UNIVERSITY OF ILLINOIS CANCER CENTER
Bench to Community

DATA SAFETY MONITORING COMMITTEE

University of Illinois Cancer Center Data and Safety Monitoring Plan (DSMP)

Policy Release:

The following UICC Data and Safety Monitoring Plan (DSMP) was developed to provide guidance, policies and processes that will ensure oversight and coordination for data and safety monitoring for all cancer-related trials pursuant to the current National Institutes of Health (NIH) Policy for Data and Safety Monitoring and the National Cancer Institute's Cancer Center Support Grant (CCSG) Data and Safety Monitoring guidelines for NCI-designated Cancer Centers.

Version:	7
Last Reviewed:	8/14/2020
Effective Date:	8/14/2020

Cancer Center Approval

Title: Associate Director of Clinical Sciences

Approval Signature: **Date:**

John H. Stewart, III, MD

August 14, 2020

DATA SAFETY MONITORING COMMITTEE

DATA AND SAFETY MONITORING PLAN

DATA SAFETY MONITORING COMMITTEE

Data & Safety Monitoring Plan Revision History

Version #	Date	Section	Details of Changes
7	8/14/2020	3.4 Protocol Review Committee (PRC)	Revision to match PRC Policy guidelines
7	8/14/2020	5.5 Membership Appointments	Revision to conclude that the Cancer Center Director will review and approve membership of the DSMC
7	8/14/2020	Appendix 3: DSMC Summary Report	Revision to include all reports being used for Routine Summary Reports.
7	8/14/2020	General Policy	Addition of Vice Chair role
6	1/13/2020	2.2.1 Externally Monitored Studies	Clarification and addition of point “d” to allow safety oversight for UICC studies by other NCI Designated Cancer Centers.
6	1/13/2020	2.2.2 UICC-Monitored Studies	Clarification to allow safety oversight for UICC studies by other NCI Designated Cancer Centers.
6	1/13/2020	Appendix 4: Medical Monitor Report Template	Revision of Medical Monitor Form to improve documentation and medical monitor requests for SAE, Protocol Deviation, Dose Escalation, Cohort Expansion, and Routine Reviews.

Table of Contents

1. Introduction 6
2. Definition of Clinical Trials and Monitoring Requirements for Study Types 6
2.1 Clinical Trial Definition 6
2.2 Monitoring Requirements by Study Type 7
2.2.1 Externally Monitored Studies 7
2.2.2 UICC-Monitored Studies 8
3. Clinical Research Committee Structures and Relationships 8
3.1 Principal Investigator of Individual Clinical Trials 8
3.1.1 Role 8
3.1.2 Investigator-Sponsor Responsibilities 9
3.1.3 Education and Training Requirements 9
3.2 UICC Clinical Trials Office (CTO) 9
3.3 Disease Teams 10
3.4 Protocol Review Committee (PRC) 10
3.5 Institutional Review Board (IRB) 11
3.6 Data and Safety Monitoring Committee (DSMC) 12
4. Data and Safety Monitoring Policies and Processes 12
4.1 Protocol Review and Activation Process 12
4.2. Protocol Monitoring Processes 13
4.3 Requirements for Submission of Monitoring Plan 15
4.4 Determination of Risk 15
4.5 Definition of Risk Levels 16
4.6 Determination of Monitoring Frequency Based on Risk Assignment 16
5. UICC Data and Safety Monitoring Committee Role and Responsibilities 17
5.1 Role 17
5.2 Authority 18

5.3 Responsibilities 18
5.4 Membership Composition of the DSMC 19
5.5 Membership Appointments 20
5.6 Member Responsibilities 20
5.7 DSMC Personnel 21
5.8 DSMC Monitoring Process 21
5.9 Meeting Frequency 22
5.10 Meeting Format 22
5.11 Frequency of Trial Review 24
5.12 DSMC Dose Escalation/Expansion Approval Meeting 24
5.13 Reporting of DSMC Outcomes to the IRB 25
6. Individual Data and Safety Monitoring Boards 25
7. Serious Adverse Event/Adverse Event Reporting for UICC Investigator Initiated Studies 26
7.1 Reports and Recording 27
7.2 AE/SAE Reporting Addendum 28
8. Protocol Deviation Reporting for UICC Investigator Initiated Studies 29
8.1 Reports and Recording 29
9. Quality Assurance 29
Appendix 1: Dates of Prior Versions of UICC DSMP 35
Appendix 2: Abbreviations 36
Appendix 3: DSMC Summary Report 37
Appendix 4: Medical Monitor Report Template 38

1. Introduction

The University of Illinois Cancer Center (UICC) places the highest priority on ensuring the safety of patients who participate in clinical trials. All clinical trials conducted at the UICC must include provisions for data and safety monitoring.

The following UICC Data and Safety Monitoring Plan (DSMP) was developed to provide guidance, policies and processes that will ensure oversight and coordination for data and safety monitoring for all cancer-related trials pursuant to the current National Institutes of Health (NIH) Policy for Data and Safety Monitoring and the National Cancer Institute's Cancer Center Support Grant (CCSG) Data and Safety Monitoring guidelines for NCI-designated Cancer Centers. As described herein, the extent of monitoring will vary by the degree of risk encountered by subjects on a study, the study sponsor, the type of agent(s) involved, and the phase of the trial.

The UICC Data and Safety Monitoring Plan (DSMP) provides a blueprint for the oversight of all clinical trials conducted at the UICC regardless of the trial phase or sponsor type. The DSMP covers all cancer-related clinical trials that have been approved through the UICC Protocol Review Committee (PRC). The DSMP requires that every interventional study submitted to the PRC include a DSMP that is appropriate for its level of risk, which is assigned by the PRC. This helps ensure the safety of participants and the quality, validity and integrity of the data of these trials. The DSMP also provides for the appropriate and timely suspension or early termination of trials based on efficacy results, unfavorable benefit-to-risk, or inability to answer study questions.

2. Definition of Clinical Trials and Monitoring Requirements for Study Types

2.1 Clinical Trial Definition

The UICC Data Safety and Monitoring Plan (DSMP) has adopted the National Cancer Institute (NCI) policy for Data and Safety Monitoring of Clinical Trials. For the purposes of this plan, UICC uses the National Institutes of Health definition of a clinical trial, which is "clinical research studies involving human participants assigned to an intervention in which the study is designed to evaluate the effect(s) of the intervention on the participant and the effect being evaluated is a health-related biomedical or behavioral outcome."

Participants in clinical trials may be patients with cancer or people without a diagnosis of cancer, but at risk for developing cancer in the future.

With respect to diagnostic research employing tissue and/or body fluids, a study is considered to be a clinical trial if it uses the information from the diagnostic test in a

manner that somehow affects Medical decision-making of the study subject. Such information may impact some aspect of the study's outcome, and the assessment of this impact may be a key goal of the trial. In contrast, tissue and body fluid studies that do not use the resulting information in any manner that can affect the outcome of study subjects are not clinical trials and are NOT covered by this policy (unless gathering the tissue or body fluids itself imposes additional risk on study subjects).

For diagnostic research utilizing molecular or imaging diagnostics, a study is considered to be a clinical trial if it uses the information from the diagnostic test in a manner that somehow affects Medical decision-making of the study subject. This information may impact some aspect of the study's outcome and the assessment of this impact may be a key goal of the trial. In contrast, studies that do not use this information in any manner that can affect the outcome of study subjects are not clinical trials and are NOT covered by this policy (unless performing the diagnostic test itself imposes some risk on study subjects). These are studies in which the only objective is gathering data on the characteristics of a new diagnostic approach.

Behavioral clinical trials test interventions aimed at eliminating or reducing human activities associated with enhanced cancer risk (e.g. tobacco use, poor nutrition, and sun exposure), or eliminating or reducing morbidity associated with cancer screening, diagnosis, and treatment. In contrast, studies that do not test interventions are considered observational and are not clinical trials.

2.2 Monitoring Requirements by Study Type

2.2.1 Externally Monitored Studies

If a study is already being monitored by a data and safety monitoring committee that has been formed by a national cooperative group, a pharmaceutical sponsor, a study-specific Data and Safety Monitoring Board (DSMB) for a Phase III trial, or the Data and Safety Monitoring Committee of another Cancer Center that is NCI Designated, then the UICC Data and Safety Monitoring Committee (DSMC) does not actively monitor the study. These protocols will be monitored as follows:

a. Studies Monitored by A DSMB

Multicenter/Phase III studies are required by the FDA and NIH to be monitored by an independent DSMB.

b. National Clinical Trials Network (NCTN)

Clinical trials by the NCTN are monitored based on established group practices for data submission, reporting, review, and monitoring.

c. Industry Trials

Trials sponsored by the pharmaceutical industry are monitored based on the sponsor's

established practices for data submission, reporting, and review and monitoring as described in the protocol.

d. NCI Designated Cancer Center Oversight

At the discretion of the DSMC Chair, multi-site institutional trials conducted at another Cancer Center with NCI Designation may be monitored by that Cancer Center's Data and Safety Monitoring Committee according to their NCI approved DSMP. Documentation of review by the external DSMC demonstrating adequate data and safety monitoring must be on file with the UICC DSMC.

2.2.2 UICC-Monitored Studies

If a study is UICC investigator-initiated, and not monitored by an independent DSMB or another DSMC at an NCI Designated Cancer Center, then it will adhere to the policies and processes described in this plan and the UICC DSMC will serve as the protocol's DSMC and will adhere to the policies and processes described in the DSMP. If the study is an investigator-initiated trial from an external institution, then the sponsoring institution's DSMC will be responsible for monitoring the study.

3. Clinical Research Committee Structures and Relationships

The UICC Director and Associate Director for Clinical Research bear the ultimate responsibility for the conduct of cancer clinical research at UICC, including data and safety monitoring. This responsibility is shared with the various offices and committees that they oversee and appoint. Below is a summary of the individuals and bodies involved in the UICC Clinical Research Program, and their respective roles and responsibilities in data and safety monitoring.

3.1 Principal Investigator of Individual Clinical Trials

3.1.1 Role

The UICC Director and Associate Director for Clinical Research hold the designated local PI responsible for the conduct of the study and for the data and safety monitoring for his/her clinical trial, including those trials conducted across multiple sites. All PIs are subject to the UICC policies regarding the conduct of cancer clinical research. The UICC PI is responsible for the design, conduct, analysis, and dissemination of each protocol. The PI also is expected to monitor the conduct of the study, including data and safety, from activation to study completion. The PI is responsible for assuring that the protocol has a DSMP and that procedures are in place for appropriate implementation.

3.1.2 Investigator-Sponsor Responsibilities

The PI is responsible for:

1. Developing a protocol with an appropriate DSMP and consent form, and submitting for review and approval to PRC and IRB in accordance with institutional policy.
2. Constituting a DSMB, if needed, prior to activation.
3. Creating a structured adverse event determination, monitoring and reporting system, including standardized forms and processes for treating or referring patients with adverse events.
4. Notifying the PRC when there are substantive changes in the scientific merit of protocols.
5. Submitting protocol amendments in a timely manner to applicable committees/boards.
6. Providing complete, accurate, and timely data and safety monitoring reports.
7. Reporting adverse events, serious adverse events, unanticipated problems, and protocol deviations as required to applicable agencies and committees/boards.
8. Presenting and publishing results, and reporting these to the IRB.

3.1.3 Education and Training Requirements

Every UICC investigator is required to successfully complete Human Subjects Research (HSR) and Good Clinical Practice (GCP) Collaborative Institutional Training Initiative (CITI) training modules. The courses must be completed and renewed every three years. Investigators keep up-to-date on the latest rules and regulations regarding the design and conduct of research involving human subjects through the UIC IRB website and through training provided by the CTO.

3.2 UICC Clinical Trials Office (CTO)

The UICC Clinical Trials Office (CTO) serves as the UICC's Clinical Protocol and Data Monitoring resource (CPDM). The CTO provides the centralized administration coordination, management, education, policies and procedures, and ongoing support to all UICC clinical research coordinator and to those committees which conduct scientific review and accrual monitoring, provide data and safety monitoring, and ensure

adherence to UICC, institutional, state and federal regulations. The CTO works closely with the Associate Director for Clinical Research to assure that there is sufficient staffing to meet the current and anticipated needs of the clinical research program at UICC.

The CTO reports directly to the Associate Director of Clinical Research. Its role is to foster an effective and efficient clinical research infrastructure. The office provides all of the necessary resources, staffing, informatics, and processes required to support the development, activation, and conduct of protocols, and quality assurance, through protocol close-out, under a single, centralized organizational structure.

3.3 Disease Teams

UICC Disease Teams oversee the clinical trials activities conducted within disease groups. Disease Team leaders are appointed by and report to the Associate Director for Clinical Research. Each is responsible for the ensuring the overall effectiveness of their respective disease team.

Disease Teams (DTs) are responsible for the overall quality and conduct of protocols in their portfolio. In this role, teams evaluate proposed clinical trials at least monthly. This includes assessing the protocol's scientific merit, accrual feasibility based on an assessment of fit with UICC's patient population and clinical feasibility based upon UIC clinical practices, the ability of the trial to fill gaps in the clinical trial portfolio for particular patient populations, overlap with existing studies or competing clinical trials that are ongoing, and the alignment of the study with the mission of the UICC.

Regardless of type or sponsor, all new cancer-related studies enrolling UIC cancer patients are to be reviewed and endorsed by the relevant UICC DT before they can be submitted to the Protocol Review Committee. The DSMB will communicate with the Disease Teams as needed, and will inform Disease Team of any issues or concerns that may impact the Disease Team's clinical trial portfolio.

3.4 Protocol Review Committee (PRC)

The Protocol Review Committee serves as the scientific review and monitoring body for all UICC new and enrolling protocols. The role of the PRC is to assure that only those trials that are scientifically meritorious, statistically sound, have a high probability of completion within a reasonable timeframe, and meet the scientific mission and goals of UICC are approved and activated.

The PRC is composed of faculty from the basic sciences, clinical sciences, and population and control sciences. The PRC Chair is appointed by the Cancer Center Director and the Associate Director of Clinical Research with the endorsement of the UICC Clinical Research Executive Committee. Voting faculty members represent a

diverse range of clinical research disciplines, including medical, surgical and radiation oncology, and biostatistics. The goal is to have a balance of senior and junior faculty and representatives from needed specialties to provide high quality, scientific review of protocols. The PRC meets twice a month. No PRC meeting may commence with the review of new protocols unless quorum of voting faculty is reached. Day-to-day support of the PRC is provided by the PRC Committee Manager, who is administratively based in the CTO.

The PRC will not accept an interventional study for review if it does not have a DSMP. The presence of a plan is confirmed by PRC staff prior to placing the protocol on the PRC agenda.

A PRC member who is the PI of a study being reviewed at a PRC meeting must be recused from the meeting during the review, discussion, and voting on the protocol. A PRC member who is a Co-Investigator of a study being reviewed at a PRC meeting is allowed to be present for discussion, however he or she must abstain from voting. A PRC member that has a financial conflict with a study being reviewed at a PRC meeting must be recused from the meeting during the review, discussion and voting on the protocol. The primary reviewer presents the protocol during the PRC meeting, and discussion ensues. The PRC approves the protocol and DSMP. If it's an UICC investigator-initiated study, they also assign a risk category. The risk level is used to determine the frequency and type of monitoring/auditing. Only protocols approved or exempted by the PRC can be submitted to the IRB.

Once a protocol is activated, the PRC is also responsible for monitoring the scientific progress of the clinical protocol. This occurs at least annually. Additionally, amendments that change any of the following must be submitted for review and approval by PRC: study rationale, response criteria, eligibility criteria, objectives, study design, treatment plan, sample size, stopping rules, or statistical plan. The PRC has the authority to suspend or close a trial for issues related to scientific merit. The PRC is also responsible for monitoring accrual to all interventional hypothesis-driven cancer trials beginning six months after a protocol opens. The PRC has a policy for monitoring trial accrual and process of closing low accruing trials.

The PRC and IRB have complementary yet non-overlapping roles in the review, approval and monitoring of cancer clinical protocols conducted by the UICC. As the PRC focuses on scientific review, the IRB focuses on ethical conduct and patient safety. Similarly, the PRC has a complementary but not duplicative role with the DSMC, although there is appropriate communication and collaboration among these bodies relative to their scope.

3.5 Institutional Review Board (IRB)

DATA SAFETY MONITORING COMMITTEE

The human research protection program at University of Illinois, Chicago (UIC) is fully accredited by the Association for Accreditation of Human Research Protection Program (AAHRPP). The UIC IRB or external IRB review all research involving human subjects conducted by UIC faculty, staff, and students. The IRB of record assures that research adheres to the highest ethical standards and is conducted in accordance with federal, state, and institutional regulations. As such, the IRB has primary responsibility for the protection of the welfare of human subjects participating in human subject research. The major work of the IRB consists of the assessment of research related benefit-risk ratios and assuring that informed consent is properly obtained and documented. The IRB has full authority to approve, require modifications prior to final approval, disapprove, suspend, or terminate for cause all research activities that fall within its jurisdiction. The IRB also has a responsibility to society in general, and to the UIC community in particular, to review and approve worthwhile studies in a timely fashion.

It is an institutional policy that the IRB will not review any cancer study until it has been reviewed and approved by the PRC, or deemed exempt from PRC review. In addition to the PRC, the UIC IRB reviews the clinical trial DSMP in each study to ensure that it is appropriate for that specific trial.

3.6 Data and Safety Monitoring Committee (DSMC)

Once studies are IRB approved and activated, the DSMC is charged with reviewing all investigator initiated, interventional UICC clinical trials. In regards to the relationship that the DSMC has with other persons and committees outlined above, DSMC review outcomes and audits are distributed to the study PI, as well as the IRB with the continuing review. The details of the DSMC are described extensively in a later section of this document.

4. Data and Safety Monitoring Policies and Processes

Below is a summary of the process of review and activation, monitoring, reporting, and outcome decisions for UICC protocols. This process shows the responsibility, inter-relationships and interactions of UICC clinical research bodies to assure the appropriate levels of review, approval monitoring, and closure of protocols.

4.1 Protocol Review and Activation Process

Below are the steps in protocol development, activation, and monitoring, along with individuals or bodies tasked with each of these steps.

1. ***Protocol Development and Identification***: UICC investigators develop innovative protocols based on clinical experience and translational research, or identify a suitable protocol based on the UICC patient base.

2. ***Disease Team Review*:** As previously stated in the Disease Team (DT) section 3.3.

3. ***Protocol Review Committee and Approval***: Previously defined in the Protocol Review Committee section 3.4.

4. ***IRB Review and Approval***: Previously stated in section 3.5.

5. ***Activation*:** Studies approved by the IRB are readied for activation. This step includes site initiation visits and confirmation of the availability of drug. Budget and contract negotiations for externally funded studies occur simultaneous with the above reviews, and must be completed prior to trial activation. The CTO is responsible for 'activating' the protocol in the clinical trials management system, OnCore, and assuring that study is listed on clinicaltrials.gov.

4.2. Protocol Monitoring Processes

1. ***Subject Registration:*** The UICC tracks and reports all subjects who enroll in cancer-related clinical trials in the clinical trials management system, OnCore. Investigators, with the support of their research coordinators or the CTO, are responsible for subject registration. The PI has overall responsibility for ensuring patient eligibility in accordance with protocol criteria. The Clinical Research Coordinator (CRC) provides a crosscheck to ensure compliance with eligibility criteria. Once the investigator signs the consent document and crosschecking is complete, the CRC enrolls the subject in OnCore.

2. ***Data and Safety Monitoring***: The principal investigator is ultimately responsible for the data and safety monitoring of the trial and shall ensure that reportable serious adverse events and other unanticipated problems are reported to the IRB and other bodies as required within the appropriate timeframe. For investigator initiated interventional trials, the PI reports a summary of all trial activities, including AE/SAEs, to the DSMC for review at the timeframe indicated by the risk level assigned by the PRC.

   DSMC monitors UICC initiated studies in accordance with the identified risk level and decides whether a study should be continued based on criteria outlined in DSMP. This recommendation is communicated to the PRC.

3. ***Scientific Progress Review***: The PRC is responsible for the ongoing scientific review of all UICC studies. A determination of whether there have been changes in the scientific merit occurs at least annually through the continuing review process. PI must submit annual progress reports to the PRC for all open to accrual clinical trials. The monitoring of accrual occurs more frequently and in accordance with the accrual monitoring policy of the PRC. The goal is to terminate low accruing trials that will not realize their accrual targets within a realistic timeframe.

   The PRC determines whether a study should be allowed to continue based on accrual and scientific integrity of the study. Its determination to terminate a protocol is reported to the IRB.

4. ***Annual IRB Review***: All UICC investigators are required to submit an application to the IRB for continuing review each year. The submission includes the data and safety monitoring reports received by the investigator, information on accrual, a summary of adverse events, publications based on study findings, and publications within the scientific community that may affect the outcome of the current trial.

   The continuing renewal application is reviewed by the IRB and a determination is made as to whether the study should be continued based on a review of all materials and other information that may have been submitted to the IRB in the form of amendments. A letter is sent to the UICC investigator notifying him/her of the recommended action with a copy sent to the CRC or CTO for inclusion in the study file. If the IRB determines that a study should not be allowed to continue based on the DSMC report and/or the audit of data, the IRB immediately notifies the UICC investigator that the study has been closed (or suspended until the necessary amendments are submitted and approved by the IRB as required).

   Any determination by the IRB due to safety or non-compliance issues that results in temporary or permanent suspension of an NCI-funded clinical trial shall be reported by the IRB to the NCI grant program director responsible for funding the trial, and other appropriate agencies, with a copy of the communication to the principal investigator. These closures will be reported to the NCI Program Director within 10 working days of the determination.

5. ***Reporting:*** The actions taken by the DSMC, PRC, or IRB, are communicated in writing to the investigator. The investigator is responsible for complying with any required actions and providing a timely response, as required.

   Reports of study non-compliance, closure, or suspension are also sent to the Associate Director for Clinical Research.

The Committee Chairs and/or the Associate Director for Clinical Research are responsible for verifying that the investigator has complied with the recommended action.

4.3 Requirements for Submission of Monitoring Plan

Every interventional UICC protocol must include a plan for data and safety monitoring. The PRC will not accept an interventional protocol for review unless it has a monitoring plan.

The requirements for externally monitored trials were previously described in section 2.2.1. The requirement for UICC investigator-initiated pilot, phase I and phase II studies are that they are reviewed by the DSMC as described below. The requirement for Phase III studies is that they will be reviewed by an independent DSMB, as described in the study DSMP, which will list the Chair and the members of the DSMB.

4.4 Determination of Risk

Each UICC investigator-initiated trial undergoes scientific review by the PRC, in part, to ensure that procedures are in place to ensure the safety of subjects depending on the degree of risk of the study. The PRC assigns a category of risk to every UICC interventional study and the DSMC follows the plan of review for that category.

The purpose of assigning a level of risk (low, moderate, or high) to an UICC investigator-initiated trial is to ensure that data and safety monitoring activities are appropriate for the level of subject risk. In order to make a decision, the PRC reviews the following criteria:

- Expected duration of the study based on the study design and estimated rate of enrollment.
- Whether the study is multicenter
- Study population (e.g. children, pregnant women).
- Procedures to ensure the safety of subjects in accordance with the degree of risk.
- Methods to ensure the validity and integrity of the data, including an adequate biostatistical design and appropriate data analysis.

- Adequate data management systems including case report form records and a plan for data collection.

- Procedures for reporting serious adverse events to the appropriate departments/committees (e.g. IRB, FDA, NIH).

The risk level determines the frequency of monitoring for a protocol, which may be altered (i.e., increased) if issues arise.

4.5 Definition of Risk Levels

There are three levels of risk that may be assigned: High, Moderate and Low. Each category is described below.

High Risk
Studies assigned to the high-risk category include any therapeutic investigator-initiated pilot, phase I, II, or trials involving IND/IDEs, investigator-initiated multi-center trials, as well as any research involving recombinant DNA molecules (gene transfer) and cell-based therapies. These clinical trials will be reviewed on a quarterly basis by the DSMC.

Moderate Risk
Studies assigned to the moderate-risk category include most investigator-initiated, single center, Phase I or II trials using FDA-approved, commercially available compounds. Moderate Risk trials will be reviewed biannually (every 6 months) by the DMSC.

Low Risk
Studies assigned to the low-risk category include investigator initiated non-therapeutic trials. Low risk trials will be reviewed annually by the DSMC.

Investigator initiated phase III trials will also be reviewed by a study specific DSMB at timeframes specified in their approved DSMP.

4.6 Determination of Monitoring Frequency Based on Risk Assignment

The level of monitoring is dependent on the type of study and the level of monitoring conducted by an outside entity. For investigator-initiated interventional studies, the PRC will assign the risk level and this will determine the frequency of monitoring per the DSMP risk-monitoring policy. Once the protocol is approved and the risk is assigned by the PRC, then the DSMC follows the plan, making adjustments in frequency (i.e., increased monitoring) if and as needed over the course of the trial conduct.

The method and level of monitoring will correspond with the degree of risk involved in participation and the size and complexity of the study.

The CTO QA Specialist will monitor participant research charts on a quarterly basis and communicate audit results to the DSMC for review, per below:

Type of Trial	% of cases audited
UICC Investigator Initiated Interventional Therapeutic	50%
UICC Investigator Initiated Interventional Non-Therapeutic	10%

Above is the minimum percentage of charts, however if a major trend is identified, more charts will be reviewed.

5. UICC Data and Safety Monitoring Committee Role and Responsibilities

5.1 Role

The UICC Data and Safety Monitoring Committee (DSMC) serves as the body directly responsible for the data and safety monitoring of approved and activated UICC investigator-initiated interventional trials. DSMC serves as the Data and Safety Monitoring Board (DSMB) for UICC-approved cancer protocols that require, but lack, an external DSMB. The DSMC is a multidisciplinary committee that provides independent oversight of clinical trials conducted at UICC. The Committee is specifically charged with monitoring of safety of participants in cancer clinical trials, and the conduct and progress of the trial for all interventional investigator initiated cancer clinical trials at the UICC. The DSMC's efforts to assure patient safety in this regard complement those of other UICC offices and committees engaged in fostering and overseeing the conduct and compliance of these trials. The DSMC ensures effective communication, collaboration, awareness and compliance with federal, state, CCSG and institutional requirements as it relates to data and safety monitoring. The DSMC's roles include but are not limited to:

1. Initial review of newly opened protocols, or changes in protocol (including but not limited to: accrual, toxicity and efficacy analysis, statistical rules for dose escalation or cohort expansion) requiring DSMB review
2. Ongoing study monitoring: including accrual, reported adverse events, compliance issues (including major protocol deviations)
3. Consider factors external to study when relevant information becomes available, such as scientific or therapeutic developments which may have an impact on the safety of the participants or ethics of the study

4. Review of CTO QA audit findings and action plans (corrective and preventive) relating to data integrity or patient safety
5. Safety review: SAE and including all reportable adverse events
6. DLT review
7. FDA IND report review for PI held INDs
8. Recommend early termination based on efficacy results
9. Recommend termination due to unfavorable benefit-to-risk or inability to answer study questions
10. Recommend continuation of ongoing studies
11. Approve dose escalation or cohort expansion
12. Consideration of overall picture; primary and secondary analysis
13. Modify sample sizes based on ongoing assessment of event rates
14. Review final results for accuracy and completeness of data

5.2 Authority

The DSMC has the authority to require amendments to a protocol, suspend a protocol, or recommend termination of a trial within its jurisdiction for data integrity and patient safety reasons.

Based on the DSMC committee vote, the DSMC may suspend a trial or recommend termination to the IRB for safety and ethical reasons, or may refer scientific merit concerns to the PRC for follow-up. The DSMC may also institute other appropriate conditions needed for subject safety. As an example, if a trial has been deemed high risk and the DSMC would like monthly meetings with the PI this can be mandated or if the PRC has flagged an inadequate DSMB from a pharmaceutical company they can request that the DSMC have a regular review of the study.

5.3 Responsibilities

The DSMC is charged with reviewing all institutional cancer related prospective studies involving human subjects designed to answer specific questions about the effect or impact of particular biomedical research or behavioral interventions; these interventions may include drugs, treatments, procedures, devices, or behavioral or nutritional strategies. Participants in clinical trials may be patients with cancer or people without a diagnosis of cancer, but at risk for developing cancer in the future. It is recognized that clinical trials sponsored by NCI, NCTN, and industry are continually monitored for compliance by external parties. However, institutional clinical trials without outside sponsorship are not audited and are the focus of the monitoring system described here.

The types of trials covered under the scope of the DSMC are:

1. An *investigator-initiated* (sometimes referred to as *institutional*) clinical trial is defined for the purposes of these guidelines as a clinical research study authored by a member of the UIC faculty or staff. Such studies are not primarily sponsored or subject to scientific review or monitoring by an outside agency (e.g. industry, cooperative group, NCI, NIH, FDA, or other institution). Although an investigator may obtain investigational drugs and/or funding from an outside agency or industry in support of the research, if the clinical trial is not subject to monitoring by that agency it is categorized as an investigator-initiated clinical trial and internally monitored by the DSMC.

2. Any study that a UIC Principal Investigator is collaborating/participating in that does not have an adequate DSMP as determined by the PRC.

The types of trials not covered by the DSMC are:

1. Phase III investigator initiated therapeutic interventional clinical trials involving significant risk are reviewed by Independent Data and Safety Monitoring Boards (DSMBs) established by the Principal Investigator and supported through the funding agency. The study specific DSMP containing plans for the study's DSMB is reviewed for appropriateness by the PRC. Individuals who are invited to become members of the Independent DSMB should identify any perceived or real conflicts of interests, and these should be considered before formal appointment. Study specific DSMB reports are provided to the DSMC.

2. Externally sponsored investigator initiated trials. This type of investigator initiated trial will follow its own institution's DSMP. That institution will be the one responsible for monitoring of the trial.

5.4 Membership Composition of the DSMC

The DSMC includes representation from the following groups: the Department of Pharmacy, Department of Biostatistics, UICC members involved in clinical research, other UIC faculty who provide relevant expertise, and the UICC OCTO.

Current voting members include:

1. The DSMC Chair
2. The DSMC Vice Chair
3. Pharmacy representative
4. Biostatistician representative
5. UICC members with representation from Medical oncology (including neuro-oncology), surgery, radiology, radiation oncology, and nursing

Non-voting attendees include:

1. QA Specialist
2. DSMC Personnel
3. CTO Clinical Research Manager or CRC

5.5 Membership Appointments

The DSMC Chair and Vice Chair are identified by the Associate Director of Clinical Research and presented for review and approval by the Cancer Center Director. Potential DSMC members are identified by Associate Director for Clinical Research and the DSMC Chair and Vice Chair and presented for review and approval by the Cancer Center Director. Membership from the groups listed above ensures appropriate representation and communication with those groups that share responsibility for patient/participant safety issues related to UICC trials.

Members are appointed for three years, which is renewable annually by mutual consent with a two-term limit subject to extension by the Associate Director for Clinical Research. Ad hoc members may be appointed by the Chair, as needed.

5.6 Member Responsibilities

The members of the DSMC are expected to be familiar with protocols being reviewed. Members are also expected to be familiar with scientific and therapeutic advances as they relate to the protocols being reviewed. Members are expected at a minimum to attend 10 of 12, or 85%, of regularly scheduled meetings.

Each study will be assigned a primary and secondary Medical Monitor. Medical Monitors are responsible for reviewing all adverse events (in addition to unexpected adverse events), safety data, efficacy data, and protocol deviations in the ongoing clinical trial at each new dose level prior to dose escalation. It is important to note that the Medical Monitor reviews all SAEs and major protocol deviations reported on their assigned studies in real time. The Medical Monitor also provides a summary of his/her review to the DSMC for review prior to the DSMC meeting, and makes recommendations to the DSMC during the meeting. Secondary Medical Monitors will be responsible for reviewing all adverse events (in addition to unexpected adverse events), safety data, and protocol deviations in the ongoing clinical trial at each new dose level prior to dose escalation. If the primary Medical Monitor is unavailable for study review, the secondary Medical Monitor will serve as the primary Medical Monitor in the interim.

A Biostatistician should provide suggested formats or templates for data presentation including efficacy reporting for the initial meeting of the DSMC for initial study

presentation. The Biostatistician will also be responsible for reviewing all adverse events (in addition to unexpected adverse events), safety data, efficacy data, and protocol deviations in the ongoing clinical trial at each new dose level prior to dose escalation. The Biostatistician is responsible for making appropriate statistical recommendations regarding the ongoing design of the study, and presenting quarterly efficacy reports for review.

5.7 Conflict of Interest

UICC DSMC members are subject to the UIC and UICC policies regarding standards of conduct and conflict of interest. Individuals who are invited to be voting members, non-voting members, or attendees of DSMC meetings must disclose any potential or real conflict, including financial terms, to the Chair and the relevant UICC official prior to accepting a position. Decisions relative to conflict of interest are to be made based on institutional policy.

No one who has a direct or indirect relationship with the study under review is allowed to serve as a Medical Monitor (see description below). In addition, the PI is not allowed to be present during DSMC deliberations or cast a vote if they are a research team member of the study being reviewed or if they have a conflict of interest due to a relationship with the sponsor, intellectual property ownership with study investigators, or personal financial investments related to the study or study sponsor. Co-investigators are allowed to be present during discussion but must abstain during voting.

5.8 DSMC Personnel

The DSMC Personnel provides administrative support to the DSMC Chair, Vice Chair and committee. The DSMC Personnel prepares the meeting packet and informs the Committee with any updates. These include studies in progress and other information to facilitate the committee's ongoing review of protocols. The personnel maintains and distributes the meeting minutes from the DSMC. The minutes include attendance, quorum, conflict of interest, study title, review comments, votes and outcome of the trial review.

5.9 DSMC Monitoring Process

The monitoring process is as follows:

1. Each protocol is assigned to a primary and secondary Medical Monitor and a Biostatistician. This is a physician or another qualified member of the DSMC who has expertise in the therapeutic area of the protocol and is not directly involved in this trial. The Medical Monitor is responsible for reviewing all adverse events (in addition to unexpected adverse events), safety data, and activity data observed

in the ongoing clinical trial at each new dose level prior to dose escalation. The Medical Monitor also provides a summary of his/her review to the DSMC for review prior to the DSMC meeting. It is important to note that the Medical Monitor reviews all SAEs and major protocol deviations reported on their assigned studies in real time.

2. The PI, or their designee, is responsible for entering all adverse experiences and protocol deviations into OnCore to allow for reporting to the DSMC of all AE/SAEs, safety and toxicity data, and protocol deviations that have occurred for review at the frequency specified by the risk level assigned to the study.

3. The summary of all adverse events and protocol deviations are submitted to the DSMC, and these reports are reviewed during the DSMC meetings that take place per the frequency specified by the study's risk level. Participants are only identified by initials and no other personal health information (PHI) is included in the reports.

The Medical Monitor may recommend reporting adverse events and relevant safety data not previously reported, and may recommend suspension or termination of the trial based on their review of AE/SAE data and protocol deviations observed throughout the life of a clinical trial. In such circumstances, an ad hoc DSMC meeting will be convened to discuss corrective actions with the PI.

PIs can appeal any DSMC decision by submitting a written request for an additional review to the DSMC. However there is no appeal process beyond the DSMC and the final DSMC decision cannot be overturned.

5.10 Meeting Frequency

The DSMC meets monthly to review the all active research protocols under DSMC purview. Additional DSMC meetings are scheduled based on the nature and number of trials being monitored over a specified time period. The DSMC meets (by conference call or in person) within one business day following the notification of an unexpected serious adverse event felt to be related to the study treatment (see section 7, Serious Adverse Event Reporting).

5.11 Meeting Format

For DSMC meetings, the DSMC personnel is responsible for meeting preparations under the direction of the Chair and for preparing the DSMC meeting packet, which includes an agenda, minutes from the prior meeting, a list of current internally-reviewed

DATA SAFETY MONITORING COMMITTEE

IITs, applicable PI study reports, and any other pertinent information to be discussed. Also in the meeting packet, which is sent to members at least one business day in advance, are copies of all reported AEs, SAEs, and major protocol deviations during the reporting period for each clinical trial under review. The PI may be asked to provide a detailed and comprehensive narrative assessment of current adverse events to date, indicating their possible significance and whether these toxicities have affected the conduct of the trial. DSMC members are provided with the principal investigator's assessment in a report summarizing adverse events, safety data, and activity data observed during the specified time period described in each protocol.

Before commencing the meeting, members are reminded that meeting proceedings are confidential and conflicts of interest are noted in the meeting minutes. The DSMC Personnel confirms that the meeting has a quorum. Quorum for DSMC meetings is defined by having 50% of voting members in attendance in person or via conference call. Final decisions will not be made without appropriate representation.

New UICC investigator initiated interventional studies are assigned a primary and secondary Medical Monitor by the DSMC Chair or Vice Chair. Medical Monitors receive SAE reports within 1 business day of the study team becoming aware of the event. Medical monitors are responsible for reviewing the all reported information as submitted to the DSMC meeting, and in turn completing a Medical Monitor Report (see attached template) for inclusion in the DSMC meeting packet. During the meeting, the Medical Monitor leads a discussion on the general conduct of the trial, a review of outcome results (toxicity and adverse events). The Medical Monitor for the specific trial makes a recommendation (full approval, conditional approval, suspension, closure, including recommendation about amendments), and then voting members vote on the status of each study.

A summary of the committee's determination and findings are sent after the meeting within 5 business days to each investigator and his/her study team, as well as the PRC, for submission by the study team to the UIC IRB.

In its notification to the PI, the DSMC provides the rationale for its determination. It may also include recommendations/requirements that will lead to improved participant safety and/or efficacy, significant benefits or risks that have developed, or other changes determined to be necessary. The DSMC determination and rationale are included in the continuing review application submitted to the UIC IRB.

Should the DSMC take note of slow accrual or lack of scientific progress during its review of a protocol, it will refer such matters to the PRC for appropriate review.

Type of DSMC Meeting	**Frequency**	**Outcomes**
Regular DSMC Meeting	Quarterly	- Full Approval

		- Conditional Approval - Suspension - Closure
Ad Hoc DSMC Meeting	As Needed	- Full Approval - Conditional Approval - Suspension - Closure
Dose Escalation/Cohort Expansion	Per Protocol	- Full Approval - Conditional Approval - Suspension - Closure

5.12 Frequency of Trial Review

All UICC Investigator-initiated studies require continuous monitoring by the PI of the study. However, the determination of how often a study will be reviewed at a DSMC meeting is dependent of its level of risk that was assigned by the PRC.

Level of Risk	**Frequency of DSMC Review**
Low Risk	Once a year
Moderate Risk	Every 6 months
High Risk	Quarterly

RISK CATEGORY	STUDY PROJECT CHARACTERISTICS	UICC DSMC STUDY PROGRESS REPORTING REQUIRED?[1]	UICC DSMC AUDIT FREQUENCY[1]
Low	- Investigator initiated non-therapeutic trials.	Annually	Quarterly
Moderate	- Investigator-initiated, single center, Phase I or II trials using FDA-approved, commercially available compounds.	Semi-Annually	Quarterly
High	- Therapeutic investigator-initiated Pilot, Phase I, II, or trials involving IND/IDEs - Investigator-initiated multi-center trials - Research involving recombinant DNA molecules (gene transfer) and cell-based therapies	Quarterly	Quarterly

[1] Time points are based from the date of trial activation.

5.13 DSMC Dose Escalation/Expansion Approval Meeting

Prior to proceeding to the next dose cohort or expanding the current cohort the PI must get DSMC Medical Monitor approval, with input from the DSMC Chair or Vice Chair and DSMC Biostatistician. The procedure for obtaining approval is as follows:

- The PI or their designate must contact the DSMC Personnel to inform them that they would like to expand the current cohort or proceed to the next cohort.
- OnCore, UICC's clinical trial management system, is utilized to collect data for all investigator initiated therapeutic clinical trials. The DSMC Personnel will run a report of toxicities and efficacy for subjects in the current cohort, and for all patients on study, and provide it to the Biostatistician and Medical Monitor for the study.
- The DSMC Personnel will inform the Medical Monitor and Biostatistician of the specific trial that the PI is seeking a dose escalation or cohort expansion (whichever is applicable). At that time, the DSMC Personnel will begin working with study team to coordinating a meeting within 5 business days of the PI request.
- The Medical Monitor, DSMC Chair or Vice Chair, Biostatistician, PI and the DSMC Personnel (or designee) must be present at the meeting.
- Once the meeting has been held, the DSMC Personnel will draft the decision letter (approval/disapproval), and this will be forwarded to the PI.
- Dose Escalation and/or Cohort Expansion cannot begin prior to approval being granted at the meeting with the Medical Monitor.
- The DSMC Decision Letter must be maintained in the regulatory files and sent to the IRB at the time of Continuing Review.
- PIs can appeal any DSMC decision by submitting a written request for an additional review to the DSMC. However there is no appeal process beyond the DSMC and the final DSMC decision cannot be overturned.

5.14 Reporting of DSMC Outcomes to the IRB

The summary of all discussions of adverse events are included in the UICC investigator's reports to the UIC IRB as part of its annual progress report.

6. Individual Data and Safety Monitoring Boards

DATA SAFETY MONITORING COMMITTEE

An individual DSMB is to be formed if the study is an interventional investigator initiated randomized Phase III trial. Members are selected by the PI and should largely be comprised of individuals that are not affiliated with UICC or UIC. Members will be selected for the knowledge of clinical research and may include clinical investigators, biostatisticians, other scientists and lay individuals who are familiar with clinical research methodology.

The DSMP outlined in the Phase III UICC investigator-initiated trial is reviewed by the PRC and IRB as part of the protocol submission and review process. The plan will include a description of the reporting mechanisms of adverse events to the IRB, the FDA, and, if applicable, the NIH. The plan is also expected to reflect the IRB's requirements for reporting serious adverse events occurring at UIC and off-site locations.

Individuals who are invited to be members of the Independent DSMB must disclose any potential or real conflict, including financial terms, to the PI and the relevant UICC official prior to accepting a position. Potential conflicts that develop during a member's tenure must be disclosed in a similar manner. Decisions relative to conflict of interest are to be made based on institutional policy.

The protocol-specific, independent DSMB reports its findings and recommendations to the DSMC. The DSMC reviews the report and makes a final recommendation to the UIC IRB, or to the PRC for scientific merit and progress-relevant matters.

Recording and reporting requirements for Phase III trials include:

1. All AEs/SAEs must be recorded for each subject within the subject's research file.

2. Each event must include grade, relationship, expectation and intervention (if applicable)

3. All AEs/SAEs and protocol deviations must be reported according to the DSMC AE/SAE reporting Guidelines (please see DSMC Reporting Guidelines below), unless otherwise excepted by the DSMC and noted in the approval letter (see AE/SAE Reporting Addendum below).

7. Serious Adverse Event/Adverse Event Reporting for UICC Investigator Initiated Studies

7.1 Definition of Serious Adverse Event (SAE)

An SAE is any adverse event occurring at any dose level that:

- Is fatal;
- Is life-threatening (subject is at immediate risk of death as a result of the event);
- Is disabling or incapacitating;
- Requires inpatient hospitalization or prolongs current hospitalization (Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization, the event is an SAE.);
- Is a persistent or significant disability/ incapacity;
- Is a congenital abnormality in the offspring of a subject who received the drug; or,
- Is an event which, though not included in the above points, may jeopardize the subject or may require intervention to prevent one of the outcomes listed above.

7.2 Reports and Recording

All AEs/SAEs must be recorded for each subject within the subject's research file and in OnCore. In addition, each event must include severity, relationship to intervention, expectedness and action taken (if applicable). Every UICC investigator-initiated interventional protocol includes requirements for the reporting of adverse events based on the current version of the Common Terminology Criteria for Adverse Events (CTCAE). The investigator is required to submit all local, unanticipated, SAEs to the IRB within 5 days and all related unanticipated AEs associated with a greater risk of harm than previously known require a report within 15 days. In addition, if the study is conducted under an IND, unexpected, related and serious adverse events (SAEs) are reported to the Food and Drug Administration (FDA).

For interventional investigator initiated studies reviewed by the DSMC, the investigator is required to submit all unexpected and serious adverse events to the DSMC Medical Monitor, with a copy to the DSMC Chair or Vice Chair, within one business day of becoming aware of the event. All AE/SAEs will be reported to the DSMC as required by the risk level assigned to the study. However, if the Medical Monitor determines corrective action is necessary, an "ad hoc" DSMC meeting will be called. For an unexpected serious adverse event felt to be related to the study treatment, the DSMC will meet (by conference call or in person) within one business day following the notification of the event to review the report. Sites of multi-site investigator initiated trials for which UICC is the lead site are required to enter serious adverse events (SAEs), dose-limiting toxicities and stopping rule events into UICC's Clinical Trials Management System, OnCore. If subject data is not being collected in UICC's OnCore system, data reports consistent with the requirements outlined in this DSMP must be provided to the UICC DSMC as requested for review. In addition, clinical trial sites are required to submit SAE reports electronically to the DSMC according the same timeframes as for local SAEs. Reporting requirements for Phase III investigator-initiated studies are described in the study specific DSMP reviewed by the PRC and UIC IRB. For studies with an approved DSMC AE/SAE reporting Addendum reporting exclusions will only

reflect those specified in the DSMC decision letter, all others must adhere to the DSMC Reporting Guidelines.

7.3 AE/SAE Reporting Addendum

A DSMC AE/SAE Addendum is provided on a study specific basis to allow for certain expected SAEs to be excluded from the reporting requirements to the DSMC. The DSMC AE/SAE Addendum is documented in a DSMC approval letter. If a PI receives an approval for an addendum the specific approval letter will detail specific reporting procedures that differ from the DSMC Reporting Guidelines.

The procedure for obtaining an AE/SAE Addendum is as follows:

- The Principal Investigator must provide written documentation addressed to the Medical Monitor for their study and the DSMC Chair or Vice Chair. This documentation must detail the rationale for the requested addendum.
- The rationale should detail the specific events and the applicable grades that the PI is seeking to addend in reference to reporting as per the current DSMC Guidelines.
- This drafted documentation should be forwarded to the DSMC Personnel.
- The DSMC Personnel will then forward all documentation to the Medical Monitor and the DSMC Chair or Vice Chair for review and filed as documentation of the request.
- In order to maintain proper documentation, all questions or communications from the Medical Monitor and DSMC Chair or Vice Chair should be sent in written format (i.e. email) to the DSMC Personnel.
- When both Medical Monitor and DSMC Chair or Vice Chair come to an agreement, this is sent to the DSMC Personnel, who sends the decision out to the DSMC for agreement with the decision.
- All DSMC decisions letters (approval/disapproval) will be prepared by the DSMC Personnel and sent to the PI and the Clinical Research Coordinator for the specific study.
- The DSMC decision (approval/disapproval) letter must be retained in the regulatory file and presented to the IRB at the time of continuing review.
- All reporting procedures will follow the current DSMC Guidelines until an approval is granted.
- The PI will amend the protocol to reflect the approved amended AE/SAE reporting language and submit the amendment through the standard process.
- If an approval is not granted for the requested addendum all AEs/SAEs must be reported following the current DSMC Reporting Guidelines.

8. Protocol Deviation Reporting for UICC Investigator Initiated Studies

8.1 Definition of Protocol Deviations (PDs)

A protocol deviation is defined as any deviation, whether accidental, unintentional or intentional, from the IRB-approved protocol that is implemented prior to IRB approval. For the purposes of this policy, deviations are categorized as Major and Minor:

- Major protocol violations are those that cause harm to subjects or others, place them at increased risk of harm, impact the scientific integrity of the research, compromise the human subject protection program, have the potential to recur or represent possible serious or continuing non-compliance Major protocol violations may represent an unanticipated problem (particularly when unintentional) and/or potential serious noncompliance and require prompt reporting.
- Minor protocol violations are those not meeting at least one of the criteria in the preceding sentence and do not require reporting to the IRB. They should be reported to the sponsor as described in the protocol and written documentation of their occurrence filed with the investigator's study records.

8.2 Reports and Recording

All PDs must be recorded in the research file and in OnCore. The investigator is required to submit all Major PDs that are unplanned and unintentional to the IRB within 5 days. For interventional investigator initiated studies reviewed by the DSMC, the investigator is required to submit all Major PDs to the DSMC Medical Monitor, with a copy to the DSMC Chair or Vice Chair, within 24 hours of becoming aware of the event. All PDs will be reported to the DSMC as required by the risk level assigned to the study. However, if the Medical Monitor determines corrective action is necessary, an "ad hoc" DSMC meeting will be called. Sites of multi-site investigator initiated trials for which UICC is the lead site are required to enter all PDs into UICC's Clinical Trials Management System, OnCore. In addition, clinical trial sites are required to submit Major PDs electronically to the DSMC according the same timeframes as for local Major PDs. Reporting requirements for Phase III investigator-initiated studies are described in the DSMP reviewed by the PRC and UIC IRB.

9. Quality Assurance

9.1 Quality Assurance Unit

The Quality Assurance Unit (QAU) is administratively managed in the CTO and is charged with ensuring protocol compliance with all UICC policies and procedures, IRB

policies, FDA regulations, ICH-GCP, CTMB guidelines, and CCSG guidelines, as well as adherence to the protocol through auditing and monitoring activities performed throughout the year. All studies approved by the PRC fall within the Unit's purview regardless of study type and sponsor. While administratively located within the CTO, the auditor reports to the Associate Director for Clinical Research and the DSMC.

The QAU is directly responsible for conducting required and ad hoc DSMC audits. Audits include the review of consent, eligibility, treatment, AEs/SAEs, adherence to study parameters, accuracy of case report forms, drug accountability, and review of the regulatory file. The QAU oversees the creation of any corrective and preventative action plans (CAPAs) to ensure that issues are addressed satisfactorily and the QAU will then follow-up and confirm the staff's compliance with the CAPAs.

For externally monitored studies, the QAU receives all study monitor reports. The QAU identifies issues and trends emanating from those reports. The QAU also participates in external audits of studies performed at UICC. The results of audits and reporting of trends are presented to the DSMC and the Clinical Research Executive Committee. Major concerns about PI behavior, scientific misconduct, or systemic issues are reported to the Associate Director for Clinical Research.

9.2 Quality Assurance Auditing

All UICC investigator-initiated interventional studies are audited according to the risk level assigned to the study.

9.2.1 Auditing Standards

The audit will be conducted in accordance with internal policies and the NCI Clinical Trials Monitoring Branch audit guidelines to ensure the accuracy of data, adherence to the protocol and the protection of human subjects.

9.2.2 Case Selection

Once a clinical trial is identified for auditing, the QAU staff member or designee arranges for a random selection of cases to audit from among all subjects registered in the database, as specified in section 4.6. If subjects of UIC affiliate sites are enrolled, cases from those sites are randomly selected for review as well. Copies of these case materials are to be sent by the affiliate to UIC for review.

9.2.3 Study Team Notification

The Principal Investigator and Study Coordinators are notified in advance of the audit. The QAU staff contacts the study team to arrange for a mutually agreed upon time for the auditing session.

9.2.4 Audit Preparation

The investigator and the research staff are responsible for gathering all of the materials germane to the review, including Medical records, case reports forms, and any other research records as requested. If affiliate sites are enrolling subjects, materials needed for the review from the outside centers must be provided to the Quality Assurance Specialist.

9.2.5 Audit Focus

Audits have three primary areas of focus:

1. Regulatory/IRB procedure compliance: Review of current protocol, amendments, participant consent form, adverse event submissions, and continuing review documents.
2. Pharmacy/IND procedure compliance: Review of procedures for drug storage, a system for tracking IND drugs and drug accountability.
3. Case records: Each case audited is reviewed to determine that there is a signed and dated participant consent form, the subject has met the eligibility criteria, received the correct treatment, dose modifications per protocol (if required), that there is an objective treatment response, and any toxicities are documented and reported to the UIC IRB.

9.2.6 Access to Information

The UICC investigator is required to provide the audit staff with access to all source documentation. Source documentation may include, but is not limited to the following:

1. Inpatient and outpatient Medical records, including progress notes, diagnostic reports (imaging studies, ECGs, pathology reports), laboratory data, and admission forms
2. Study flow sheets and other research records that are signed and dated
3. Appointment books
4. Subject diaries/calendars

9.2.7 Exit Interview

At the end of each audit visit, an exit interview with the auditor, PI, and study staff takes place. During this time, all audit findings are reviewed and discussed, and

any questions can be answered. Additionally, the PI and study staff will receive a copy of the audit report, which includes corrective action items.

9.2.8 Distribution and Review of Audit Reports

All audit reports are submitted to the DSMC for a review of the findings and follow up actions as appropriate. A copy of the report and recommended DSMC actions is sent by the PI to the IRB via an IRB prompt report. The committee regards the review process as dynamic and constructive rather than punitive. The review process is designed to assist Principal Investigators in ensuring the safety of study subjects and the adequacy and accuracy of any data generated. The DSMC may, based on the audit report, request modifications to, suspend or terminate the trial.

9.2.9 DSMC Action Based on Audit Report

Audit reports are presented at the next scheduled DSMC meeting. The DSMC can take the following actions:

1. Accept the report without further comment.
2. Accept the report with recommended/required changes to the protocol and/or participant consent form as evidence by the submission of amendments to the protocol and/or participant consent form as required.
3. Recommend the suspension of the study accrual until the necessary amendments have been submitted and approved by the PRC and IRB as required.
4. Ask the investigator(s) and/or research staff for additional information pending action
5. Suspend accrual to study

A copy of the final audit report, including the DSMC's determination and recommendation, as relevant, is provided to the UICC investigator with instructions to submit the report to the UIC IRB. If the DSMC determines that a study should be closed or suspended (pending submission of amendments to the protocol and/or participant consent form), the DSMC will also notify the UIC IRB.

9.3 Additional Randomly Selected Audits

In addition to the risk-level dependent audit frequency, the QAU may elect to perform random audits of participants entered into interventional UICC trials to verify that there

is a signed and dated patient consent form, that the participant has met the eligibility criteria, and that AEs/SAEs are documented and reported to the sponsor if applicable and the UIC IRB.

9.4 For Cause Audits

Any study of UICC may also be audited at any time by the QAU at the request of the DSMC, PRC, IRB, and/or the UICC Associate Director of Clinical Research. Reasons for special audits may include prior monitoring or audit findings, allegations of scientific misconduct, and where significant irregularities are found through quality control procedures. Any irregularities identified as part of this process would result in a full audit of that study.

9.5 UICC Investigator-Initiated Multi-Site Trials

The PI is ultimately responsible for monitoring compliance at all participating sites and has the authority to suspend and/or close a participating site based on lack of compliance.

Institutions participating in UICC lead investigator-initiated interventional multi-center trials may self-monitor. They are required to follow the UICC DSMP and CTO Internal Audit SOP or, if an NCI Designated Cancer Center, they may follow their own NCI approved Data and Safety Monitoring Plan. Alternatively, an external monitoring entity can be used to monitor the trial if the UICC DSMP and CTO internal audit SOP are followed. The site must forward a copy of the final audit report to the PI and study staff.

The audit report is submitted by the UIC PI or study staff to the DSMC for review and action. A copy of this report and recommended DSMC action is sent to the PRC and IRB. The UIC IRB may, based on the DSMC and auditor's recommendation, suspend or terminate the trial.

In addition, participating institutional investigators must, on an ongoing basis, submit case report forms with copies of corresponding source documentation (as described above) to the principal investigator for each participant entered into the study. The principal investigator or his/her designee is responsible for reviewing documentation submitted by the participating institution for accuracy.

Each participating institutional investigator is required to submit all serious on-site adverse events to the UICC principal investigator within 1 business day of awareness of the event. The UICC principal investigator must submit information regarding non local SAEs to the DSMC, and to the UIC IRB consistent with the requirements for the submission of non-local adverse events, and other regulatory agencies as necessary (e.g. FDA for IND trials).

DATA SAFETY MONITORING COMMITTEE

Any SAEs occurring at UIC must also be reported to participating sites in accordance with the same timeframes as listed above for sites reporting to UIC. The participating sites will be responsible for reporting UIC SAEs to their respective IRB in accordance with their institutional expedited reporting policies.

Appendix 1: Dates of Prior Versions of UICC DSMP

Date	Version	Summary of Changes
XX-Jun-20	7.0	Seventh Iteration of DSMP
13-Jan-20	6.0	Sixth Iteration of DSMP
22-July-19	5.0	Fifth Iteration of DSMP
1-Feb-18	4.0	Fourth Iteration of DSMP
6-Oct-2015	3.0	Third Iteration of DSMP
13-Aug-2014	2.0	Second Iteration of DSMP
01-Mar-2011	1.0	First Iteration of DSMP

DATA SAFETY MONITORING COMMITTEE

Appendix 2: Abbreviations

CTO	Clinical Trials Office
CRC	Clinical Research Coordinator
CTAC	Clinical Trials Advisory Committee
CTEP	Cancer Therapy Evaluation Program
DM	Data Manager
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
EDDO	Early Drug Development Office
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IND	Investigational New Drug
IRB	Institutional Review Board
MM	Medical Monitor
NCI	National Cancer Institute
NIH	National Institutes of Health
CTO	UICC Clinical Trials Office
OHRP	Office for Human Research Protections
PHI	Personal Health Information
PI	Principal Investigator
PRC	Protocol Review Committee
PSU	Protocol Support Unit
QAU	Quality Assurance Unit
SAE	Serious Adverse Events
UICC	University of Illinois Cancer Center
UIC	University of Illinois, Chicago

DATA SAFETY MONITORING COMMITTEE

Appendix 3: DSMC Summary Report

Protocol SAE Counts

Protocol No.:	Library:	PI:		Sponsor:
Protocol Target Accrual:		Accrual To Date:		Protocol Status:
CC Total Accrual Goal (Upper):				IRB Expiration:
Short Title:				
Sources:				

Protocol SAE Counts

Arm	Category	Adverse Event Detail	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Relapse or Progression	Total							

Subject Specific Events Details

Study Site	Subject MRN	Subject Name	Event No.	Event Date	Follow-Up No.	Hospitalization	Death Occurred (days)	Adverse Event Details		
								AE Detail	Grade	Attribution

Subject Deviations Details

Study Site	Subject MRN	Subject Name	Deviation Category	Deviation Description	Date Discovered	Deviation Date	Effect on Patient Safety	Action Taken	Role Responsible for Action Taken	Has the integrity or validity of the data been compromised?	Was an IRB waiver granted?	IRB Reported Date

Protocol Toxicity Summary (AE Details are color coded to highlight trends)

Study Site	Subject MRN	Subject Name	Event No.	Event Date	Follow-Up No.	Hospitalization	Death Occurred (days)	Adverse Event Details		
								AE Detail	Grade	Attribution

Protocol SAE Report

Protocol No	PI	Protocol Status	SAE #	Overall Protocol Attribution	AE Grade	Event Narrative	AE Category	AE Detail	AE DLT	Source	Source Attribution	Event Date	Event End Date	Reported Date	Death Date	Death Occurred

Custom SAE Data Report

Protocol Details	Protocol Accrual	Protocol Disposition	Protocol Demographics	Protocol Status History	Protocol Responses	Protocol Survival	Protocol Accrual History	Subject Deviations	Protocol SAEs

Appendix 4: Medical Monitor Report Template

Data Safety Monitoring Committee (DSMC)
Medical Monitor and Biostatistician Report

IRB #:	
Principal Investigator:	
Protocol Title:	
Study Risk Level	☐ Low ☐ Medium ☐ High
Status of protocol: ☐ Open, accruing ☐ Suspended ☐ Open, not-accruing ☐ Closed ☐ Hold	
Study Type: ☐ Single Institution	☐ Multi-Institutional

Review Type:

☐ SAE (complete section A within 48 hours of receipt)
☐ Protocol Deviation (complete section B within 24 hours of receipt if serious, unexpected and related, 48 hours for all others)
☐ Dose Escalation/Cohort Expansion (complete section C by 48 hours prior to the DSMC meeting)
☐ Routine Review (complete section D by 48 hours prior to the DSMC meeting)

Review Instructions: Complete the section corresponding to each review type indicated AND section E, Preliminary Study Outcome Recommendation.

A. SAE:

Do you agree with how the SAE was categorized/attributed by the study team?: ☐ Yes ☐ No
If no, indicate areas of disagreement:

Do you recommend any changes to the SAE attributions?: ☐ Yes ☐ No
If yes, please specify and provide a rationale for this change:

Is corrective action necessary to alleviate risks to subjects (requires an Ad Hoc DSMC meeting)?:
☐ Yes ☐ No
If yes, please specify suggested corrective action:

Do you recommend any changes to the study protocol?: ☐ Yes ☐ No
If yes, please specify:

Do you recommend study closure?: ☐ Yes ☐ No
If yes, please justify reasons for study closure:

Was this SAE a Dose Limiting Toxicity?: ☐ Yes ☐ No
If yes, please complete section C below.

B. Protocol Deviation:
☐ Major Protocol Deviation ☐ Minor Protocol Deviation

Is corrective action necessary to alleviate risks to subjects (requires an Ad Hoc DSMC meeting)?:
☐ Yes ☐ No
If yes, please specify suggested corrective action:

Do you recommend any changes to the study protocol?: ☐ Yes ☐ No
If yes, please specify:

Do you recommend study closure?: ☐ Yes ☐ No
If yes, please justify reasons for study closure:

C. Dose Escalation/Cohort Expansion:
Total Number of DLTs:

Number of DLTs per each dose level:

Do you approve escalation to the next cohort, if applicable: ☐ Yes ☐ No

Do you recommend any changes to the study protocol?: ☐ Yes ☐ No
If yes, please specify:

Do you recommend study closure?: ☐ Yes ☐ No
If yes, please justify reasons for study closure:

D. Routine Review:

Are there any issues regarding accrual trend or history? ☐ Yes ☐ No
If yes, please specify:

Are there any issues regarding SAE trend or history? ☐ Yes ☐ No
If yes, please specify:

Are there any other issues and/or study flaws that need to addressed? ☐ Yes ☐ No
If yes, please specify:

E. Preliminary Study Outcome Recommendation (Required for all reviews, check all that apply):

☐ **Full Approval**
☐ **Conditional Approval**
Specify approval conditions:

☐ **Suspension**
Specify conditions for lifting suspension:

☐ **Closure**
☐ **Recommended protocol amendments**
Specify recommended amendments:

☐ **Other corrective actions (please specify):**

Medical Monitor/Biostatistician Signature: _____

☐ **Primary Reviewer**
☐ **Secondary Reviewer**

DATA SAFETY MONITORING COMMITTEE

For DSMC Administration Use Only

Final Committee Decision (check all that apply):
☐ **Full Approval**
☐ **Conditional Approval**
Specify approval conditions:

☐ **Suspension**
Specify conditions for lifting suspension:

☐ **Closure**
☐ **Recommended protocol amendments**
Specify recommended amendments:

☐ **Other corrective actions (please specify):**

Re- review study in:
☐ **3 months**
☐ **6 months**
☐ **1 year**
☐ **Other:**

<u>If applicable</u>:

DSMC Meeting Date

Agenda #