the ADCR will notify the IRB and the trial sponsor of the decision to authorize trial resumption.
Data and Safety Monitoring Report Formats

Listings of the specific data items required in each section of the report are noted in Table 1 and can be reviewed in the DSM report templates included in the Appendices. For all trials, the DSM report includes standard demographic data describing the patient population.

Table 1. Information Included in DSM Report Templates

| Section 1: Protocol Administration | Number, title, PI  
|                                  | Dates of IRB approval and activation  
|                                  | Listing of agents, dose level, route, schedule  
| Section 2: Demographics          | Number of pts enrolled, M/F, ages, diagnoses, prior treatment, performance status, disease status  
| Section 3-I: Phase I by Dose Level | Dose, number of pts, number of courses  
|                                  | Adverse event table with frequency and severity  
|                                  | DLT’s observed, SAE’s encountered  
|                                  | Dose escalation performed  
| Section 3-II: Phase II [per arm]  | Dose, number of pts, number of courses  
|                                  | Adverse event table with frequency and severity  
|                                  | DLT’s observed, SAE’s encountered  
|                                  | Efficacy parameters: RECIST response, and biomarkers  
|                                  | Multi-stage study decisions  
| Section 4: SAE’s                 | All SAE reports  
| Section 5: Patient Listing       | Date enrolled, dose level, # courses, maximum AE severity, DLT observed, SAE seen, overall response [phase II], status [Note: no HIPAA-defined protected health information will be included; patients will be identified by a sequential number (1, 2, 3,...) reflecting the sequence of their enrollment]  

For all studies, the DSM report requires a listing of all patients enrolled on the trial with a notation of their overall outcome and status. These data include starting date, dose level, number of courses received, maximum grade of AE, presence/absence of DLT’s or SAE’s, and current status.
Presently, reports will prepared by and submitted in hard copy form signed by the principal investigator. Future plans for CTMS will allow for electronic submission of DSM reports by the investigator.
Data and Safety Monitoring Boards

As previously specified, formal DSMBs are required for large, randomized phase III trials and other studies posing an unusually high risk to larger numbers of patients.

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.

DSMB Responsibilities

The DSMB must meet on a regular schedule [not less than twice a year] over the course of study [with additional meetings as needed] 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, trials 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. If the ADCR requests this advice, it should be provided by the DSMB in writing within two weeks of the date of the request.
• 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).

8.2 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.

8.3 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 will 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 recommendation(s) 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. The trial principal investigator, DSMB Chair, and the DSMC Chair will be responsible for reaching a mutually acceptable decision about the study. 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 mutually acceptable 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, the MCW CC ADCR, the MCW IRB, and the study sponsor [to include NIH, Department of the Army, pharmaceutical industry sponsors, and other external sponsors of all or part of the study] will be notified within 24 hours of such action.

8.4 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.

8.5 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.

8.6 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 officials(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.
IRB Review and Approval of Data and Safety Monitoring Plans

According to NIH policy, the MCW CC Data and Safety Monitoring Plan and individual protocol data and safety monitoring plans require MCW IRB review and approval.
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  
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  
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  
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  
NCI Essential Elements of a Data and Safety Monitoring Plan

http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1

Essential Elements of a Data Safety and Monitoring Plan for Clinical Trials Funded by the NCI

This document outlines the essential elements of an adequate plan for data and safety monitoring (DSM) of clinical trials. It is intended to assist investigators and institutions in the formulation of DSM plans for all phases of cancer clinical trials, in accordance with National Institutes of Health (NIH) requirements. We suggest that institutions sponsoring a significant number of clinical trials formulate institutional DSM plans that can be broadly applied to the individual trials in their portfolio. Investigators from institutions or organizations without institutional DSM policies may also find this document useful as a guide in fashioning suitable DSM plans for their individual trials.

To get an idea of what a final DSM plan might consist of, see Data and Safety Monitoring Example Plans.

Background

NIH policy (http://grants.nih.gov/grants/guide/notice-files/not98-084.html) with additional description at http://grants.nih.gov/grants/guide/notices-files/NOT-OD-00-038.html requires that grantees have in place procedures for DSM of clinical trials. This is to insure the safety of participants, the validity of data, and the appropriate termination of studies for which significant benefits or risks have been uncovered or when it appears that the trial cannot be concluded successfully. The NIH DSM policy covers clinical trials of all phases for which grant support is sought. DSM plans must be in place before grants supporting such studies can be funded. Applicants must submit a general description of the DSM plan for peer review as part of the grant application and, subsequently, a more detailed plan for review and approval by NCI staff prior to issuing a Notice of Grant Award.

Operational Definition of a Clinical Trial

For purposes of this document, we define a clinical trial operationally as 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.

DATA AND SAFETY MONITORING PLAN
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.

Requirements for a DSMB

For some time now NCI policy has required that Data Safety Monitoring Boards (DSMB) be in place for all Phase III randomized clinical trials (http://deainfo.nci.nih.gov/grantspolicies/datasafety.htm). The present document modifies this policy, in that there is no longer a blanket requirement for DSMB in the cases of low-risk behavioral and nutritional trials. As discussed further below, all such trials should include a DSM plan, but this may or may not include a DSMB, depending chiefly on the anticipated level of risk to participants.

Nor does NIH or NCI policy require that formal DSMB's be constituted for clinical trials other than Phase III, though investigators or institutions may wish to do so for certain non-Phase III trials involving particular risk, complexity, likely decisions about early stopping, or the need to obviate conflict of interest.

The Role of Institutional DSM Plans

Cancer clinical trials funded by the NCI are conducted in thousands of institutions nationwide. Many of these institutions -- notably the comprehensive and clinical cancer centers -- have particularly intensive clinical research portfolios that include dozens or hundreds of trials. It makes sense for such institutions to have in place institutional plans for an effective DSM process. An effectively formulated and executed institutional plan should improve both participant protection and trials conduct and should greatly reduce the need to set up new policies ad hoc on a trial-by-trial basis. For most investigator-initiated grant applications supporting clinical trials in an institution with an already approved institutional plan, the investigator should only have to supply the approved institutional plan in the human subjects section of the grant application and describe how it applies to the specific trials.

Tailoring Institutional DSM Plans to Specific Studies

The NCI clinical trials portfolio encompasses a vast array of investigation; examples range across early feasibility studies in treatment, prevention, or diagnosis; nutritional interventions to modulate risk of cancer; gene transfer; and behavioral research relating to cessation of tobacco use. Accordingly, the essential elements for DSM outlined below are described in general terms, and we do not stipulate details of how this process should be carried out. We have used general language to describe the essential content of such plans, leaving to individual institutions and investigators wide discretion in how to carry out these activities in an effective manner.

Clearly, a sensible DSM plan for a particular clinical trial must be based on the medical or health-related context of the particular study and, in particular, the degree of risk to which participants in the trial are exposed. In applying an institutional plan to a particular trial, therefore, the principal investigator will consider whether the institutional plan is sufficiently specific or whether it needs some further tailoring to the conditions of the particular trial. An institution might choose to have one general plan, which investigators tailor to individual trials. Alternatively, the institution might choose to have a plan that is essentially formulated in modules, each of which describes in adequate detail how monitoring will be accomplished for a major class of trials that the institution supports (e.g., early-
phase studies in treatment, behavioral studies, bone-marrow transplantation, chemoprevention studies in healthy populations, etc.). Investigators can then apply these plans to particular protocols with little or no change in the description. For purposes of NCI review, as noted above, investigators may append the institutional plan to the human subjects section of their own grant applications and use these institutional documents in their interactions with NCI staff reviewing their plan. Under most circumstances NCI anticipates that a properly prepared institutional plan should suffice both for peer review and for NCI staff review.

Review of DSM Plans by NCI Staff

NCI staff review of institutional or individual DSM plans prior to grant award will focus on the adequacy with which the plan covers the essential elements outlined below. It is not necessary that submitted plans (whether they are institutional or individual) cover all possible aspects of each element down to the last detail. Rather, the plan should describe processes for dealing with these elements such that a reasonable reviewer would conclude that the institution or investigator has a serious, robust process in place for assuring the safety of research participants and the oversight of data integrity.

Essential Elements

1. Monitoring the progress of trials and the safety of participants. Description of these monitoring processes should include a number of elements. Who actually monitors the trials? How often are the data examined in the course of trial conduct? What do the monitors look for? What procedures are in place to insure adequate feedback of information to researchers and medical decision-makers, so that trials involving excessive risk in relation to anticipated benefits are terminated appropriately? What is the oversight or supervisory role of institutional committees, if appropriate? What procedures does the institution have for coordinating multi-center trials, if applicable?

In relation to who actually has responsibility for monitoring a trial, DSM plans should explain how the institution averts or manages any conflict of interest implicit in having a principal investigator (or a direct report of the PI) as the only monitor of trials that pose significant risk to study subjects.

2. Plans for assuring compliance with requirements regarding the reporting of adverse events (AEs). The plan should describe the processes and oversight that the institution has in place for assuring that AE reporting requirements are actually met. For multi-center trials coordinated by the institution, the plan should outline procedures by which the institution establishes a central reporting entity that collects and reports AEs to all necessary destinations, including co-investigators at participating institutions.

The requirements for proper reporting of AEs on clinical trials are complex (summarized in the Appendix). Possible destinations for AE reports include the institutional IRB, the sponsor (if an IND is involved), the FDA (for AEs from commercially available agents), and, if gene transfer is involved, the NIH Office of Biotechnology Activities (OBA). Note that current federal regulations almost always require reporting of AEs in all categories of clinical trials to the institutional IRB, in addition to what is specified in the Appendix.

Note also that there is no requirement that individual AEs be reported in real time to the NCI, unless NCI is also the IND sponsor of the study (see the Appendix). Where appropriate, investigators should summarize toxicities or adverse consequences of interventions as part of the progress reports in their non-
3. Plans for assuring that any action resulting in a temporary or permanent suspension of an NCI-funded clinical trial is reported to the NCI grant program director responsible for the grant. These actions include, for example, any FDA actions that affect NCI-funded trials (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-053.html). It also includes actions by an IRB or by a commercial sponsor, or by the investigator him/herself, if an NCI-funded trial is involved.

4. Plans for assuring data accuracy and protocol compliance. Institutions should describe what quality-control procedures are in place for assuring data accuracy and completeness in studies funded by NCI.

If an IND is in place, quality-control procedures are generally stipulated by the IND sponsor and may be simply referenced or summarized in the DSM plan. For studies not done under an IND, the institution should describe whatever procedures are in place to assure data integrity and protocol adherence. Appropriate procedures may range, for example, from regular data verification and protocol compliance checks performed by a data manager and a principal investigator, to a formal external data-audit process by an agent external to the institution.

**Special Circumstances**

A. Behavioral and Nutritional Studies

For behavioral and nutritional Phase I-III trials, the NCI requires that a DSM plan be in place appropriate to the anticipated level of risk involved in the particular study. A DSMB can be constituted at the investigator’s discretion and seems particularly appropriate when investigators anticipate the possibility of early stopping based on emerging differences in either risk or benefit.

B. Training Grants

Certain types of NCI career and training awards may support clinical trials, directly or indirectly. NCI's DSM policy covers those career and training awards in which the trainee has direct responsibility for conduct of the clinical trial or in which award funds directly support the trial. Responsibility for compliance with NCI's DSM policies rests with the grant recipient; this may be either the trainee or the training program director, depending on the award (individual versus institutional). Trainees in a mentored career program should consult with their mentors about adapting or designing suitable DSM plans for their clinical trials. In most cases the trainees will be in a mentored stage of their career and will lack the experience needed to provide appropriate oversight of the trial. The DSM plan must therefore clearly identify the senior individual responsible for monitoring the trial and the function of the trainee in this process.

DATA AND SAFETY MONITORING PLAN
For institutional career development programs (e.g., K12, R25T) in which clinical trials are an integral part, applicants should provide with their application a “Special Institutional Statement Regarding Human Subjects Research under K12 or R25T Support”. This statement must be provided to NCI Program staff for evaluation and approved before the initial grant award can be issued, and submitted for evaluation and approval with each “Application for a Continuation Grant.”

More information about these awards is available on the NCI’s Cancer Training Branch (CTB) Web site. Specifically,

- [K12 Special Institutional Statement Regarding Human Subjects Research](#) (PDF file).
- [R25T Special Institutional Statement Regarding Human Subjects Research](#) (PDF file).

For individual career development awards in which the grantee has direct responsibility for trial conduct or in which award funds directly support the trial, the DSM plan covering the trial may NOT be an institutional plan. The DSM plan must be tailored specifically to the clinical trial. Guidance on the content and organization of an NCI DSM plan may be found under the Essential Elements section of the Data and Safety Monitoring Guidelines.

A DSM plan does not need to be provided for individual career development awards in which:

- The trial is a component of an NIH Cooperative Group trial;
- The trial is a CTEP-supported protocol;
- The trial is being partially or completely supported by an investigator-initiated NIH R-grant, viz. R21, with an approved DSM Plan.

For individual career development awards in which a clinical trial will be conducted that does not require the submission of a DSM plan, the grantee must submit for evaluation a letter to NCI program staff describing their situation and explaining why a DSM plan is not needed. This letter must be co-signed by the institutional official authorized to evaluate issues pertaining to data safety and monitoring; and, in the case of mentored awards, by the grantee’s mentor.

If the clinical trial is not to be started immediately upon award of an individual career development award but will follow after a considerable lapse of time (years), submission of a DSM plan to NCI for approval may be delayed until the nature of the trial is clear and its initiation is in the near future. This will insure that the DSM plan suits the needs of the trial.

For NCI career development awards for established investigators (K05, K24), a DSM plan does not need to be provided. However, a Restriction term (Appendix C) will be included in each Notice of Grant Award requiring that the grantee remain in compliance with the NCI's policy on data and safety monitoring throughout the project period.

Appendix

Appendix: Summary of Reporting Requirements for Adverse Events on NCI Trials Supported by Grant or Contract Funding

A. Trials for which NCI is also the IND sponsor (for details, see NCI’s Investigator’s Handbook, available online at [http://ctep.cancer.gov/handbook/index.html](http://ctep.cancer.gov/handbook/index.html))

DATA AND SAFETY MONITORING PLAN
### TABLE A: Expedited Reporting for Phase I Studies (including hospitalization*)

<table>
<thead>
<tr>
<th>UNEXPECTED EVENT</th>
<th>EXPECTED EVENT</th>
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</thead>
<tbody>
<tr>
<td><strong>GRADES 2 - 3</strong> Attribution of Possible, Probable or Definite</td>
<td><strong>GRADES 4 - 5</strong> Regardless of Attribution</td>
</tr>
<tr>
<td><strong>GRADES 1 - 3</strong> Regardless of Attribution</td>
<td><strong>GRADES 4 - 5</strong> Regardless of Attribution</td>
</tr>
<tr>
<td><strong>Grade 2</strong> - Expedited report within 10 working days</td>
<td>Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days.</td>
</tr>
<tr>
<td><strong>Grade 3</strong> - Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days.</td>
<td>Adverse Event Expedited Reporting NOT required.</td>
</tr>
<tr>
<td>(Grade 1 - Adverse Event Expedited Reporting NOT required.)</td>
<td>Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days.</td>
</tr>
<tr>
<td>This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution.</td>
<td>This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution.</td>
</tr>
<tr>
<td>Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.</td>
<td>Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.</td>
</tr>
</tbody>
</table>

### TABLE B: Expedited Reporting for Phase II and III Studies (including hospitalization*)

<table>
<thead>
<tr>
<th>UNEXPECTED EVENT</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>GRADES 2 - 3</strong> Attribution of Possible, Probable or Definite</td>
<td><strong>GRADES 4 - 5</strong> Regardless of Attribution</td>
</tr>
<tr>
<td><strong>GRADES 1 - 3</strong> Regardless of Attribution</td>
<td><strong>GRADES 4 - 5</strong> Regardless of Attribution</td>
</tr>
<tr>
<td>Expediting report within 10 working</td>
<td>Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days.</td>
</tr>
<tr>
<td></td>
<td>Adverse Event Expedited Reporting NOT required.</td>
</tr>
<tr>
<td>Expedited report, including Grade 5 Aplasia in leukemia patients, within 10</td>
<td></td>
</tr>
</tbody>
</table>

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(Data and Safety Monitoring Plan)
DATA AND SAFETY MONITORING PLAN

**Grade 1 - Adverse Event Expedited Reporting NOT required.**

This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution.

Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.

**Grade 4 Myelosuppression or other Grade 4 events that do not require expedited reporting will be specified in the protocol.**

This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution.

Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.

* For Hospitalization Only — Any medical event equivalent to CTC Grade 3, 4, 5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for Phase of study, expected or unexpected and attribution.

Expedited reporting may not be appropriate for specific expected adverse events for certain later Phase II and Phase III protocols. In those situations the adverse events that will not have expedited reporting must be specified in the text of the approved protocol. An expected Grade 3 event that is definitely related to the investigational agent is only to be reported if the patient is hospitalized using the generic reporting criteria, for instance. In a trial of an investigational agent where Grade 3 diarrhea requiring hospitalization is expected, only diarrhea requiring ICU care (Grade 4) might be designated for expedited reporting.

**B. Trials of an investigational agent for which NCI is not the IND holder**

The controlling regulations are those of the Food and Drug Administration (21 CFR, Part 312.32: Expedited Safety Reporting Requirements for Human Drug and Biological Products) and are available at [http://www.fda.gov/cder/aers/fr07oc97.htm](http://www.fda.gov/cder/aers/fr07oc97.htm). They describe the responsibilities of the investigator and the IND holder. Additional sponsor or institutional requirements may be appropriate for specific agents and included in the pertinent protocol sections.
C. Trials involving commercially available agents only (no INDs involved)

Serious adverse events that occur with commercially available agents/devices are reported through Food and Drug Administration Medwatch (http://www.fda.gov/medwatch/index.html).

D. Trials involving recombinant DNA molecules (gene transfer)

In addition to the reporting requirements for investigational agents (see A or B above, as appropriate), investigators should adhere to NIH Guidelines for Research Involving Recombinant DNA Molecules (Gene Transfer).


E. Food and Drug Administration reporting requirements of serious adverse events for post-marketing trials of vaccines (no cancer vaccines yet in this category)

Serious adverse events must be reported according to applicable FDA regulations (http://www.fda.gov/cber/vaers/vaers.htm).

F. Trials involving behavioral or nutritional interventions that do not use an investigational agent

Since there are no standard grading scales for adverse events, defining suitable grades for adverse events is the responsibility of individual investigators for each protocol. Adverse events of a psychological nature can occur with behavioral trials and should be specified for the particular intervention in question.