DATA AND SAFETY MONITORING PLAN

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EXECUTIVE SUMMARY

The Masonic Cancer Center (MCC) at the University of Minnesota (UMN) places the utmost importance on minimizing risk for the individuals participating in cancer related investigations. The primary responsibility for ensuring this safety is held by the principal investigator (PI) for the clinical trial. This data and safety monitoring plan outlines the roles and responsibilities of the principal investigator, Masonic Cancer Center and the University of Minnesota in maintaining the safety of cancer related clinical investigations. Diagrams of the clinical trial process and MCC’s organizational structure are found in Attachment 1: Clinical Trial Process and Attachment 2: MCC Organizational Chart.

The MCC Data and Safety Monitoring Plan (DSMP) details the roles and responsibilities of the three accountable units (PI, MCC and UMN) and the processes that are utilized by these accountable units to ensure the highest quality clinical research is conducted while optimizing participant safety.

The PI is responsible for all aspects of trial conduct including clinical trial management, data acquisition and data and safety monitoring. The monitoring and oversight of clinical trial conduct is directly based on risk assessment. This DSMP provides the detail necessary for the PI to provide the oversight necessary for compliance with local and federal regulations.

The MCC has the responsibility of clinical research oversight through the Executive Clinical Research Leadership (CRL) Committee. This committee oversees the function of the Cancer Protocol Review Committee (CPRC) and the Data and Safety Monitoring Council (DSMC) of the Masonic Cancer Center. The CPRC has the role of assessing scientific merit, assessing trial risk and confirming prioritization of clinical trial conduct within the Masonic Cancer Center. The DSMC has the responsibility of ensuring the safe conduct of clinical trials and compliance with trial data and safety monitoring plans.

The MCC exists and functions within the structure of the UMN and as such is subject to the University’s conflict of interest guidelines and regulatory standards. Links to these guidance documents are provided in the DSMP.
1. PRINCIPAL INVESTIGATOR RESPONSIBILITIES

The Masonic Cancer Center at the University of Minnesota places the highest priority on minimizing risk to individuals participating in cancer-related research. The PI of a clinical trial is responsible for the adequacy of the design and oversight of the trial. The PI holds full responsibility for personally conducting or supervising the conduct of the clinical study, including all clinical and regulatory activities.

The PI of a clinical trial may delegate tasks, but not responsibilities.

Principal Investigators must be aware of the specific responsibilities they undertake when conducting research. These responsibilities include all actions taken by anyone acting on the PI’s behalf, members of the research team, or any organization to whom the PI delegates tasks and activities. Regardless of who carries out a study-related activity, the PI is accountable for how the task is conducted.

1.1 UMN REQUIRED TRAINING

The University of Minnesota requires PIs to complete training in Human Subjects Protection, Good Clinical Practice (GCP) and Fostering Integrity in Research, Scholarship, and Teaching per Section 3.1 of the DSMP.

1.2 PROTOCOL DESIGN

The PI must ensure the protocol contains an adequate data and safety monitoring plan prior to submission to the Cancer Protocol Review Committee. The protocol data and safety monitoring plan must include, but is not limited to the elements listed below. The data and safety monitoring plan or a supplemental protocol document must specify who is responsible for conducting onsite monitoring, extent, frequency, and scope.

- Management, quality assurance, storage, and access to data
- Adverse event collection and reporting
- Dose limiting toxicity
- Stopping rules

1.3 RISK ASSESSMENT PLAN

The CPRC is responsible for determining a trial’s level of risk. Risk is determined by multiple factors including, but not limited to: trial phase, conflict of interest, trial complexity, whether the trial is conducted under an IND/IDE, and PI experience leading clinical trials. Assigned trial risk determines if a trial meets the requirements for clinical trial monitoring and the frequency of DSMC review. (see Attachment 3: MCC Risk Assessment Checklist)

1.4 CONFLICT OF INTEREST

The potential for a conflict of interest arises when a member of the study team is in a position to influence research decisions or trial conduct in ways that could lead directly or indirectly to financial gain or advantage for the study team member or his or her family.

The UMN has established mechanisms to identify and manage potential conflicts, including annual disclosure requirements, research and sponsored project application questions, and informal communications.

[http://www.compliance.umn.edu/conflictHome.htm]
1.5 TRIAL CONDUCT
Prior to implementing a trial, the PI must receive written approvals from the CPRC, Institutional Review Board (IRB), and Food and Drug Administration (FDA) if applicable. If the PI is a member of any of the approval committees, the PI must recuse himself/herself from the review and vote. The PI must ensure the trial is conducted according to the approved protocol and relevant regulations. To adequately conduct and supervise the conduct of the trial, the PI must:

- Know and follow MCC and University requirements and applicable FDA regulations
- Ensure continued scientific and clinical relevance and validity of the trial

1.6 REQUIRED REPORTING
The PI is responsible for ensuring the following reports are submitted appropriately and within their required timeframes as applicable for the scope and design of the trial per University and Federal guidelines:

<table>
<thead>
<tr>
<th>Report</th>
<th>Must Submit To</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAE Reports, including events that occur at affiliate and satellite sites (see Attachment 4: Serious Adverse Event Reporting SOP)</td>
<td>IRB, FDA, SAE Coordinator, Sponsor</td>
</tr>
<tr>
<td>Protocol Amendments</td>
<td>IRB, FDA, CPRC, Sponsor</td>
</tr>
<tr>
<td>Continuing Review Applications</td>
<td>IRB, FDA, CPRC</td>
</tr>
<tr>
<td>DSMC Progress Reports</td>
<td>DSMC</td>
</tr>
<tr>
<td>Suspension or termination of trial for safety or non-compliance</td>
<td>IRB, CPRC, FDA, DSMC, Executive CRL, Sponsor, NCI Program Director responsible for funding the trials</td>
</tr>
</tbody>
</table>

1.7 AFFILIATE SITE MANAGEMENT
Affiliate sites participation in investigator-initiated studies is the direct responsibility of the study PI. (see Attachment 5: MCC Procedures Manual for Affiliate Sites Template)

1.8 TRIALS CONDUCTED UNDER AN IND/IDE
A PI who holds an IND/IDE holds all PI obligations as well as all sponsor responsibilities, including all commitments outlined in FDA Form 1572 or the Protocol Statement. [http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?CFRPart=312&showFR=1&subpartNode=21.5.0.1.3.4]
2. MASONIC CANCER CENTER OVERSIGHT

2.1 EXECUTIVE CLINICAL RESEARCH LEADERSHIP COMMITTEE

The MCC’s Executive Clinical Research Leadership (CRL) Committee is responsible for overseeing all cancer-related clinical research. Executive CRL membership includes: MCC Director; Deputy Director; Associate Directors for Administration, Experimental Therapeutics, and Cancer Prevention and Control; CTO Medical Director and CTO Program Manager; Oncology Service Line Leadership: The Executive CRL meets monthly and its responsibilities include:

- Approving the Masonic Cancer Center’s Data and Safety Monitoring Plan
- Appointing the committee chairs and membership for the Data Safety and Monitoring Council and Cancer Protocol Review Committees
- Semi-annually reviewing both CPRC and DSMC action summaries

The Executive CRL Committee may take immediate action to suspend a trial if there appears to be excessive risk to subjects or the institution. (See Attachment 9: Executive CRL Roster.)

2.2 CANCER PROTOCOL REVIEW COMMITTEE

Responsibility

The Cancer Protocol Review Committee (CPRC) is responsible for reviewing cancer-related clinical trials for scientific merit and prioritizing protocols within the MCC. To ensure safety oversight throughout a trial, the CPRC must ensure the protocol data and safety monitoring plan includes all required elements, as referenced in section 1.2 of the DSMP. In addition, for investigator-initiated trials, the CPRC must assign trial risk.

The CPRC reviews all cancer-related protocols prior to IRB submission and continues to evaluate the scientific merit, priority, and progress towards accrual at least annually as long as a trial remains open to accrual.

The CPRC must close a trial to further accrual if the study:

- Is unlikely to meet its enrollment goal in the required timeframe
- No longer has scientific relevance

Membership

The CPRC is a multidisciplinary committee whose members’ expertise includes Adult and Pediatric Hematology/Oncology, Blood and Marrow Transplantation, Nursing, Surgical Oncology, Radiation Oncology, Pharmacology, Epidemiology, Biostatistics, and others. Members are selected by area of expertise to form a diversified group of clinicians and other professionals able to provide rigorous scientific review of study rationale and design. (See Attachment 7: CPRC Roster.)

Conflict of Interest

To preclude any conflicts of interest, when a member of the CPRC is the PI of a protocol under review, the member is recused from participating in the review and vote.
2.3 DATA AND SAFETY MONITORING COUNCIL

Responsibility
The DSMC provides ongoing data and safety oversight for investigator-initiated clinical trials in the MCC. The DSMC reviews trial progress reports to assess trial conduct and safety-related events and to determine if the potential benefit to subjects continues to outweigh the risks. The frequency of DSMC review is based on the trial risk determined by the CPRC per sections 1.3 and 2.2 of the DSMP.

The DSMC has authority to request clinical trial monitoring or DSMC review at more frequent intervals.

DSMC Clinical Trial Reviews
The DSMC reviews all interventional investigator-initiated clinical trials regardless of protocol type, e.g. therapeutic, supportive Care, etc. at least annually from the time a protocol is opened to accrual until it is closed to accrual and all subjects have completed treatment. These trial progress reports cover trial activity at the Masonic Cancer Center and, if applicable, any affiliate site(s) and include:

- Assessment of expectancy, attribution, and seriousness of adverse events
- Monitoring findings
- Protocol deviations
- Dose limiting toxicities and stopping rule events
- Independent notification of safety concerns from the IRB, CPRC, Executive CRL, or PI

If the DSMC identifies serious safety concerns, the Chair communicates these in writing to the trial PI with a specified timeframe for the PI to respond or resolve the issues, or requests a for cause audit to be conducted of the trial.

Suspending or Closing Trials
The DSMC has the authority and responsibility to suspend a trial if the risk to subjects or the institution seems excessive relative to the benefit to the subject. The full DSMC or the DSMC Chair acting independently may temporarily close a trial.

When the DSMC or DSMC chair rules to temporarily close a trial, the trial PI must communicate the decision to the Executive CRL, CPRC, IRB, and, if applicable, the sponsor, FDA, or other appropriate bodies.

Serious Adverse Event (SAE) Review
The DSMC reviews all SAE reports regardless of trial sponsor type or risk category to ensure that protocol and regulatory reporting requirements have been met. The PI is required to submit a corrective action plan if the number of SAE reports deficient in meeting these requirements is unacceptable.

Membership
DSMC membership is multidisciplinary, and members are selected from diverse areas including, Biostatistics, Adult and Pediatric Hematology/Oncology and Transplantation, Surgical Oncology, Pharmacology and others. (See Attachment 8: DSMC Roster.)

Conflict of Interest
When a member of the DSMC is the PI of a protocol under review, the member is recused from participating in the review and vote to avoid any conflict of interest.
Data and Safety Monitoring Boards

A Data and Safety Monitoring Board (DSMB), separate from the DSMC, is required for any investigator-initiated trial meeting the following criteria:

- Trial generating blinded, randomized data [DSMB members have access to un-blinded data.]
- Phase III single institution trial presenting more than minimal risk
- Phase III multi-institutional trial for which Masonic Cancer Center is the lead site presenting more than minimal risk without an external DSMB

A DSMB is required to meet at least annually or more often depending on the activity and nature of the clinical trial being monitored.

Multi-Site Investigator-Initiated Trials

Affiliate sites of multi-site Investigator-Initiated trials for which Masonic Cancer Center is the lead site are required to enter subject data, including adverse event and serious adverse events (SAEs), dose-limiting toxicities and stopping rule events into MCC’s Clinical Trials Monitoring System, OnCore. In addition, affiliate sites are required to submit SAE reports electronically to the MCC Clinical Trials Office. SAE and outside safety reports meeting the FDA’s criteria of a reportable SAE are distributed to all affiliate sites. (see Attachment 5: Masonic Cancer Center Affiliate Procedures Manual)

3. UNIVERSITY OVERSIGHT

3.1 PI RESEARCH EDUCATION REQUIREMENTS

The University of Minnesota has developed a comprehensive curriculum for the responsible conduct of research. [http://www.research.umn.edu/training/] The Office of the Vice President for Research (OVPR) is responsible for ensuring investigators complete OVRP-required training. Principal investigators and study staff must complete training workshops on Fostering Integrity in Research, Scholarship and Teaching, In addition, Principal Investigators and study staff must complete training in Human Subjects Protection and Good Clinical Practice before Institutional Review Board approval is granted. The OVPR holds the PI responsible for ensuring all study staff working under the PI complete the required research training.

3.2 INSTITUTIONAL REVIEW BOARD

The Principal Investigator of a cancer-related trial may not submit the protocol to the UMN Institutional Review Board (IRB) until permission is granted by the CPRC.

The IRB provides comprehensive oversight of clinical research to ensure the safety of all human subjects. The IRB is responsible for reviewing and monitoring research involving human subjects to protect the rights and welfare of the trial participants. The IRB is responsible for reviewing and ensuring:

- Risks and benefits to subjects are appropriate
- Trial is conducted in compliance with Federal regulations for the protection of human subjects
The IRB reviews the protocol, consent forms, amendments, related adverse events, protocol and regulatory compliance, and accrual progress at least annually until the trial is terminated. The IRB has the authority to approve, require modifications in, or disapprove all research activities, including proposed changes in previously approved human subject research. The IRB can suspend or terminate research for serious or continuing non-compliance with the Common Rule, DHHS regulations, institutional requirements, FDA regulations, or the IRB’s own findings, determinations, and requirements.

If the IRB suspends or terminates a trial, the PI must notify the Executive CRL, DSMC, CPRC, sponsor and other appropriate agencies.

3.3 IND/IDE OVERSIGHT

University faculty members who file an Investigational New Drug Application (IND) or Investigational Device Exemption (IDE) with the FDA must submit a copy of the IND/IDE application and other related documents (communications, safety reports, amendments, annual reports, etc.) to the Office of the Vice President for Research (OVPR).

OVPR is responsible for governing IND/IDE regulatory compliance and developing oversight processes to ensure IND/IDE holders meet their commitments and mitigate risks to faculty investigators and the institution.

OVERSIGHT PROCESS

4. MONITORING CLINICAL TRIALS

4.1 MONITORING OVERSIGHT

The National Cancer Institute (NCI) mandates that NCI-designated Comprehensive Cancer Centers maintain a system for oversight of all clinical research conducted in the cancer center. Clinical trial monitoring is critical to ensuring appropriate trial conduct, the validity and integrity of data, protocol compliance, and patient safety. Quality assurance and compliance oversight is provided by the coordination of MCC’s Clinical Trials Office (CTO) and Cancer Informatics Shared Services (CISS).

4.2 MONITORING ACTIVITIES

The Masonic Cancer Center may delegate or contract monitoring activities to organizations external to the MCC. All monitoring of institutional trials must comply with the UMN MMC Clinical Trials Monitoring Plan, UMN MCC Clinical Trials Office SOPs, and the UMN Cancer Center Data and Safety Monitoring Plan. The CTO Quality Assurance (QA) Manager is responsible for ensuring monitoring is conducted in compliance with these documents.

The QA Manager is required to routinely review monitoring reports to identify common issues across trials, investigators, IND/IDE holders, and time and develop a targeted corrective action plan for improvement.

4.3 MONITORING SCOPE

Cancer-related clinical trials must be monitored as described in this plan if either of the following conditions are met:

- High or moderate risk MCC investigator-initiated study (see Attachment 3: MCC Risk Assessment Checklist)
• Other high or moderate risk institutional trials where the sponsor organization has transferred monitoring responsibility to the MCC

The MCC does not monitor the following:
• Low risk trials, e.g. trials not meeting the definition of high or moderate risk (see Attachment 3: MCC Risk Assessment Checklist)
• Industry trials
• National Cooperative Group trials

4.4 MONITORING EXTENT AND FREQUENCY

The CPRC is responsible for assigning a risk level to each trial under its review (see Section 1.3). The risk level assigned determines the extent of clinical trial monitoring and frequency of DSMC review.

The MCC Monitoring Plan provides a detailed description of monitoring expectations with regard to extent. (see Attachment 6: MCC Clinical Trials Monitoring Plan) Complete and adequate monitoring visits must be conducted at least every six months and include:

• Review of regulatory documents
  o Including review of product accountability and integrity of the study blind

• Review of consent forms
  o 100% of subjects

• Verification of eligibility
  o 100% of subjects

• Verification of subject data against source records
  o 100% of subjects enrolled on high risk trials
  o 10% of subjects enrolled on moderate risk trials

• Protocol compliance (all tests and procedures completed in window)
  o 100% of subjects enrolled on high risk trials
  o 10% of subjects enrolled on moderate risk trials

• Adverse event and stopping rule reporting
  o 100% of subjects enrolled on high risk trials
  o 10% of subjects enrolled on moderate risk trials

At the end of each monitoring visit, a monitoring report is prepared and sent to the study PI. Monitoring reports include: 1) verification that all required essential documents and elements of the study were reviewed and 2) a list any findings. The monitor works with the PI and research staff until all findings are resolved. The monitor forwards any significant and ongoing compliance issues to the QA Manager who forwards to the DSMC as appropriate.
Multi-Site Investigator-Initiated Trials

Affiliate sites may self-monitor on multi-site Investigator-Initiated trials for which Masonic Cancer Center is the lead site. They are required to follow the MCC Monitoring Plan 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 MCC Monitoring Plan is followed.

5. QUALITY ASSURANCE AND COMPLIANCE AUDITS

Audits play a critical role in assuring that trials are conducted and data are collected, documented and reported in compliance with the protocol and all local and federal regulations. All active investigator-initiated trials may be subject to an internal audit of any aspect of trial conduct. Audits may include but are not limited to review of subject records, consent process and documentation, regulatory compliance, product accountability, PI oversight and protocol adherence.

5.1 ANNUAL AUDIT PLAN

The QA Manager develops an audit plan approved by the DSMC and carried out by the QA Manager or designee for verifying monitoring integrity and the effectiveness of CTO training and policies. Audit plans include any routine and process audits as described below. These plans are intended to guide quality oversight throughout the year, but may be modified to achieve the goal of quality assurance and compliance throughout the CTO.

- **Routine Audits**
  Focus on high risk investigator-initiated trials such as phase I trials or trials conducted under an IND or IDE. High risk trials will be subject to an audit after enrolling three or more subjects. A minimum of 3 subjects will be audited.

- **Process Audits**
  Used to identify trends of non-compliance and guide in the implementation of change and training as needed.

Directed (for cause) audits occur at the directive of the DSMC. These audits are typically conducted when clinical trial monitoring identifies a single egregious finding of non-compliance or continual documented accounts of possible noncompliance, data discrepancies or concerns over the ethical conduct of the study by the investigator.

Routine audits of high risk investigator-initiated trials will not be conducted at Masonic Cancer Center affiliate sites; however, affiliate sites are subject to directed audits as appropriate.

5.2 AUDIT FINDINGS

Audit reports are reviewed by the DSMC which categorizes the findings as acceptable, acceptable with follow up, or unacceptable. The PI is required to submit a corrective action plan for audit results not categorized as acceptable. The DSMC has the authority to suspend or terminate a trial at any time (see Section 2.3).

ADMINISTRATIVE INFRASTRUCTURE

The Masonic Cancer Center Clinical Trials Office provides the infrastructure necessary to assist investigators in the conduct of their clinical research. Specifically, the CTO provides administrative support to the Cancer Protocol Review
Committees and the Data and Safety Monitoring Council, and in addition, provides trial management services including protocol development, regulatory management, IND/IDE support, study coordination, data management and budget management, etc. (see Attachment 1: Clinical Trial Process and Attachment 2: MCC Organizational Chart)

The University of Minnesota requires all research support staff to complete training in Human Subjects Protection, Good Clinical Practice (GCP) and HIPAA and Data Privacy.

**DEFINITIONS**

**Affiliate site**: Hospital, clinic, or other provider of medical services that participates in an MCC investigator-initiated trial under the jurisdiction of a local IRB. Affiliate sites agree to abide by the processes for affiliates outlined in this DSMP.

**Cancer Protocol Review Committee (CPRC)**: MCC committee that conducts scientific review of all clinical research protocols conducted in the MCC. The CPRC monitors the progress of trials and may terminate protocols if found deficient in accrual or scientific merit.

**DSMB**: (Data and Safety Monitoring Board): An impartial group established to oversee a clinical trial and review the results to determine if they are acceptable. Members of a DSMB must be multidisciplinary and include members with relevant clinical and statistical expertise.

**DSMP**: Data and Safety Monitoring Plan: Describes how the PI will oversee research participant safety and welfare.

**IDE (Investigational Device Exemption)**: Authorization granted by the Food and Drug Administration (FDA) to use an investigational, non-commercial device in clinical trials. The FDA requires IDEs for significant risk devices.

**IND (Investigational New Drug)**: Authorization from the FDA to administer an investigational, non-commercial drug or biological product in clinical trials.

**Investigator-Initiated trial**: Trial planned and managed by the Principal Investigator.

**Monitoring**: Systematic, ongoing review of data integrity and investigator compliance with the protocol, GCPs, and regulatory requirements.

**Principal Investigator**: Person responsible for the conduct of the study at the clinical trial site. If a trial is conducted by a team of individuals at a trial site, the PI is the responsible leader of the team.
ATTACHMENT 1: CLINICAL TRIAL PROCESS

Pre-Approval

- PI Completes Trial Utilization Committee (TRUC) Application
- PM completes TRUC application and sends to TRUC Admin
- TRUC Team reviews study for feasibility

TRUC Approval

- TRUC Admin sends approval letter to research team

TRUC Disapproval

- TRUC Admin sends disapproval letter to PI stating reasons for disapproval

Regulatory Review

- CPRC Review
- FDA Review (if applicable)
- IRB Review

Active Trial Performance

- CPRC Disapproval
- CPRC Approval
- Disapprove/Clinical Hold
- FDA Approval
- IRB Disapproval
- IRB Approval

*DSMC: Monitoring, Auditing and Reviews
*CPRC & IRB: Change Reviews and Annual Reviews
*FDA: IND Amendments and Annual Reviews
*Indicates the ability to suspend or close a clinical study

Analysis

- Data Clean-Up
- Data Analysis

Dissemination of Results

- Patient Enrollment
- Treatment Administered According to Protocol
- Data Management
Masonic Cancer Center

Executive Clinical Research Leadership Committee

Data and Safety Monitoring Council

Cancer Protocol Review Committee
ATTACHMENT 3: MCC RISK ASSESSMENT CHECKLIST

Check the following as applies to the trial under review:

- Phase I/Pilot study for possible Phase I study
- Trial involves agent, device or process initiated or developed by UMN faculty
- Faculty held IND/IDE

If one or more of the risk criteria above is checked, the trial will be assigned “high risk”. If no boxes were checked, check the following as applies to the trial:

- Phase II
- Score of >2 on trial complexity scale (each of the following equals one point)
  - Involves pharmacokinetic studies
  - Requires use of a health care provider for infusion or administration of protocol directed therapy and/or direct monitoring for toxicity following study drug administration
  - Involves collection of biological samples for correlative science and/or observational studies
  - Has an unusual route of administration and/or safety issues regarding administration
  - Is an MCC multi-center trial with affiliate site(s)
- PI of < 2 completed clinical trials (applies to interventional drug, biologic and device trials only)

If one or more of the risk criteria above is checked, the trial will be assigned “moderate risk”. If no boxes were checked, the trial will be assigned “low risk”.

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Minimum Extent of Monitoring</th>
<th>Minimum Monitoring Frequency</th>
<th>Minimum DSMC Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>100% of subjects: consent forms, eligibility, protocol compliance and verification of subject data against source records*</td>
<td>Twice Yearly</td>
<td>Quarterly</td>
</tr>
<tr>
<td>Moderate</td>
<td>100% of subjects: consent forms and eligibility 10% of subjects at each monitoring visit: protocol compliance and verification of subject data against source records</td>
<td>Twice Yearly</td>
<td>Twice Yearly</td>
</tr>
<tr>
<td>Low</td>
<td>Not required</td>
<td>Not Required</td>
<td>Annually**</td>
</tr>
</tbody>
</table>

*For high enrolling studies, i.e. accrual goal >100 subjects, monitoring will consist of a review of 100% of subject data up to the first 50 subjects. If no significant compliance issues are identified, the DSMC may approve decreasing monitoring extent to 10% of subject data for the remaining enrollment.

**Excludes trials with protocol type of epidemiologic or observational. After initial DSMC review, low risk trials of other protocol types, e.g. ancillary, supportive care, etc., may have the annual review requirement waived by the DSMC.
ATTACHMENT 4: SERIOUS ADVERSE EVENT REPORTING SOP

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UNIVERSITY OF MINNESOTA
MASONIC CANCER CENTER
CLINICAL TRIALS OFFICE
STANDARD OPERATING PROCEDURES

PROCEDURE # 402.1

Serious Adverse Event Reporting

1.0 Overview

This SOP outlines the process for reporting a serious adverse event (SAE) that occurs on any trial conducted by the Masonic Cancer Center (MCC). SAE reporting timelines and requirements are determined by UMN IRB, 21 CFR 312, and 21 CFR 812.

National Cancer Institute guidelines published by the Cancer Therapy Evaluation Program distinguish treatment related events from disease related events. Treatment related SAEs will be reported unless excluded by the protocol. If a protocol excludes certain events or limits SAE reporting to certain conditions or outcomes, only those targeted SAEs will be reported. Disease related events include relapse, disease progression, or other conditions that may result from the natural course of the disease. These will not be reported as SAEs unless specifically required by the protocol.

For any trial conducted under a locally-held IND, the Principal Investigator (PI) is responsible for analyzing the significance of each SAE in the context of the trial or protocol. The Local Sponsor is responsible for determining the significance of the event in light of previous SAEs, per FDA regulations. The Local Sponsor or Principal Investigator if designated by the Sponsor determines if an event qualifies for submission to the FDA and for submitting IND safety reports.

Trial staff should be familiar with and refer to the protocol-specific reporting rules for all trials they support.

2.0 Definitions

External Sponsor: Industry, National Clinical Trials Network, academic institution or cancer center which initiates the protocol or holds the IND/IDE under which the trial is conducted

Funding Sponsor: Industry that provides drug or funding for a locally sponsored trial

Local Sponsor: MCC faculty member who holds the IND/IDE under which the trial is conducted or who takes responsibility for and initiates the trial. This individual may be the same or different from the study Principal Investigator.

UPERTOS: Any problem or event which in the opinion of the local investigator was unanticipated, reflects new or increased risk to the subjects, and was possibly related to the research procedures

3.0 Procedure

3.1 Serious Adverse Event Reporting

1. Study Coordinator: Upon identifying or being notified of a potential SAE:
   a. Review the SAE section in the current approved protocol to determine the protocol definition of an SAE and the reporting requirements.
   b. Notify study PI and Local Sponsor (if different from study PI) within 24 hours.

SOP # 402.1 Version 05/01/2015  Previous versions: 03/27/2013, 05/17/2012, 05/07/2012, 01/03/2012, 04/29/2010
c. Gather relevant clinical information and initiate an SAE report in OnCore for local trials or on report template provided by External Sponsor.
   i. For local trials, complete all fields specified under the Help (?) icon in the upper right corner of the OnCore screen.
   ii. Do not complete 1) Expectedness, 2) Is event at least possibly attributable to the investigational therapy? (attribute), 3) In the principal investigator’s opinion, does this event represent a new or increased risk... or 4) Does this event affect risk information contained in the consent form?; these require PI assessment.
   iii. For externally sponsored trials enter the minimum required information below in OnCore's SAE screen:
      - Event Date
      - Reported Date
      - Reported by
      - Outcome
      - Category
      - Toxicity
      - Grade
      - Attribution
d. Print the SAE report:
   i. Local trials - print from OnCore
   ii. Externally sponsored trials - use Sponsor's SAE report template
e. Print spreadsheet of Similar Suspected Adverse Reactions filtered for the appropriate IND if study is under a local IND (\ICTOR\Reports\DR_774_SAEs_by_INDs)
f. Give the SAE report with relevant clinical information and, if applicable, the Similar Suspected Adverse Reactions spreadsheet to the PI to assess, edit, sign, and date.
g. Record the following information from PI assessment in OnCore:
   i. Attribution
   ii. Expectedness
   iii. Risk
   iv. Any other changes to the SAE report
h. Distribute the SAE as follows:
   i. For local trials email copy of the signed SAE report to:
      - Regulatory Specialist
      - Funding Sponsor (if required)
      - Local Sponsor if PI and Local Sponsor are different
   ii. For externally sponsored trials email copy of signed SAE form provided by Sponsor to:
      - Regulatory Specialist
      - Sponsor
i. Determine protocol-specific SAE reporting requirements. Inform the Regulatory Specialist if the SAE must be:
   i. Reported to the regulatory authorities in an expedited timeframe or
   ii. Included in the FDA annual report or IRB continuing review application
j. Enter the date sent to the Funding Sponsor, Local Sponsor and External Sponsor in OnCore.
k. File the original report in the SAE section of the subject binder.
I. **Note:** Distribution dates recorded in OnCore are considered source data and paper copies of fax reports, etc. do not have to be maintained.

2. **Regulatory Specialist:**
   a. Email a copy of the SAE report to:
      i. SAE Coordinator
      ii. BMT Database – if the SAE occurs on a BMT trial
   b. If the SAE meets the criteria for prompt submission of information to the IRB, submit the SAE report to the IRB in the required timeframe.
   c. If CTO INDIIDE Management Agreement is on file and the SAE requires expedited reporting, send the SAE report to the FDA.
   d. Record the following in OnCore, if applicable:
      i. Date the SAE report was received by Regulatory Specialist
      ii. Date the SAE report was sent to SAE Coordinator
      iii. Date the SAE report was sent to BMT database
      iv. Date the SAE report was sent to IRB (If SAE does not meet reporting criteria for prompt submission of information to the IRB, leave blank and enter this date at time next continuing review is submitted.)
      v. Date the SAE report was sent to FDA (if there is a CTO INDIIDE Agreement)
   e. File copy of the SAE report in the regulatory binder.

3.2 Additional SAE reporting Requirements for Local Trials with Affiliate Sites

   **If the SAE occurs at the University of Minnesota or satellite site:**

   1. **Regulatory Specialist:**
      a. If the SAE meets the criteria of prompt submission of information to the IRB, FDA criteria for expedited reporting, or if directed by MCC PI or Local Sponsor.
         i. Distribute the SAE report to all affiliate sites.
         ii. Record date sent to affiliate sites in OnCore.

   **If the SAE occurs at an affiliate site:**

   2. **Study Coordinator:**
      a. Give copy of the SAE report to the MCC PI to review.
      b. Assist MCC PI to record his/her assessment of the SAE in the PI Comments field on the SAE screen in OnCore paying particular attention to attribution, expectedness and increased risk.
      c. Amend the appropriate fields on the SAE screen to match the MCC PI’s assessment.
      d. Print the revised report and have MCC PI sign and date.
      e. Email the SAE report to Regulatory Specialist.

SOP # 402.1 Version 05/01/2015  Previous versions: 03/27/2013, 05/17/2012, 05/07/2012, 01/03/2012, 04/26/2010
3.3 Data and Safety Monitoring Council (DSMC) Review

Per the MCC Data and Safety Monitoring Plan, the DSMC reviews all reportable SAEs regardless of trial sponsor. The DSMC delegates this responsibility to the MCC SAE Coordinator. Trial specific SAEs are summarized in interim trial reports to the DSMC.

1. SAE Coordinator:
   a. Review the SAE report for omissions, errors, and appropriate and timely distribution.
   b. Return incomplete SAE reports to the reporting staff for completion or resubmission.
   c. For high or moderate risk local trials or other trials monitored by the DSMC:
      i. If there are urgent concerns, send the SAE report to the DSMC Chair for expedited review.
      ii. If there are no urgent concerns, include in the next trial progress report SAE summary.
   d. Record the following in OnCore
      i. Date the SAE report was reviewed by the SAE Coordinator
   e. Distribution dates recorded in OnCore are considered source data and paper copies of fax reports, etc. do not have to be maintained.

2. DSMC Coordinator: Record the date in OnCore that the SAE report was summarized or presented to DSMC.

3.4 Follow-up SAE Reporting

This section applies to local trials only. Externally sponsored trials should follow Sponsor process for follow up reporting.

1. Study Coordinator:
   a. Initiate a follow-up SAE report for changes to any of the following (only):
      i. Event name
      ii. Risk
      iii. Expectedness
      iv. Attribution
      v. Fatal outcome
   b. Ensure PI reviews and signs off on the follow-up report.
   c. Update OnCore to match the signed follow-up SAE report.
   d. Per Section 3.1, send follow-up report to Funding Sponsor, Local Sponsor and Regulatory Specialist.
   e. Enter the date sent to the Funding Sponsor and Local Sponsor in OnCore.
   f. File original follow-up SAE report in the subject binder.

2. Regulatory Specialist:
   a. If the follow-up information changes the SAE to an event that meets the criteria of prompt submission to the IRB, submit the report as required.
   b. Email a copy of the follow-up SAE report to the BMT Database and the SAE Coordinator.
   c. Record dates in OnCore, per SAE SOP section 3.1.
d. File copy of SAE follow-up report in the regulatory binder.

3. SAE Coordinator:
   a. Review follow-up SAE report and record review date in OnCore.
   b. Update DSMC per section 3.1(1)(c).

4. DSMC Coordinator: Record the date in OnCore that the SAE report was summarized or presented to DSMC.

3.5 Quality Assurance

1. SAE Coordinator: Send a quarterly summary report of all SAEs not reported appropriately or within the required time frame to the DSMC Coordinator.

2. DSMC Coordinator: Place the quarterly summary report on the upcoming DSMC agenda. Ensure the MCC PI submits a corrective action plan to the DSMC if required by the council.
ATTACHMENT S: MCC PROCEDURES MANUAL FOR AFFILIATE SITES TEMPLATE

Begins on next page.
Procedures Manual for Affiliate Sites

Protocol Title: Click or tap here to enter text.

Protocol Number: Click or tap here to enter text.

Version Click or tap to enter a date.
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# Masonic Cancer Center Key Study Contacts

<table>
<thead>
<tr>
<th>Role</th>
<th>Phone</th>
<th>Fax</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Principal Investigator:</strong></td>
<td>Insert #</td>
<td>Insert #</td>
<td>Insert email</td>
</tr>
<tr>
<td>Insert name</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Affiliate Manager:</strong></td>
<td>(612) 626-5174</td>
<td>(612) 625-2652</td>
<td><a href="mailto:eorchols@umn.edu">eorchols@umn.edu</a></td>
</tr>
<tr>
<td>Erica Orcholski</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contact for: Point of contact for study questions, CRF questions, IRB submissions, regulatory updates, data and monitoring requirements, recipient of local SAEs and deviations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Project Manager:</strong></td>
<td>Insert #</td>
<td>Insert #</td>
<td>Insert email</td>
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<tr>
<td>Insert name</td>
<td></td>
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<tr>
<td>Contact for: Study startup process guidance, initial contact for budget/contract and departmental negotiations, contact if others are not available</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study Coordinator:</strong></td>
<td>Insert #</td>
<td>Insert #</td>
<td>Insert email</td>
</tr>
<tr>
<td>Insert name</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contact for: Urgent clinical inquiries, verification that new patient slots are still available</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Insert other key contacts as applicable, such as the research lab or other shared services.

**OnCore** and other databases as applicable Help | cc-oncore-help@umn.edu |

Contact for: OnCore and other databases as applicable technical support (training, reset password, etc.)
PROCEDURES MANUAL SIGNATURE PAGE

Protocol Title: Click or tap here to enter text.

Protocol Number: Click or tap here to enter text.

Procedures Manual for Affiliate Sites Version: Click or tap here to enter text.

Sponsor Name: Masonic Cancer Center, University of Minnesota

Declaration of Investigator

I confirm that I, and the study staff that I have delegated tasks to, have read the Procedures Manual for Affiliate Sites for the above-mentioned study. I agree to conduct this trial in accordance with all stipulations of the protocol and procedures manual.

Affiliate Site Principal Investigator Name: ________________________________

Affiliate Site Principal Investigator Signature: ____________________________

Date Signed: ____________________________
**Introduction**

The purpose of this manual is to provide guidance for institutions participating in Marpac Cancer Center, University of Minnesota investigator-initiated trials, hereby referred to as affiliate sites. This manual ensures appropriate oversight and consistency for clinical research conducted at all affiliate sites participating in the study.

All investigators, research nurses, data managers, regulatory specialists, and other study staff that are involved in the conduct of the study are required to read the Procedures Manual for Affiliate Sites.

Failure to conduct the study in accordance with the protocol and the Procedures Manual for Affiliate Sites will result in the affiliate site being contacted by the Data and Safety Monitoring Committee for resolution. Continuing noncompliance may result in suspension of the site.

**Study Overview**

Schema
Site Initiation

Site Selection
Before the Study Start-up Packet (containing the final protocol and other study documents) can be sent to a site, the following documents must be completed, signed by the affiliate site’s local Principal Investigator, and returned to the Masonic Cancer Project Manager:

- Confidentiality/Non-Disclosure Agreement
- Study Feasibility Questionnaire
- Contact information for one or more key study start-up personnel (i.e. project manager, regulatory specialist, study coordinator) to whom the Study Start-Up Packet is sent

If further information is needed before deciding to participate, the affiliate site may contact the Masonic Cancer Center Project Manager or the Principal Investigator (PI) to discuss the protocol and participation concerns and/or logistics.

Budget and Contract
Budgeting and contracting occurs during the time the study is going through the regulatory approval process. A fully executed contract should be in place before the Site Initiation Meeting occurs.

If a budget is required for IRB submission, please contact the Masonic Cancer Center Project Manager.

[Insert additional language if the study is industry-funded. Suggested template language is as follows: The affiliate portion of this research study is being funded by [insert drug company’s name], therefore a sub-contract between the U of MN and [insert affiliate site’s name] will be used which will include a statement of work, payment terms and scientific, administrative, financial, and reporting requirements.]

Study Start-Up Packet and Essential Regulatory Documents
Once the Masonic Cancer Center Project Manager has received the signed Confidentiality/Non-Disclosure Agreement and the Study Feasibility Questionnaire, the Affiliate Manager will email an initial study start-up packet to the affiliate site’s local Principal Investigator and research staff.

As soon as possible, the affiliate site must respond to the Affiliate Manager’s Study Start-Up Packet email with the following:

- Acknowledge receipt of the initial start-up packet
- Indicate whether or not the affiliate institution will participate, as follows:
  - If the decision is to participate, please provide an estimated time for submission to the local IRB.
• If the decision is to not participate, please provide the reason for refusal.

If further information is needed before making a decision, the affiliate site may contact the Masonic Cancer Center Project Manager or the Principal Investigator (PI) to discuss the protocol and participation concerns and/or logistics.

If no response is received within 30 days of providing the initial start-up package, it will be assumed that the affiliate site is not participating.

Reviews of Local Consent Documents
The Masonic Cancer Center provides a template consent form in Word format to allow editing to meet local institutional consent form format.

In general, the consent form wording should remain the same as the Masonic Cancer Center template with local institutional information added where indicated. The HIPAA language may be presented in a separate document or incorporated into the consent based on local institutional preferences.

The edited consent form with the changes tracked must be approved by the Affiliate Manager or designee before the affiliate site submits the study to the local IRB. The Affiliate Manager is typically able to review the consent form within one week. Affiliate sites must retain documentation that Masonic Cancer Center has approved the affiliate consent document in the site's Regulatory Binder.

Note: The affiliate site may proceed with any institutional reviews (i.e. scientific review) that do not require submission of the consent document(s) while preparing the consent.

Initial IRB Approval
At the time of IRB submission, the affiliate site is expected to email the Affiliate Manager the submission date and expected date of review.

If any local review committee submission results in stipulations or questions, the affiliate site is welcome to contact the Affiliate Manager for assistance in a response. If a local review committee requires further changes to the Masonic Cancer Center approved consent form, the updated consent form must be reviewed and approved by the Affiliate Manager before re-submission.

Upon receipt of local IRB approval, the affiliate site emails the approval letter, documentation of the study documents that were approved by the IRB (if not listed in the approval letter) and the IRB approved consent form to the Affiliate Manager.
Identification of Study Staff
Included in the study start-up packet will be an excel spreadsheet for the affiliate site to complete with contact information for key personnel. The key personnel spreadsheet should be completed and emailed back to the Affiliate Manager as soon as possible to assist in beginning to initiate the site.

The Delegation of Authorities Log is used by each affiliate site to specify the names of staff who will be responsible for implementing specified protocol activities (see the Essential Documents checklist). This document will be completed prior to site initiation. When staff join or leave the affiliate site’s study team, the Delegation of Authorities Log must be updated and a copy sent to the Affiliate Manager.

OnCore Access
The Masonic Cancer Center uses OnCore® Enterprise Research as its clinical research database. Access to the Masonic Cancer Center OnCore database will be required for all study staff, even if the affiliate site uses OnCore locally as its own clinical database. Subject enrollment, clinical data capture (via electronic case report forms (eCRFs)), serious adverse event reporting, regulatory tracking, and study monitoring are some of the functions performed in the Masonic Cancer Center OnCore database.

The Affiliate Manager will provide an OnCore Access Request Form contains instructions for accessing the Masonic Cancer Center OnCore database.

OnCore navigation training and study-specific eCRF training is provided by the Masonic Cancer Center OnCore support staff around the time of activation of the study at the affiliate site.

For OnCore technical support, email cc-oncore-help@lists.Masonic Cancer Center.edu. For protocol-specific questions, email the Affiliate Manager.

Essential Regulatory Documents Checklist
The Affiliate Site will not be permitted to enroll patients until the essential documents are received. The Initial Essential Documents Checklist identifies the documents that must be in place prior to site activation (see Appendix A).

Site Initiation Meeting
Once the contract/budget is finalized and all initial essential documents are received, or an agreed-upon plan is in place to obtain the remaining documents, the Affiliate Manager will contact the site to schedule a Study Initiation Meeting.
Site Activation
A Site Activation email will be sent to the affiliate site and the institution’s status changed to “Open to Accrual” in OnCore when all requirements are met. At this point patient screening/enrollment may begin.

Subject Screening and Enrollment
Informed consent must be obtained prior to initiation of any screening procedures that are performed solely for the purpose of determining eligibility for research. The informed consent process must be documented thoroughly in the subject’s research chart. The original signed consent form(s) must be kept in the subject’s research chart.

Screening Log
Affiliate sites are required to maintain subject screening records in OnCore in a real-time basis. Screening records must be entered in the Pre-Screening Console (click the “new” button to start entering information on a new subject).

It is recommended that the site contact the Affiliate Manager and Masonic Cancer Center Principal Investigator to verify the current enrollment status and confirm that there is a slot available, especially once the study gets close to meeting the accrual goal.

If a subject signs consent but doesn’t meet the eligibility requirements, the subject’s ineligibility status must be documented in OnCore. If the study has a waiting list, notify the Affiliate Manager and Masonic Cancer Center Principal Investigator to have the subject removed from the potential patient list.

Eligibility Checklist
The study’s eligibility checklist included as an appendix to the protocol and is also available in OnCore’s Documents tab. OnCore Enrollment will occur after the consent has been signed and eligibility is confirmed.

Subject Enrollment
Enrollment in OnCore is done by the affiliate site. As detailed in the study’s consent and HIPAA documents, the participant’s name, demographics, and medical record number are entered into OnCore.

The date that the local PI signs the eligibility checklist is considered to be the subject’s “On-Study Date.”

Assignment of a Sequence Number: All patients [add: “and donors”, if applicable] who sign consent, including screen failures, must be assigned a sequence number. The sequence number is used in place of the subject’s name, medical number, and other direct identifiers on all documents and samples sent to the Masonic Cancer Center. The Affiliate Site assigns the sequence number. The format for the sequence number is the
Protocol # (insert Protocol No. here), a 3-letter acronym for the study site (i.e. “OSU” for Ohio State University), followed by a 3-digit number beginning with 001. For example, the second patient enrolled on the study protocol number 2015LS123 at University of Chicago would be assigned the sequence number 2015LS123-UIC-002. Sequence numbers are consecutive and will not be re-used.

Upon completing the subject enrollment, OnCore will automatically generate an email notifying key study personnel of the enrollment and treatment assignment.

[include the following language for applicable studies] Assignment to Cell Product Processing: Assignment to the cell product processing will occur at the time of registration by the Masonic Cancer Center Study Coordinator or designee, as detailed in the protocol. The affiliate site staff and [industry supporter] will be notified of the cell product processing assignment by email.

**Regulatory Requirements**
Affiliate sites are responsible for the maintenance of local essential regulatory documents for the conduct of the study at the site. The affiliate site must submit updated regulatory documents to the Affiliate Manager.

**Institutional Review Board (IRB) Reviews**
Affiliate sites must submit the protocol, future protocol amendments, consent/assent documents, and other applicable materials to the local IRB. Prior to protocol activation at each affiliate site, the site must submit documentation of initial IRB approval to the Affiliate Manager.

The Affiliate Manager will distribute protocol amendments and other required documents to affiliate sites. Upon receipt of protocol documents, the affiliate site performs the following:

1) Submit edited local consent form in tracked-changes format to the Affiliate Manager for Masonic Cancer Center approval prior to submission to the local IRB.
2) Submit protocol documents to local IRB as soon as possible.
3) If the local IRB requests changes to the consent, these changes must be approved by the Affiliate Manager before re-submitting for final local IRB approval.
4) Email the local IRB’s approval letter, citing the version date of the documents approved, and the approved consent documents (if applicable) to the Affiliate Manager.
5) The Affiliate Manager will update the OnCore > Institution > IRB Reviews tab and upload the approved consent form in OnCore.
Amendments must be approved by the affiliate site’s IRB within 3 months from the date that the amendment was received by the affiliate site. Delinquency may result in suspension of affiliate site’s ability to enroll new patients to the study.

Throughout the conduct of the study, all IRB approval documentation (i.e. annual continuation reviews, amendments, SAEs, deviations, etc.) must be submitted to the Affiliate Manager.

Re-consenting of subjects occurs when the Masonic Cancer Center or local IRB determines that the addition of new information (e.g. risks, additional tests) needs to be shared with study subjects that are already on study. The informed consent process must be documented thoroughly in the subject’s research chart. The original signed consent form(s) must be kept in the subject’s research chart.

**Deviation Reporting**

Deviations may be defined as (1) any departure from the protocol or (2) any action associated with the conduct of a clinical trial that does not comply with IRB or federal regulations. Both the Seriousness and Expectedness of the deviation are used to determine the timeline for reporting deviations to Masonic Cancer Center, as follows:

- **Seriousness:**
  - **Major Deviation:**
    - Causes subject harm, significantly increases risk to subject or requires medical intervention to prevent harm
    - Done to eliminate apparent immediate harm caused by the protocol
    - Affects subject rights or welfare
    - Non-adherence to significant protocol requirements, regulations, or GCP guidelines
    - Repeated instances of a minor deviation, suggesting continuing noncompliance
  - **Minor Deviation:**
    - Departure from protocol (usually inadvertent) that does not affect soundness of the protocol or subject safety, rights, or wellbeing
    - Administrative oversight

- **Expectedness:**
  - **Planned deviation:** In rare circumstances, it may be permissible for the Masonic Cancer Center PI and the affiliate site’s local IRB to approve the departure from protocol prior to the deviation.
  - **Unplanned deviation:** IRB approval is not obtained prior to departure from protocol. (e.g. Follow-up visit missed).

All Major Deviations must be reported to the Masonic Cancer Center by entering the event in OnCore’s Deviations tab (training will be provided) within the timeframe.
detailed below. The affiliate site prints a copy of the OnCore Deviation Report and obtains the local PI’s signature. Minor Deviations are not reportable to the Masonic Cancer Center, unless repetitive minor deviation events suggest continuing noncompliance.

[Mention additional study-specific event reporting procedures if applicable.]

In addition to reporting deviations to the Masonic Cancer Center, affiliate sites are responsible for reporting deviations to their local IRB and other local regulatory oversight agencies as per local requirements.

**Reporting Protocol Deviations Timeframe:**
1. Deviations that are both **Major** and **Unplanned** must be entered in OnCore and reported to the Affiliate Manager within 24 hours of knowledge.
2. Deviations that are **Major** and **Planned** must be discussed with the Masonic Cancer Center Principal Investigator and Affiliate Manager prior to deviating from the protocol. The affiliate site enters the deviation in OnCore and notifies the Affiliate Manager within 7 days of knowledge.
3. Minor deviations are not reported to Masonic Cancer Center in real time, unless the events suggest continuing noncompliance. Minor deviations are to be addressed during monitoring visits.

**Subject Safety Oversight and Event Reporting Requirements**

**Adverse Event and Serious Adverse Event Reporting**
Clinical research studies must be monitored for safety and potential risk to the subject. Monitoring of subject safety is described in detail in the protocol.

Assessing adverse events is performed by the local Principal Investigator, and includes determining the following: severity, expectedness, and attribution of the event. It is the local Principal Investigator’s responsibility to ensure that adverse events are accurately recorded in the subject’s research chart and to ensure adequate reporting of adverse events, Serious Adverse Events, and all other reportable events as detailed in the protocol Section [insert section #].

**Serious Adverse Events** are defined in the protocol. All Serious Adverse Events are submitted to the Masonic Cancer Center by completing the SAE Form in OnCore within the timeframe described in the protocol. [Include additional industry-supporter language, if applicable. Sample language is as follows: “In addition to reporting SAEs to Masonic Cancer Center, a subset of SAEs are expeditiously reported to Miltenyi Biotec, Inc.”] Within the timeframes defined in the protocol, the affiliate site’s Study Coordinator prints the completed SAE Form, the local Principal Investigator reviews and
signs the form, and the Study Coordinator emails the form along with relevant de-
didentified source documentation to the Affiliate Manager.

[Include additional study-specific details as needed. Suggested template language is as follows:
Targeted Toxicities - Adverse event collection will start on Day 1 of the 1st dose of study
drug and will focus on targeted adverse events and unexpected adverse events at
specific time points in relation to the study drug. This protocol also uses a targeted
toxicity form to be completed at times specified in the study and entered into OnCore.
This avoids over reporting of events related to standard of care treatment/procedures
while focusing on the investigational element of the study.]

Dose Limiting Toxicities and Early Study Stopping Events - In addition to monitoring
and recording adverse events as defined in the protocol, this protocol also has dose
limiting toxicities (DLTs) and early study stopping rule event reporting. Such events may
not constitute an adverse event, however they do require immediate reporting by
completing the applicable form in OnCore (Stopping Rules eCRF or Event Form located
in the Reports tab) and by notifying the Affiliate Manager.

IND Safety Reports
All SAEs, whether originating from the Masonic Cancer Center or an affiliate site, will be
reviewed by the Masonic Cancer Center Principal Investigator to confirm the treating
physician’s determination of relatedness and expectedness. All SAEs that have a
reasonable possibility of having been caused by the study procedures and that are both
serious and unexpected are reported to the FDA in an IND Safety Report by the Masonic
Cancer Center Principal Investigator. The Affiliate Manager distributes IND Safety
Reports, along with a description of modifications to the study if applicable, to the
affiliate sites. Affiliate sites are responsible for submitting the IND Safety Report to their
local IRB or other regulatory oversight committees per local institutional guidelines.

Data Management

Data Collection Database
The Masonic Cancer Center uses OnCore® Enterprise Research as its data entry and data
management database. The Masonic Cancer Center OnCore support staff provides
OnCore navigation training and study-specific electronic Case Report Form (eCRF)
training.

Case Report Form (CRFs) Completion Deadline
Study personnel must complete all CRFs for a subject within [insert deadline as
documented in the Data Management Plan] of a study visit.
Conference Calls
Within the protocol’s Conduct of Study section will be the plan for communication between the Masonic Cancer Center and the affiliate sites. To make these communications meaningful, it is important that OnCore be kept current especially in regards to enrollment, serious adverse events and stopping rule/dose limiting toxicity events.

A regular conference call with the study PI and all affiliate sites will be scheduled at an agreed upon time. The Affiliate Manager will distribute an agenda with the conference call information before the meeting. A typical agenda for conference calls will include review of screening/accrual, adverse events, eCRF completion, regulatory updates and any issues including study deviations.

Affiliate Site Monitoring Plan
Affiliate sites are responsible for monitoring their own subject data and protocol compliance. Affiliate sites will be expected to self-monitor following the Masonic Cancer Center Affiliate Site Self-Monitoring SOP and Masonic Cancer Center’s Data and Safety Monitoring Plan (DSMP) unless otherwise arranged. All sites are expected to comply with the Masonic Cancer Center’s DSMP when fulfilling these monitoring obligations, as the University of Minnesota in its capacity as the study coordinating center is responsible for FDA reporting and communication.

For this study, complete and adequate monitoring visits must be conducted at least every 6 months. The first monitoring visit is due 6 months after the first patient is enrolled at the site. For a detailed description of monitoring expectations, refer to the Masonic Cancer Center’s DSMP located at http://www.cancer.MCC.edu/prod/groups/ahc/@pub/@ahc/@mcc/documents/conten t/ahc_content_487799.pdf

Monitors must record their visits in a Monitoring Log (template available upon request). This document should be retained in the affiliate site’s study regulatory binder.

Affiliate sites are expected to resolve monitoring findings promptly. Failure of the local PI to adequately address protocol deviations/issues may result in suspension or termination of affiliate participation.

Source documents and study records may be subject to a Masonic Cancer Center audit at the discretion of the Masonic Cancer Center Data and Safety Monitoring Council (DSMC).
**Awards and Payments**

In order to initiate a sub-award agreement, the affiliate site completes and submits the Collaborator and Contact Information Form, Statement of Work, Budget/Payment Terms and Schedule, and Audit Certification and Financial Questionnaire (if applicable) to the CTO Contract Administrator assigned to the study.

Study reimbursement and other compensation may be provided for the conduct of the study, shall be made according to the budget and payment schedule of the sub-award agreement. Affiliate sites are required to submit itemized invoices according to sub-award agreement terms with necessary back up information such as a list of patients (identified by sequence number or other data that do not include Protected Health Information) that the affiliate site is billing for. Final invoice must be submitted no later than thirty days after sub-award end date or after receiving notice of termination from primary site. Final invoice must be marked “FINAL.” If invoices are not received within thirty days after notification and request of final invoice, the primary site cannot guarantee payment for services performed by affiliate sites.

**Site Close-Out**

Study close-out with the local IRB will occur after all participants have completed the study related follow-up and all data has been submitted. The procedures for the study closure will be carried out according to the Masonic Cancer Center Affiliate Study Close-Out SOP.
Appendix A: Initial Essential Documents Checklist

This checklist can be used to guide collection of documents to be reviewed by the Masonic Cancer Center Affiliate Manager for activating an affiliate site planning to participate in a Masonic Cancer Center investigator initiated clinical trial. The essential documents listed here are among the core documentation required by Good Clinical Practices (GCP) that must be in place before the site is activated.

Principal Investigator: __________________________

Affiliate Site: __________________________

Protocol Number: __________________________

DOCUMENTS TO BE COMPLETED BY SITE PRIOR TO ACTIVATION:

☐ FDA Form 1572
☐ Laboratory Certification(s)
☐ Medical Licenses and CVs (Principal Investigator and Sub-Investigators)
☐ Financial Disclosure Statements (Principal Investigator and Sub-Investigators)
☐ IRB approval letter, documenting the version date of the documents reviewed and approved
☐ IRB approved consent form(s)
☐ Agreement to List Affiliates in Government Registration Databases
☐ Procedures Manual for Affiliate Sites Signature Page
☐ Delegation of Authorities Log (A Delegation of Authorities Log is to be used by each site. A template log will be provided for each site’s use; alternatively, the site may use their own log if the site provides their DOA log policy to the MCC Affiliate Manager.)
☐ Human Subjects Protection training certificates for all study personnel
☐ Protocol Training Documentation (It is required that all study personnel are trained on the protocol and for the training to be documented. The protocol training documentation is started at the Site Initiation Meeting, unless local institutional procedures include earlier training. Documentation of training for any staff who were not present at the Study Initiation Visit must be obtained prior to the site being activated.)
☐ OnCore Access Request Form (It is required by Masonic Cancer Center that at a minimum the main Study Coordinator obtains access prior to activation. It is acceptable for all other staff to obtain access soon after activation.)

Send the completed essential documents to the Affiliate Manager via email or fax.

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ATTACHMENT 6: MCC CLINICAL TRIALS MONITORING PLAN

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1.0 Purpose of Monitoring Plan

This document describes monitoring requirements for investigator-initiated clinical trials conducted in the Masonic Cancer Center (MCC). The Data and Safety Monitoring Plan (DSMP) defines the scope of trials that require monitoring. The MCC encourages compliance with good clinical practice guidelines, however the standard to which all trials are held is compliance with FDA regulations, CRS SOPs, and IRB requirements.

2.0 Definitions

Authorized designee: Individual authorized by the Principal Investigator to perform specific tasks documented on the Delegation of Authority log

Clinical Research Services (CRS): Department within the MCC that supports clinical research. The CRS offers Clinical, Finance, Protocol Development, Regulatory, and Technology support.

Enrolment: Enrollment occurs when the subject signs the consent form, regardless of eligibility or participation in the study

Investigator-initiated trial: Trial planned and managed by the Principal Investigator

Source document: The first permanent medium where data are recorded (e.g., medical records, subject research file, lab reports, etc.). Shadow charts or printed copies of medical records are not considered source documents

Subject research file: Collection of source documents that are not maintained in the medical record such as outside medical records, RECIST documentation, subject interview forms, documentation of telephone discussions, performance status (Karnofsky, Lansky, ECOG). Subject research files may also contain consent, HIPAA, and SAE forms. Subject research files are not shadow charts and do not contain printed medical records.

3.0 Minimum Elements Reviewed

Monitoring includes review of consent, HIPAA, and eligibility forms, regulatory documents, and subject case report forms to ensure compliance with the protocol, CRS SOPs, and local and FDA regulations. Consent, eligibility, and subject data must be verified against source documents.

The study elements reviewed as part of a monitoring visit are described below:

3.1 Protocol Compliance

a. The monitor must verify:
   • Protocol required visits and procedures have been conducted appropriately
   • All submissions to oversight entities (IRB, FDA, etc.) have been made appropriately and within the required timeframes
   • No deviations from the protocol have been made without prior IRB approval except where necessary to eliminate an immediate hazard to subjects or when the change is only logistical or administrative

3.2 Subject Screening and Enrollment

a. The monitor must verify:
   • Enrollment does not exceed number of subjects approved by the IRB
   • Enrollment and Subject Screening logs are maintained (Screen failures are documented)
3.3 Informed Consent & HIPAA

a. The monitor must review all applicable consent, assent and HIPAA forms and verify:
   - Subject name is printed, labeled, or imprinted on the form
   - Subject signed and dated the correct version of the form
   - Consent was signed prior to any protocol-specific procedures and this is documented in
     the subject's medical record or other source document (e.g. subject research file)
   - All fields or blank lines on the form are complete
   - Legal guardianship is recorded in source documents.

3.4 Eligibility

a. The monitor must verify each subject met all eligibility requirements as documented in:
   - Medical record
   - Subject research file
   - Eligibility checklist signed by investigator or designee. Note: A signed eligibility checklist
     may serve as source documentation for some requirements such as life expectancy, birth
     control discussion, etc.

3.5 Data Verification

a. The monitor must verify:
   - All case report forms (CRFs) are completed by the investigator or authorized designee
   - All required CRFs are complete, legible, and well organized
   - CRF data are accurate and supported by source documentation
   - All data corrections are initialed and dated appropriately

3.6 Adverse Event and Deviation Review

a. The monitor must verify:
   - Adverse events are documented and reported as required
   - Other UPIRTSO events (e.g. breach of confidentiality, deviations that meet UPIRTSO
     criteria) are reported appropriately

3.7 Essential Document Review

Essential documents may be maintained in the regulatory binder, OnCore, CRS central file, or subject
research file or binder.

a. The monitor must verify all of the following essential documents are well maintained,
   complete, and current, if applicable.
   - 1572
   - Adverse event logs and reports
• Correspondence with:
  • Affiliate sites
  • Investigators
  • Monitors
  • Sponsors (IND/IDE holder or funding sponsor)
• Investigational product accountability documents
• Investigator qualification documentation (License, CV, or CV letter)
• Lab certifications
• Monitoring log
• Randomization procedure
• Regulatory applications, reports, and correspondence. IRB approval letters must specify the version of the documents approved
• IRB approved documents
  • Protocol
  • Assent
  • Consent
  • HIPAA
  • Materials provided to subjects
  • Other IRB-approved documents
• Sample CRFs
• Financial disclosure documents
• Screening and enrollment log
• Signature authorization log captures all study staff
• Training documentation
• UPIRTSO event reports

3.8 Investigational Product Accountability

As part of essential document review, the monitor must verify disposition of investigational products, including those managed by the Fairview Investigational Drug Service (IDS). The monitor must verify:

• Study files contain guidelines and instructions for handling product
• Study documents describe how subjects are instructed on using, handling, storing, and returning product
• Logs indicate name of person who received, used, or disposed of product
• Product disposition records are accurate and complete, including:
  • Shipping receipts (name and address of consignee, type and quantity of the product, date of shipment, batch number or code)
  • Dispensing log
  • Product return and disposal/destruction logs
• Investigational products are not stored with non-investigational products
• Investigational products are stored under conditions specified in labeling or packaging
• Investigational products have not been stored beyond the specified shelf life
• Labels on individual patient bottles/medical devices comply with the requirements for investigational drug or device labeling

The MCT Quality Assurance Director is responsible for quality assurance oversight of products developed or modified by the Cell Therapy Clinical Laboratory. This includes oversight of chain of custody, lot release criteria, etc.

4.0 Required Review and Reporting

4.1 Extent and Frequency

The DSMP defines the minimum extent and frequency of monitoring for investigator-initiated studies in the MCC. More frequent or extensive monitoring may be conducted at the discretion of the DSMC or CTO management.

4.2 CTO Quality Assurance Oversight

a. The designated monitor schedules monitoring visits to meet monitoring requirements and sends an updated monitoring tracker monthly.
b. The tracker includes all trials subject to monitoring in the MCC.
c. The tracker clearly indicates all of the following for each trial:
  • Previous dates trial was monitored in last 12 months
  • Total subjects on trial
  • Percentage of subjects fully monitored to date and at last visit
  • Percentage of consent and eligibility monitored to date
  • Number of new subjects enrolled since last monitoring visit
  • Number of subjects that currently require monitoring
d. The DSMC or CTO management may change monitoring priorities.
e. Masonic Cancer Center trials conducted at a facility other than MCC must follow this monitoring plan.
f. The CTO may permit sites to self-monitoring or allow monitoring to be conducted by an entity other than the MCC; however, all monitoring must comply with Clinical Trials Office SOPs, and the MCC Data and Safety Monitoring Plan.
4.3 Monitoring Reports

a. All monitoring activities must be documented on a CTO-approved monitoring report template.

b. Each monitoring report must specify all essential documents and elements of the study the monitor reviewed at the visit.

c. Each monitoring report must document all findings, including those resolved during the visit.

c. The monitor must send a monitoring report to the Principal Investigator, Nurse Manager, Regulatory Manager, and other CTO managers as requested within two weeks of any monitoring activity.

5.0 Acronyms

CRF  Case Report Form
CRS  Clinical Research Services
CTO  Clinical Trials Office
DSMC  Data and Safety Monitoring Council
DSMP  Data and Safety Monitoring Plan
GCP  Good Clinical Practice
HIPAA  Health Insurance Portability and Accountability Act
IDE  Investigational Device Exemption
IDS  Investigational Drug Service
IND  Investigational New Drug
MCC  Masonic Cancer Center at the University of Minnesota
MCT  Molecular and Cellular Therapeutics lab
NCI  National Cancer Institute
REGIST  Response Evaluation Criteria in Solid Tumors
UPIRTSO  Unanticipated Problems Involving Risk to Subjects or Others (See IRB website for more details)
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<td>Pediatric Cancers</td>
<td>Professor of Pediatrics, Division of Pediatric Hematology/Oncology, Department of Pediatrics</td>
</tr>
<tr>
<td>CO-CHAIR: Mark Kirstein, PharmD</td>
<td>Pharmacology</td>
<td>Associate Professor, College of Pharmacy and Masonic Cancer Center</td>
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<tr>
<td>Casey Hooke, PhD</td>
<td>Pediatric Epidemiology</td>
<td>Assistant Professor, School of Nursing</td>
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<tr>
<td>Celalettin Ustun, MD</td>
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<td>Christopher Warlick, MD</td>
<td>Urologic Cancer/Surgery</td>
<td>Assistant Professor of Medicine, Department of Urologic Surgery</td>
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<td>Claudio Brunstein, MD</td>
<td>Blood and Marrow Transplantation</td>
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<tr>
<td>Deanna Teoh, MD</td>
<td>Gynecologic Cancers/Surgery</td>
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<td>Bruce Lindgren, MS</td>
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<td>Saonli Basu, PhD</td>
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<td>Chair: Erica Warlick, MD</td>
<td>Hematology and Blood and Marrow Transplantation</td>
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<tr>
<td>Frank Ondrey, MD, PhD</td>
<td>Head and Neck Surgery</td>
<td>Associate Professor, Department of Otolaryngology, Head and Neck Surgery</td>
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<tr>
<td>John Rogosheske, PharmD</td>
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<td>Clinical Assistant Professor, PHARM Professional Education</td>
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<tr>
<td>Heather Stefanski, MD, PhD</td>
<td>Pediatric Blood and Marrow Transplantation</td>
<td>Assistant Professor of Pediatrics, Division of Blood and Marrow Transplantation</td>
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<td>Emil Lou, MD, PhD</td>
<td>Gastrointestinal Oncology</td>
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<td>Shernan Holtan, MD</td>
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<td>Katie Mellskog, RN, MS</td>
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<td>Todd DeFor, MS</td>
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<td>Qing Cao, MS</td>
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<tr>
<td>Douglas Yee, MD</td>
<td>Chair, Executive Clinical Research Leadership; Director, Masonic Cancer Center</td>
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<tr>
<td>Jeffrey Miller, MD</td>
<td>Vice Chair, Executive Clinical Research Leadership; Deputy Director, Masonic Cancer Center</td>
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<td>Brenda Weigel, MD, MSc</td>
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<tr>
<td>Marie Brown, MHA, FACHE</td>
<td>Oncology Service Line Co-Lead, Fairview Health Services</td>
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<tr>
<td>Sarah Cooley, MD, MS</td>
<td>Director of Investigator Initiated Clinical Research, Masonic Cancer Center</td>
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<td>Seanne Falconer, MBA</td>
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<td>Badrinath Konety, MD, MBA</td>
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