THE UNIVERSITY OF CHICAGO MEDICINE

Comprehensive Cancer Center

Data and Safety Monitoring Plan

Revised: December 2016

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I. INTRODUCTION

This document outlines the policies established by the University of Chicago Medicine Comprehensive Cancer Center (UCCCC) for the appropriate oversight and monitoring of the conduct of cancer clinical trials at the University of Chicago. Adherence to these guidelines is a requirement of Cancer Center membership. Failure to comply with the policies and procedures outlined in this document will result in suspension of UCCCC membership privileges including lack of access to, or discounts on, shared facilities as well as other Cancer Center resources (e.g., services of the Cancer Clinical Trials Office [CCTO], or review by the Clinical Trials Review Committee [CTRC, required for IRB approval]). The purpose of these policies is to ensure the safety of participants, the validity of data, and the scientific progress of studies including termination of studies for which significant risks have been uncovered or when it appears that the trial cannot be conducted successfully. These policies apply to all cancer clinical trials regardless of study sponsorship or source of support.

In accordance with National Cancer Institute (NCI) guidelines, a clinical trial is operationally defined as a prospective study involving human subjects designed to answer specific questions about the effects or impact of a particular biomedical or behavioral intervention. Participants may be patients with cancer or people without a diagnosis of cancer but at risk.

a) In the area of molecular imaging diagnostics, a study is determined to be a clinical trial if it uses information from the diagnostic test in a manner that affects medical decision making for the study subject; purely descriptive studies where performing the diagnostic test itself imposes some risk on study subjects are also subject to this Data and Safety Monitoring (DSM) policy.

b) Behavioral clinical trials include interventions that aim to increase or decrease behaviors to lower cancer risk and/or improve coping or quality of life and/or reduce the negative sequelae of treatment. Observational studies are not considered clinical trials for the purposes of this document.

II. OVERVIEW OF RELEVANT COMMITTEES AND CONFERENCES

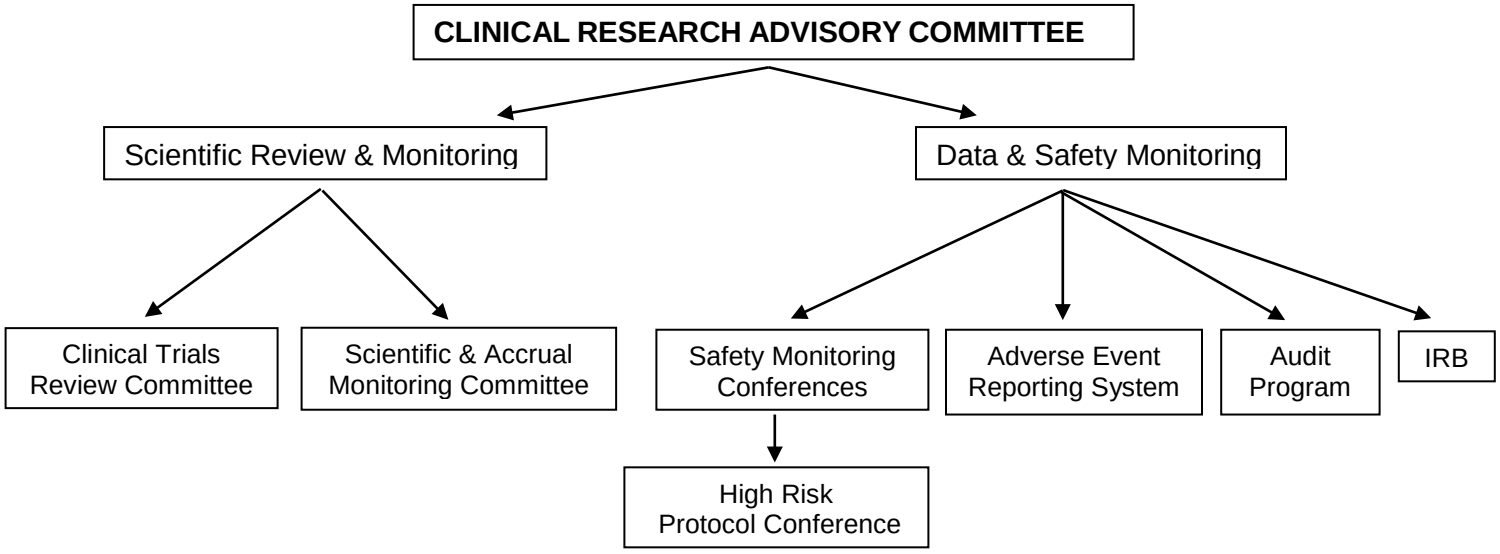
Consistent with NCI guidelines, all oncology trials at the University of Chicago are carefully monitored through both institutional and UCCCC-specific central processes and committees including, the Institutional Review Board (IRB), the UCCCC Clinical Research Advisory Committee (CRAC), the Clinical Trials Review Committee (CTRC), the Scientific and Accrual Monitoring (SAM) Committee, regular safety monitoring conferences, and a High Risk Protocol Conference.

CRAC oversees all aspects of clinical research conducted at the UCCCC, and makes final decisions with respect to all issues outlined in this document. The CRAC is composed of the UCCCC Associate Director for Clinical Sciences, Associate Director for Administration/Scientific Director for the Cancer Clinical Trials Office (CCTO), the Chair and co-Chair of the CTRC, the Chair and co-Chair of the SAM Committee, the Technical Director of the CCTO, and representative senior faculty.

Under the governance of the CRAC, initial scientific review is conducted by the CTRC and annual monitoring of trial progress by the SAM Committee. The study's level of risk (described below) determines the intensity of real-time data and safety monitoring, which is managed internally through safety monitoring conferences, e.g., Phase I Conference, Phase II Conference, quarterly High Risk Protocol Conferences (HRPC), a rigorous adverse event reporting system, and the UCCCC audit program. All of these entities are accountable to the Associate Director for Clinical Sciences and the CRAC. Each has specific responsibilities and each provides oversight in addition to, and independent of, the study Principal Investigator (PI). Systematic procedures are established for notifying the Associate Director for Clinical Sciences of diversions from the procedures outlined in these guidelines, as well as concerns related to data quality, toxicity, adverse events or lack of study progress. The Associate Director for Clinical Sciences, with input from the CRAC, determines and ensures compliance with appropriate action.

In addition to these UCCCC specific entities, the Division of the Biological Sciences (BSD) Institutional Review Board (IRB) provides an independent safety monitoring function. The IRB receives and reviews real time reports of all Unanticipated Problems (by phone immediately for life threatening or fatal events; written notification of all Unanticipated Problems within 10 working days) on any trial open at the University of

Chicago. In addition, the IRB reviews all clinical trials for both accrual and patient safety at least annually, with the frequency determined based on risks to subjects or other concerns. Finally, external audits and independent Data and Safety Monitoring Boards (DSMB) are in place as appropriate to, or required by, individual protocols.



III. CLINICAL RESEARCH ADVISORY COMMITTEE

This committee ensures that all aspects of the clinical research process at the UCCCC are conducted according to prescribed standard operating procedures. The Committee:

a) Reviews and approves all UCCCC policies and procedures related to clinical research; and
b) Defines the responsibilities of, and serves as a review body for, the CTRC and the SAM Committee.

CRAC meetings are held quarterly with additional meetings on an as-needed basis. If the issues in question require additional input, the appropriate individuals (e.g., Departmental or Section leadership) will be invited to attend. Current membership is presented in Table 1.

TABLE 1. CLINICAL RESEARCH ADVISORY COMMITTEE MEMBERSHIP

Name	Leadership Role
Mark Ratain, MD	UCCCC Associate Director, Clinical Sciences
Marcy List, PhD	UCCCC Associate Director, Administration/ Scientific Director of the CCTO
Susan Cohn, MD	BSD Associate Dean for Clinical Research and Director for Clinical Research in Pediatrics; Official Ad Hoc Member
Hedy Kindler, MD	Chair, CTRC
Michael Bishop, MD	Co-chair, CTRC
Lucy Godley, MD, PhD	Chair, SAM
Steve Chmura, MD, PhD	Co-Chair, SAM
Wendy Stock, MD	Professor of Medicine
Rajan Gopalakrishnan	UCCCC Director for Informatics
Walter Stadler, MD	Chief, Section of Hematology/Oncology; Official Ad Hoc Member
Amanda Spratt, BS, CCRP	UCCCC Director, Clinical Research Operations, Technical Director, CCTO

IV. PROTOCOL REVIEW AND MONITORING SYSTEM

A. Clinical Trials Review Committee

The CTRC is responsible for the evaluation of scientific merit and data and safety monitoring plans for all clinical research performed at the UCCCC. The Committee meets once a month and:

a) Reviews all new clinical trials for scientific merit;
b) Assesses adequacy of data and safety monitoring plans;
c) Determines level of study risk (criteria described below) and recommends frequency with which study is to be audited;
d) Verifies that the protocol is assigned to a safety monitoring conference;
e) Assesses the prioritization (as set by the multidisciplinary teams) of proposed trials in the context of patient and staff resources;
f) Affirms relevance of the proposed clinical trial to the mission of the UCCCC; and
g) Has the authority to terminate and/or close protocols.

CTRC members are appointed by the UCCCC Director based on an interest in, and experience with, clinical trials. Although appointments are generally for a three-year term, there is some degree of flexibility to ensure broad representation from all cancer-related specialties and departments and many members serve longer. The current committee has broad representation including Medicine, Surgery, Pediatrics, Radiation and Cellular Oncology, Pathology, Radiology, and Nursing. The committee also includes representatives from the following UCCCC core facilities: Biostatistics, the CCTO, the Human Imaging Research Office, and Pharmacology.

Cancer-related studies cannot be approved by the IRB or activated without CTRC approval. Protocols that have undergone prior external peer review, e.g., NIH, ACS, or cooperative group, are eligible for expedited CTRC review. In response to the increasing number of tissue banking, epidemiology, retrospective chart reviews and retrospective tissue analysis studies, which often consume few UCCCC resources, the criteria for expedited review have been expanded to include banking and registry studies, retrospective epidemiology or tissue use studies, and other chart reviews studies. These protocols are not required to undergo full committee review, but are reviewed by the committee chair or co-chair who has the option of bringing them to the full committee if there are specific concerns (e.g., concern regarding merit, design, or prioritization).

Protocols in which the only objectives are to evaluate or study archival diagnostic specimens do not require CTRC review if they undergo review by the Pathology Biospecimen Utilization Committee. Tissue evaluation protocols focused on cancer tissue that are not reviewed by this pathology committee, or do not meet the expedited review criteria described above (e.g. banking or retrospective tissue use studies), require full CTRC review.

Risk Determination

Level of risk, and consequent required data and safety monitoring activities are determined at the time of CTRC review as follows:

a) **Minimal Risk protocols**: no investigational intervention;

b) **Low Risk protocols**: trials for which at least some subjects receive an investigational intervention, and which do not meet criteria for Moderate or High Risk;

c) **Moderate Risk protocols**:
   - involve investigational interventions in Phase I or Phase II trials; or
   - involve interventions for which severe toxicity is expected in the majority of subjects and which would not be expected in the context of standard management of the patient; or
   - allow for dose escalation in some cohorts;

d) **High Risk protocols**:
   - life threatening toxicity is expected in the majority of subjects and which would not be expected in the context of standard management of the patient; or

- involve gene therapy; or
- involve institutional conflict of interest; or
- any other protocol designated as High Risk at the discretion of the CTRC at the time of initial review, e.g., studies involving products manufactured in-house under Good Manufacturing Practices (GMP) guidelines.

Data and safety monitoring activities, including auditing (for those without external oversight) are based on assigned risk level as follows:

Minimal Risk (safety monitoring conference not required):
- audited every 3 years

Low Risk (safety monitoring conference not required; however, most Low Risk studies are also discussed in their designated safety monitoring conferences):
- minimum of 10% of charts audited annually

Moderate Risk (safety monitoring conference required):
- minimum of 20% of charts audited annually

High Risk (safety monitoring conference required):
- quarterly monitoring at High Risk Protocol Conference (HRPC)
- minimum of 50% of charts audited at least annually
- higher percentage of patient charts and/or more frequent audits may be recommended by the CTRC at the time of initial review.

Changes in level of risk:

a) Moderate and Low Risk protocols move down one level of risk when all subjects on the protocol have been off study treatment for 3 months.
b) Low Risk protocols become Minimal Risk after all subjects have been off study treatment for 15 months.
c) High Risk protocols remain high risk until all subjects have been off study treatment for three months at which point they become low risk, unless the level of risk has been revised by the High Risk Protocol Conference or by petition to the SAM chair.

For any protocol, the CTRC has the authority to request more frequent audits or closer safety monitoring if it is deemed appropriate for any reason.

B. Scientific and Accrual Monitoring Committee

The Scientific and Accrual Monitoring (SAM) Committee meets monthly and is responsible for performing annual protocol reviews, including reviews of all amendments, to:

a) Evaluate scientific progress of the study, including accrual to date compared to projected accrual and any new scientific findings which might alter the significance or objectives of the original study; and
b) Ensure that the conduct of the study is in compliance with the approved DSM plans, including review of documentation that audits have been carried out per CTRC recommendations.

Based on accumulating data and SAE's, the SAM Committee has the authority to change the risk level of a study.

If the committee determines that a study is not progressing and should be terminated and/or closed to accrual, a recommendation is made to the CTRC, which reviews the data and makes the final determination. The PI can provide additional information and/or appeal this determination. Failure to comply with the final determination of the CTRC will result in suspension of UCCCC membership privileges.

The UCCCC Director appoints SAM Committee members. Membership duration is flexible to maintain required depth and breadth of expertise related to the spectrum of clinical research conducted at the Cancer Center. Interim meetings are scheduled to address specific issues that require immediate attention to ensure patient safety. The SAM Committee includes representation from clinical investigators, biostatisticians and Cancer Center administration.

V. SAFETY MONITORING

The central focus of safety monitoring for UCCCC investigator-initiated protocols (approved by the CTRC) are formal data safety monitoring conferences and the quarterly HRPC. There must be a fully documented data safety monitoring conference, where all active subjects on studies are reviewed, at least once every month, although this is generally done weekly or bi-monthly. Failure to comply with this requirement will result in administrative closure of the protocol. All classes of trial, i.e., treatment, prevention, cancer control, intervention, etc., are monitored at these conferences as dictated by the CTRC-assigned "risk level" (see Risk Determination section above). All protocols approved by the CTRC, including cooperative group and pharmaceutical company studies, are assigned to a monitoring conference as required based on risk level. The CTRC has the authority to request closer safety monitoring of any protocol if it is deemed appropriate. Protocols designated as High Risk are also reviewed at the quarterly HRPC. During the data safety monitoring meetings, the research team discusses matters related to the safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, adherence to protocol requirements, and data completion. Although these conferences vary somewhat in format, to be designated as a "monitoring conference" the following criteria must be met:

a) subjects are grouped by protocol and discussion is focused on research issues rather than patient care;
b) protocols are discussed in terms of accrual, toxicities, adverse events, dose levels; and
c) for each protocol, a Data Safety and Monitoring (DSM) minutes form documenting the discussion is generated. Information from these forms may lead to a change in risk level and, thus, a change in auditing and monitoring requirements. The DSM minutes must be completed for all open studies which are Moderate or High Risk, regardless of whether or not subjects have been enrolled at the UCCCC. For trials sponsored and/or coordinated by the UCCCC that are open at affiliate sites, SAE's or other issues arising in these patients must also be discussed at the DSM conferences as they might influence study risk or require a change in procedures.

The specific procedures for data and safety monitoring for Phase III, and non-therapeutic studies, e.g., behavioral, epidemiology, nutritional, and training grants, are described at the end of this section. For randomized double-blind studies, the Biostatistics Core Facility keeps the randomization assignments and the blind is broken only after the study is complete. The Core has also set up a web-based phone notification system for emergency unblinding. These procedures allow for safety monitoring without compromising the randomization blind.

A. Phase I/Developmental Therapeutics & Phase II/Multi-Institutional Conferences

Weekly Phase I/Developmental Therapeutics and Phase II/Multi-Institutional conferences are led by a minimum of two clinical faculty (including the Associate Director for Clinical Sciences and Chief, Section of Hematology/Oncology, respectively) who have considerable expertise in the conduct of Phase I and Phase II trials. These individuals are responsible for ensuring that each protocol is adequately discussed, and they have the authority to ask for additional data from the PI or recommend study modification or closure. All open studies are discussed on a "protocol by protocol" basis, and a Data and Safety Monitoring (DSM) Minutes Form is completed for each protocol documenting the discussion outcome with respect to patient safety, risk level and study continuation. All DSM Minute Forms are signed by the conference leader or his designate in the event that the conference leader is not available on a particular week. The DSM Minutes are subsequently submitted to the CCTO. Any unexpected toxicity data will be disseminated to all collaborating institutions as soon after the meeting as possible. As described in the "Adverse Event Reporting" section of these guidelines, individual adverse event reporting occurs in real time in accordance with NCI guidelines. Conferences are attended by participating investigators, a statistician, protocol research nurses, research managers, clinical research staff (e.g. clinical research coordinators, clinical data managers), and the responsible regulatory manager(s); if multiple specialties are involved, e.g., Surgery, Radiation Oncology, representatives from these specialties will also attend. Thus, there is considerable opportunity for independent review of protocols.

For both conferences, a summary sheet listing all open studies, including accrual to date and number of "open slots" is prepared prior to the conference, and serves as the reference for protocol discussion. Phase II

summary sheets also include a cumulative list of SAEs by protocol and pending protocols and protocol concepts. For each protocol, the conference leader directs discussion of study accrual, rates and patterns of SAEs and toxicities, risk to patients and recommendations, i.e., continuation of accrual or study closure. Phase I summary sheets list the active patients on study in each protocol along with those currently in screening, by protocol; the study nurse briefly presents each patient, his/her status, drug dose, side effects, and SAEs. After all patients on a given protocol are presented, the conference leader directs a discussion of the protocol in terms of rates and patterns of SAEs and toxicities, drug level escalation, level of risk, and recommendations.

B. Other Safety Monitoring Conferences

These conferences are led by a minimum of two clinical faculty, and are generally attended by investigators, nurses, research managers, clinical research staff, and the regulatory manager(s) responsible for the program. Summary sheets listing all open studies, including accrual to date, are prepared, and serve as the reference for protocol discussion. The leader directs discussion of all open protocols for accrual, rate and pattern of toxicities and adverse events, and level of risk. A DSM Minutes Form is generated, as described above, unless the form was already submitted from a Phase II conference discussion, signed by the conference leader or designate, and submitted to the CCTO. Review of accrual and/or toxicity data at any monitoring conferences may prompt recommendation for further investigation, i.e., multiple chart review, audit, study amendments, temporary enrollment suspension or closure, change in assessed level of risk and auditing frequency. Unresolved questions or concerns will be submitted to the Associate Director for Clinical Sciences or the UCCCC Director and/or the CRAC for discussion and action.

C. High Risk Protocol Conference

In addition to regular monitoring at the assigned safety monitoring conference, trials which have been designated High Risk are subject to quarterly monitoring at the HRPC. This open conference includes the CRAC committee and PIs of High Risk trials, in addition to any interested third parties. The PI or designate is required to present the status of their protocol in terms of accrual, frequency and patterns of toxicities and Unanticipated Problems (UPs), amendments to the protocol related to patient risk, and results of the most recent audit.

D. Biological Sciences Division (BSD) IRB

The BSD IRB has three committees, each of which meets on a monthly basis to ensure timely review and protocol initiation. Two of the committees review new protocol submissions and amendments, whereas the third primarily provides continuing review of active protocols. Of relevance to Data and Safety Monitoring of UCCCC studies, the IRB provides independent, “real time” review of reportable UPs. All UPs are reported in writing to the IRB within 10 working days, and life-threatening or fatal events are immediately reported by phone. These reports are reviewed on an ongoing basis by the IRB chair or his/her designee who notifies the PI if he/she is concerned about rates and/or patterns of SAEs on a particular study. Such a letter may request additional information or suggest study closure. In addition, for every protocol, the full IRB committee performs and/or supplements the following functions:

a) reviews Conflict of Interest at the time of study initiation;
b) monitors cumulative adverse events at least annually (at the time of continuing review);
c) assesses potential change in level of risk (at the time of continuing review); and
d) monitors study accrual (at the time of continuing review).

E. Adverse Event Reporting

Adverse Event Reporting follows the guidelines as required by the protocol and sponsoring agency. The individual reporting the SAE will complete the appropriate forms as specified in the protocol and/or study manual (e.g., Medwatch, AdEERS) and submit to the appropriate agencies, e.g., pharmaceutical companies, NCI, cooperative group. If the event meets IRB reporting criteria, the IRB e-submission form will also be completed by this individual and forwarded to the PI for reporting to the IRB. In addition, all serious adverse events (SAEs, protocol-specific, and defined in each protocol) occurring in patients enrolled in adult cancer clinical trials at U of C or patients at other affiliated institutions participating in a UCCCC coordinated study, are entered into Velos within 24 hours of investigator knowledge of the event. An automated email is then immediately generated and notifies the PI, treating physician, and QA Regulatory Manager. The individual

reporting the event in Velos must also provide documentation as to whether the event meets IRB reporting criteria (as a UP). The QA Regulatory Manager monitors this flow to ensure timely completion of IRB reporting requirements. For events that occur on a protocol conducted under an IND or IDE held by a UCCCC investigator, the reporting individual must also provide documentation as to whether the event meets FDA reporting criteria (as an IND Safety Report or Unanticipated Device Effect).

If the event occurs on a protocol conducted under an IND or IDE held by a UCCCC investigator and meets FDA reporting criteria, the individual reporting the event is responsible for forwarding the completed MedWatch 3500A form to the CCTO IND Regulatory Manager within 4 calendar days of investigator knowledge of the event for fatal/life-threatening events and within 10 calendar days for all others. The IND Regulatory Manager will submit the completed forms to the FDA within their designated timelines. If the UCCCC is the coordinating site, the responsible Regulatory Manager will distribute the completed UP report to all participating affiliate sites for review and submission to their respective IRBs in accordance with local policies.

External safety reports received from the study sponsor (e.g. pharmaceutical companies or cooperative groups), which qualify as an unanticipated problem as per FDA and local definitions, are reviewed by the PI and are forwarded to the Regulatory staff, who work with their colleagues in the clinical research staff to submit reportable events to the IRB, update study documents (e.g. consent forms) as needed, and file them appropriately.

Review of Adverse Event Rates/Toxicities

As described above, for all investigator-initiated trials, both real-time and cumulative serious adverse events and toxicity reviews occur formally at the Phase I, Phase II and tumor site-specific conferences. At this time, unusual toxicities and/or UPs and patterns are discussed.

Serious Adverse Event and Unanticipated Problem Procedure

- Patient experiences a serious adverse event (SAE).
- Research Nurse, or MD refers to the SAE section of the protocol and follows applicable procedures for SAE reporting.
- The Research Nurse, MD, Clinical Research Staff enters the SAE into the Serious Event Reporting form in Velos by the end of the business day. Events occurring after business hours are entered the next business day.
- The following information is required in Velos:
  - IRB Protocol Number
  - PI of Study and email address
  - Treating Physician and email address
  - Date of Event
  - Date PI Notified of Event
  - Description of Event (including grade and attribution of the event)
  - Documentation of whether the event meets IRB Reporting criteria
  - Documentation of whether the event meets FDA Reporting criteria (if applicable)

  Clicking the Email/Submit button after the Serious Event Report form is completed generates an email alert, which is sent to the PI, CCTO QA Regulatory Manager, and IND coordinator (if applicable).
- If the event is reportable to the IRB (meets the IRB's guidelines for Unanticipated Problems), an Unanticipated Problem Report must be filled out by the clinical research staff in AURA IRB within **10 working days of the event occurrence**.
- If the event is reportable to the FDA a MedWatch 3500A form must be completed and returned to the CCTO within 4 calendar days (fatal/life-threatening events) or within 10 calendar days (all others)
- All delinquent reporting (greater than 10 working days of the Investigator's knowledge) must include documentation of reason for delinquency, and may require implementation of a corrective action plan.

F. NCI Notification of Study Suspension or Closure

All temporary or permanent closures or suspension of NCI-sponsored clinical trials (non-cooperative group) will be reported by the CCTO to the Protocol Information Office (PIO) of the Cancer Therapy Evaluation Program (CTEP). NCI-sponsored (non-cooperative group) protocols that are closed by the IRB or the HRPC for non-compliance or safety concerns will be reported immediately to the PIO.

G. Phase III Trials and Trials Enrolling Greater than 300 Patients

An Independent Data and Safety Monitoring Board (DSMB) will be formed for Phase III clinical trials (randomized, comparative trials of potentially therapeutic agents), unless such a committee is already in existence through another mechanisms, e.g., NCI cooperative group trials, which have DSMCs facilitated through the appropriate biostatistics center. An independent DSMB may also be formed in specific instances for a Phase II trial – at the discretion of the CTRC, or if the trial planners determine that it is warranted. Protocols which include an independent DSMB must describe the Board and detail the monitoring guidelines to be followed. The Scientific or Technical Director of the Biostatistics Core will serve on independent DSMBs formed for Cancer Center trials. In the event of a direct conflict, another senior level UCCCC biostatistician will serve on the DSMB. Specific guidelines as to when and how a DSMB will be established are discussed in the Biological Sciences Division's Data and Safety Monitoring Plan.

H. Phase I – III Non-Therapeutic Trials, e.g., behavioral, nutritional

These trials will have a Data and Safety Monitoring Plan appropriate to the level of risk (assigned as presented in the Risk Determination section above) to the participants in the particular study and approved by the CTRC.

I. Training Grant Trials

Studies developed by an investigator in training (supported on a training grant or mentored by a UCCCC investigator) will be subject to the following guidelines:

- For institutional career development programs, e.g., K12, R25T, in which clinical trials are an integral part, the application must include documentation that the sponsoring institution has an institutional DSM Plan that covers all trials supported by the grant, or it must include the individualized DSM plan in the application.
- For individual career development awards in which the trainee has direct responsibility for trial conduct, or in which award funds directly support the trial, the DSM plan covering the trial may be either institutional or individual at the discretion of the grant recipient.
- If the clinical trial is not to be started immediately upon award, but will follow after a considerable lapse of time, submission of a DSM Plan to NCI for approval may be delayed until the nature of the trial is clear and its initiation is planned in the near future.

VI. DATA QUALITY CONTROL: AUDIT PROGRAM

All protocols approved by the CTRC must be audited, either through the Cancer Center internal audit program as described below, or through external monitoring/audits conducted by pharmaceutical companies, cooperative groups, NCI, etc. Opened to accrual studies are subject to internal audit after they have been open to accrual for 12 months or at the discretion of the UCCCC. The UCCCC's formal, well-established internal audit program is designed to audit studies not being externally audited. In addition, UCCCC conducts audits of affiliate institutions as requested by the cooperative group PI and/or multi-center consortium PI and performs targeted audits on externally funded studies for which the CTRC requested additional data monitoring.

The frequency with which a protocol not subject to external monitoring/audits will be audited is a function of level of risk of the protocol as determined by the CTRC as follows:

Minimal Risk:	audited every 3 years
Low Risk:	minimum of 10% of charts audited annually
Moderate Risk:	minimum of 20% of charts audited annually
High Risk:	minimum of 50% of charts audited annually

For low risk studies that accrue >100 subjects annually and moderate risk studies that accrue >50 subjects annually, a minimum of 10 charts will undergo full review as described below, with any further review agreed in advance by the QA Regulatory Manager and the Associate Director for Clinical Sciences. At any time, for any protocol, if an audit identifies gross inadequacies as determined by the Associate Director for Clinical Sciences, the protocol may be targeted for more frequent audits.

Audits are scheduled and coordinated by the QA Regulatory Manager. Audits of Minimal Risk studies are completed at a minimum of every three years using a Progress Report Form completed by the PI of the study or their designee. The reports are reviewed by the QA Regulatory Manager and deficiencies of a significant nature are brought to the attention of the CCTO Technical and Scientific Directors and the Associate Director for Clinical Sciences, for consideration of an on-site audit. In addition, the UCCCC has the discretion to conduct an on-site audit of a PI of any study at any time. In the case of low, moderate or high risk study audits, PIs are notified at least 30 days in advance of the patients to be audited.

The following elements are reviewed for Moderate and High Risk studies:

a) Consent form and compliance with other IRB and external regulatory requirements;
b) Protocol compliance; and
c) Verification of source documents for eligibility, toxicity and response.

The following elements are reviewed for Low Risk studies:

a) Consent form (if applicable) and compliance with other IRB and external regulatory requirements;
b) Verification of source documents for eligibility; and
c) Any other information deemed to be relevant to the integrity of the study

Investigational pharmacy record keeping is systematically reviewed to verify compliance with FDA regulations, including those for handling and storage of investigational drugs and drug accountability.

An audit report is issued within 30 days and sent to the protocol PI. A copy is filed in the CCTO Audit files. The PI is given 30 days to respond in writing to the deficiencies identified. Responses are reviewed by the Scientific and Technical Directors of the CCTO, the Associate Director for Clinical Sciences, and the CRAC, if necessary.

VII. PROTOCOL-SPECIFIC DATA AND SAFETY MONITORING PLAN: REQUIRED ELEMENTS

All clinical trials conducted in the UCCCC must have a satisfactory Data and Safety Monitoring Plan that is described in detail in the protocol. As part of its review, the CTRC assesses patient safety and ensures that the degree and frequency of data and safety monitoring for individual studies is commensurate with the size, complexity and risk of the trial. Protocol-specific Data and Safety Monitoring Plan must include:

a) Delineation of oversight responsibilities, i.e., external DSMB, Phase I Conference, Phase II Conference;
b) Description of data and safety review process;
c) Timetable for submission of data, safety, and progress information to the designated data and safety monitoring entity, the IRB, and the sponsor;
d) Process to implement closure of studies when significant risks or benefits are identified; and
e) Description of adverse event reporting procedures.

VIII. MANAGEMENT OF MULTI-INSTITUTIONAL TRIALS

UCCCC coordinated multi-institutional clinical trials undergo safety monitoring as described in this document. Generally, multi-institutional studies for which the UCCCC acts as the coordinating center are monitored at the Phase II/Multi-institutional DSM conference. However, multi-institutional studies may be reviewed at another Safety Monitoring Conference if approved by the CTRC. All new multi-institutional clinical trials are required to outline detailed data and safety monitoring policies and procedures in the protocol. They must include the following specific procedures:

a) Central registration of all enrolled patients by the University of Chicago including verification of the eligibility requirements by UCCCC staff;

b) Data submission to the University of Chicago on a regular basis;
c) Review of subjects' toxicities and response at the designated UCCCC safety monitoring conference; and
d) Reporting of SAEs from affiliate sites consistent with the procedures described above. Reportable SAEs are either entered into the Serious Event Reporting form in Velos or emailed/faxed to the CCTO within 24 hours of site investigator knowledge of the event initiating the chain of events described in the adverse event section above.

IX. CONFLICT OF INTEREST

Conflict of Interest is assessed and monitored at two levels, at the level of the University Research Administration office (URA) and the Office of the Provost as well as at the level of the BSD IRB. The URA policy states, in part: "A member of the Faculty during the Quarters of residence may not engage in consultation, teaching at other universities, regular compensated lecturing, compensated editorial activities, or other substantial outside employment, unless such activity is consistent with the faculty member's obligations to the University, is not inimical to the fullest development of scholarly activities, and meets with the approval of the faculty member's Chairman and Dean." Faculty or Investigators initiating any grant or clinical trial are responsible for disclosing financial interests that would reasonably affect their research or educational activities within the University. This form is submitted to the URA office. The University, Office of the Provost, then has the responsibility for determining if the disclosed interests could directly and significantly affect the performance of University responsibilities and to require the management, reduction or elimination of the conflict.

In addition, as part of any IRB submission of a specific protocol, investigators are required to disclose any potential conflict of interest resulting from their involvement in the proposed study and if, they haven't already done so, they are instructed to complete the URA form described above. In addition, any potential conflict of interest must be further described in a separate letter accompanying the IRB submission. The IRB Chair reviews all letters related to potential "Conflict of Interest', and brings any concerns to the full committee for discussion and recommendation. The IRB may also recommend disclosure of conflict of interest on the patient consent form.

X. TRAINING OF RESEARCH PERSONNEL

Training in human subjects research is required and documented for all UCCCC investigators and research staff every three years. Although there are a number of options, the Collaborative Institutional Training Initiative (CITI) program is the preferred method for complying with Human Subjects Protection Training. Additional training coordinated by the BSD Office of Clinical Research (OCR) is offered monthly for investigators and research staff. New policies and/or procedures for protection of human subjects, or announcements relating to management and conduct of clinical trials are broadcast on the OCR website, and staff and researchers are notified.