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Data and Safety Monitoring Committee

POLICIES and PROCEDURES

FRED & PAMELA BUFFETT CANCER CENTER

Version 6.0, July 28, 2021

DSMC Policies and Procedures
Version 6.0, July 28, 2021

UNIVERSITY OF
Nebraska
Medical Center

FRED & PAMELA BUFFETT CANCER CENTER

DATA AND SAFETY MONITORING COMMITTEE

POLICIES and PROCEDURES

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PRMS OFFICE WEBSITE

<http://www.unmc.edu/cancercenter/clinical/prms.html>

SEARCHABLE WEBSITE OF ACTIVE CLINICAL TRIALS

http://www.net.unmc.edu/ctsearch/index_unmc.php

FRED & PAMELA BUFFETT CANCER CENTER DATA SAFETY AND MONITORING COMMITTEE (DSMC)

I. ADMINISTRATIVE POLICIES AND PROCEDURES

A. PURPOSE

The Fred & Pamela Buffett Cancer Center (Cancer Center) Data and Safety Monitoring Committee (DSMC) is assigned with the responsibility to monitor the safety of all research participants in clinical research studies sponsored by the Cancer Center members, as outlined in the UNMC Eppley Cancer Center revised Institutional Data and Safety Monitoring Plan (DSMP), Version 6.0, dated July 28, 2021.

B. SCOPE

The DSMC is an independent committee responsible for reviewing and monitoring patient safety on all Cancer Center investigator-initiated clinical research involving human subjects. The DSMC also monitors study progress for BCC investigator-initiated clinical trials. Details on the submission and review process are described in section II.B, Figure 1.

C. REPORTING RELATIONSHIPS

The DSMC reports to the Cancer Center Associate Director for Clinical Research. Minutes from the DSMC meetings are submitted to the SRC, the Cancer Center's Audit Committee (AC) and the UNMC Institutional Review Board (IRB), for informational purposes. Initial review of clinical research study/ies are coordinated at the same time as the initial review by the SRC and utilize the documents included with the SRC submission to decrease the submission burden for investigators.

D. MEMBERSHIP

The DSMC is a multidisciplinary committee consisting of a core group of individuals providing the necessary expertise in the principal disciplines of clinical oncology with additional representation from biostatistics. Members are selected by area of expertise to form a diverse group of clinicians and other professionals who provide rigorous monitoring of studies.

1. **Voting Members**: The DSMC consists of a minimum of six (6) voting members including four (4) Cancer Center members actively involved in clinical research, a biostatistician, and a patient advocate.
2. **Appointment Terms**: DSMC Members and the Chair are appointed for five-year terms by the Cancer Center Director. Terms may be renewed at the discretion of the Cancer Center Director.
3. **Administrative Support**: The DSMC is supported by the Cancer Center's Protocol Review and Monitoring System (PRMS) staff.

E. QUORUM

The number of DSMC members required to be present at any regularly scheduled DSMC meeting in order to transact business shall be three (3) members. Those present must include at least: 1) the Chair, Vice Chair or their designee; and 2) one (1) M.D.

F. MEETING SCHEDULE

The DSMC meets at least monthly on the first Friday of the month, providing it is not a holiday. Additional meetings for expedited full board review of Serious Adverse Events (SAE) may be called at the discretion of the DSMC Chair. At the discretion of the DSMC Chair, meetings may be performed via email if no items requiring full board discussion are on the agenda.

A list of scheduled meetings and DSMC submission deadlines is available from the Cancer Center PRMS office, 402.559.4969 or on the PRMS website at <http://www.unmc.edu/cancercenter/clinical/prms.html>.

1. Meetings Held Remotely:

Full DSMC meeting will be held in person, unless outstanding circumstances exist prohibiting such a meeting from occurring. In the event a full board meeting cannot proceed in person, a video conference will be utilized.

- a. The PRMS Office will schedule a video conference, including a password for security.
- b. A meeting invitation is sent to the committee member and assistants one month before the scheduled meeting.
- c. Responses are required within two weeks of the meeting to allow sufficient time to assign reviews and ensure quorum is met.

G. ROLES AND RESPONSIBILITIES:

Chair

- Appointed by the Cancer Center Director.
- Chairs monthly DSMC meetings.
- Performs reviews of clinical research studies.
- Corresponds with Principle Investigators.
- Reports to the Associate Director for Clinical Research and to the Director of the Cancer Center.

Vice Chair or Acting Chair

- Appointed by the Chair and must be a voting member of the DSMC.
- Assumes the Chair's duties, as needed.
- Reports to the Chair of the DSMC.

PRMS Office Staff

- Records meeting minutes.



- Ensures adherence of DSMC formats in submissions and supporting documentation.
- Collects and combines all Serious Adverse Event submissions
- Ensures all SAE supporting documentation has been submitted to the PRMS office for review by the DSMC members
- Maintains data on clinical research study/ies reviewed by the DSMC in Clinical Trials Management Systems (CTMS), and paper files.
- Ensures a copy of the current DSMC Policies and Procedures and the DSM Plan is available at all DSMC meetings.

Clinical Trials Regulatory Specialist (DSMC Contact)

- Develops the annual list of scheduled Adverse Event (AE) reviews
- Attends all Site Initiation Visits for UNMC IITs
- Distributes notification of the upcoming review to the Principal Investigator (PI) and appropriate study staff.
- Ensures adherence of DSMC requirements in submissions and supporting documentation.
- Notifies the PI and Study Coordinator of any issues or deficiencies in the documentation submitted for review.
- Prepares the DSMC meeting Agenda.
- Prepares the DSMC Website.
- Communicates with the Chair and committee members.
- Assigns reviews to committee members.
- Generates correspondence for signature by the Chair, Vice Chair, or Acting Chair and distributes signed correspondence to investigators following the DSMC's review.
- Orients new members to DSMC policies and procedures.
- Reports findings to the Associate Director for Clinical Research and to the Director of the Cancer Center.

H. REVISION OF POLICIES AND PROCEDURES

The DSMC policies and procedures are reviewed every two (2) years by the DSMC Chair and the PRMS Administrator and DSMC Coordinator. Minor changes or adjustments (e.g. typographical errors, change in membership) are made by the PRMS Administrator without approval by the DSMC Chair or DSMC Members. Major changes require review by the Associate Director for Clinical Research and the entire DSMC membership. Major changes must be approved by the DSMC by a simple majority vote of all DSMC members.

The DSMC will convene for a Policies and Procedures meeting once every two (2) years to review and vote on major changes before any updates are submitted to the Associate Director.

II. DSMC CLINICAL RESEARCH STUDY SUBMISSIONS

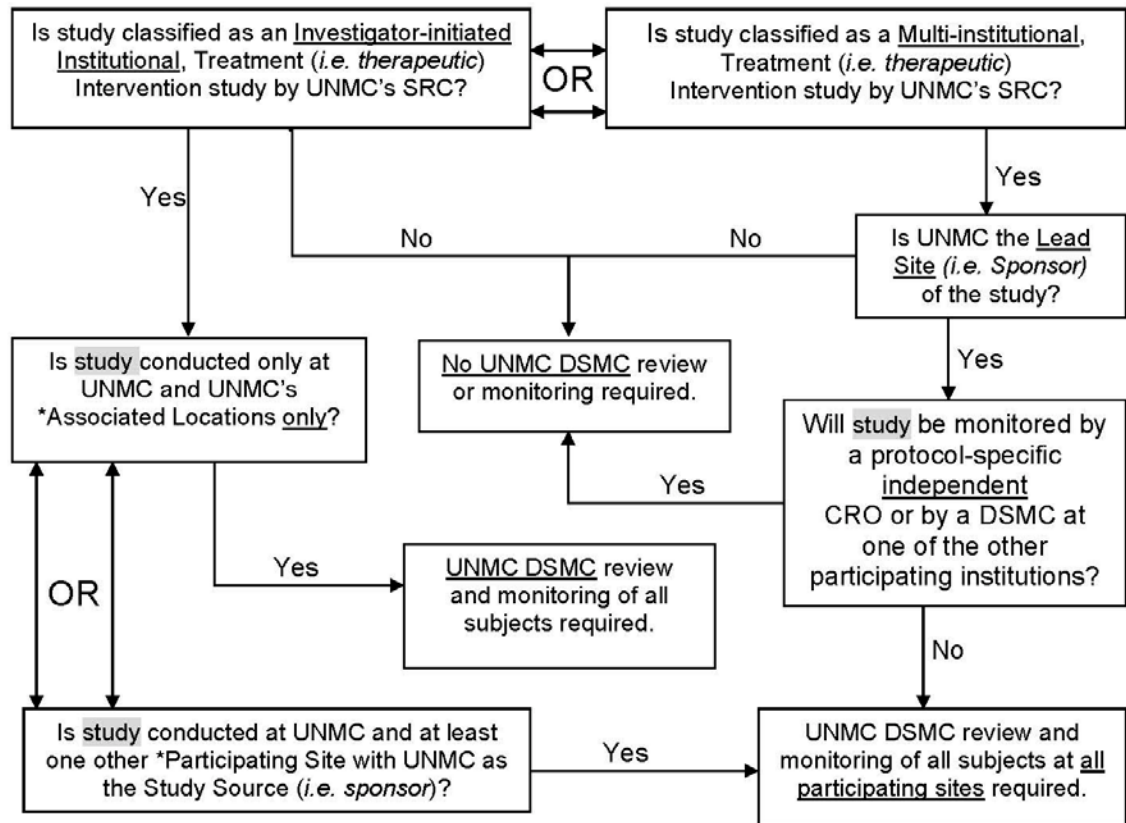
A. DSMC DEFINITION

The Data and Safety Monitoring Committee is an impartial group overseeing a clinical trial and reviews the results to determine acceptability.

B. CLINICAL RESEARCH STUDIES REQUIRING DSMC REVIEW

All cancer-related clinical research study/ies involving human subjects classified as Investigator-Initiated Institutional *treatment-intervention* studies by the Cancer Center's SRC require review by the DSMC.

Figure 1:



NOTE: UNMC/NMC Associated Locations include but are not limited to the Bellevue Medical Center, Village Pointe Medical Center, NE Orthopedic Hospital, and UNMC/NMC Clinics. Children's Hospital and Medical Center is NOT included.

* **ALSO NOTE:** All sites other than UNMC/NMC and Associated Locations are considered "Participating" sites. Children's Hospital and Medical Center is included.

1. Investigator-Initiated Institutional, Treatment Intervention Trial. The study is designed and developed by a PI who is a Cancer Center member *and* is a clinical study with a treatment intent using an agent or device (e.g. device, drugs, radiation, surgery, and/or biological agents).

**Please note: This now includes Big Ten trials, written by a UNMC PI and sponsored by UNMC. The UNMC DSMC will be the DSMC of record for all participating sites.

2. Multi-Institutional, Treatment Intervention Trial. A Cancer Center member must be participating and serving as the UNMC PI in a study designed and developed at another institution. Although more than one IRB approval may be required for these studies, UNMC is not serving as the sponsor of these studies; therefore, UNMC DSMC review is not required.
3. UNMC Sponsored Investigator-Initiated Institutional (IIT) or Investigator-Initiated, Multi-institutional, Treatment intervention Trials sponsored by UNMC with participation by multiple institutions must be monitored by UNMC's DSMC, an independent Clinical Research Organization (CRO), or a Data and Safety Monitoring Board specifically designed for the individual study. Review by the Principal Investigator or a study source's (i.e. sponsor's) Medical Monitor is not considered an independent review, and does not meet the Cancer Center's DSMC review requirements. It is the responsibility of the PI to distribute the Cancer Center's DSMP and DSMC Policies and Procedures to all participating institutions and to ensure adherence to the Adverse Event Reporting Guidelines by all participating institutions.

If the study's intent is to utilize a CRO or other participating institution's DSMC/B in place of the Cancer Center's DSMC, this must be clearly defined in the study and must be approved by the Cancer Center's DSMC prior to activation of the study. If a CRO or a participating site's DSMC/B is approved as the monitoring board for AEs and SAEs, the CRO and/or participating site must agree in writing to: 1) forward all AE DSM reports to the DSMC at regularly planned intervals consistent with the DSMC review schedule; and 2) to fully report all SAEs to the DSMC.

Please refer to the flow chart in Figure 1 on the previous page to determine if a study requires review and monitoring by the DSMC.

Submissions to the DSMC should be made directly to the Clinical Trial Regulatory Specialist via email at prmsoffice@unmc.edu.

A list of DSMC submission deadlines is available from the Cancer Center PRMS office by phone at 402.559.4969 or on the PRMS website at <http://www.unmc.edu/cancercenter/clinical/prms.html>.

III. NEW CLINICAL RESEARCH STUDY SUBMISSIONS

As outlined in the SRC policies and procedures, new cancer related clinical research study/ies must be submitted for review to the SRC. Clinical research study/ies requiring monitoring by the DSMC will be forwarded to the DSMC for initial review by the PRMS Office.

The DSMC will review the study, with a particular focus on the paragraphs pertaining to Adverse Event Reporting Guidelines and Toxicity and Biostatistical considerations including stopping criteria. The DSMC will communicate recommendations regarding changes to the Adverse Event Reporting Guidelines and Toxicity and Biostatistical considerations including stopping criteria sections of the study or study conduct to the PI in writing. The DSMC will report recommendations to the SRC Chair, and the SRC will incorporate these recommendations into the SRC review process.

Please note: Effective January 1, 2021, all UNMC Sponsored, Investigator-Initiated New Projects must be submitted by the first Thursday of the month to allow for an in-depth PRMS administrative review to ensure all requirements of submission are met for all PRMS Committees (CTMS protocol build, required documents, committee specific language, etc.).

A. Initial Review Procedure

During initial review of the study or review of significant changes to the sections pertaining to Adverse Event Reporting Guidelines and Toxicity, reviewers will pay special attention to whether the study contains:

- A clear and unambiguous definition of the instrument to be used to grade Adverse Events current version of Common Terminology criteria for Adverse Events [CTCAE] recommended, but alternatives may be acceptable if clearly defined);
- A clear and unambiguous definition of Adverse Events;
- A clear and unambiguous description of all Adverse Events to be reported to the DSMC. The DSMC requires all AEs Grade 3 or higher (using the current version of CTCAE), expected or unexpected and regardless of attribution, to be reported;
- A clear and unambiguous description of dose escalation and de-escalation criteria to be used, including a clear definition of dose limiting toxicity, where relevant;
- Stopping rules for excessive toxicity and/or lack of efficacy where relevant;
 - Stopping rules *must* be defined in the *specific* Stopping Rule section of the protocol. The Stopping Rules may be additionally included in other sections of the protocol however; they must be clearly defined in their own, independent section.
- A need for interim analysis.
 - Interim Analysis/Interim Review *must* be defined in the specific Interim Analysis/Interim Review section of the protocol. IA/IR must be clearly outlined defining time points (ex: subjects enrolled, subjects evaluable, study arms or stages.)

IV. CHANGES TO THE CLINICAL RESEARCH STUDIES PREVIOUSLY REVIEWED and APPROVED BY THE UNMC DSMC

A. The UNMC DSMC must *review and approve* changes made to the following sections:

Toxicity and Adverse Event Reporting Guidelines

Stopping Rules

Interim Analysis

All Request for Change forms submitted to the SRC for IITs, will also be submitted to the CTRS for review and may be reviewed by the full DSMC.

****Note:** If immediate changes are required to protect the safety of research subjects, the DSMC Chair may grant *conditional approval* of such changes pending review of the proposed changes by the full DSMC.

V. CLINICAL RESEARCH STUDY MONITORING

A. FREQUENCY OF MONITORING

During the initial review, the DSMC will make a recommendation for the frequency of DSMC monitoring based on an assessment of risk associated with study-associated therapy:

- Quarterly review, if the risk for study associated adverse events is considered significant;
- Semi-annual review if the risk for study associated adverse events is considered low;
- Annual review if the risk for study associated adverse events is considered very low.

The frequency of monitoring may change based upon the frequency or severity of adverse events encountered. A change in the frequency of monitoring will be communicated to the study's Principal Investigator in writing.

B. ADVERSE EVENT (AE) REPORTING:

The DSMC monitors all internal and external toxicities and adverse events occurring on Investigator-initiated Institutional clinical research study/ies \geq grade 3. All internal and external serious adverse events, grade 3 and greater using the CTCAE version specified in the protocol (expected or unexpected, and regardless of attribution) must be reported to the DSMC.

C. SCHEDULED REVIEW

Scheduled reviews begin once the first subject signs consent. Scheduled review of cumulative AEs by the DSMC takes place as outlined in the Eppley Cancer Institutional DSMP. The level of monitoring reflects the level of risk associated with the study. During the review, the DSMC will pay particular attention to the frequency and severity of expected adverse events, the occurrence of unexpected adverse events, and the correct attribution of all reported adverse events. Example: Quarterly Review, Semiannual Review, or Annual Review

1. SCHEDULED ADVERSE EVENT REVIEW FORMS

A study specific Data and Safety Monitoring Report must be submitted to the DSMC upon notification of a scheduled AE review. This report must be accompanied by an electronic copy of the DSMC AE Reporting Worksheet summarizing all Grade 3 or higher internal and external AEs (including SAEs that have been fully reported and reviewed by the DSMC). Required electronic forms are available on the PRMS website at <http://www.unmc.edu/cancercenter/clinical/prms.html>.

Please note: Effective January 1, 2019, all AE Reporting Worksheets must be submitted using the excel spreadsheet located on the PRMS website.

Please see APPENDIX 3: Tips for completing the Adverse Event Reporting Worksheet.

Results of the DSMC review of the Data and Safety Monitoring Report and the AE Worksheet will be communicated in writing to the PI, to the Scientific Review Committee, to the Associate Director of Clinical Research, and to the IRB.

Note to Study Staff: *The Scheduled Review Forms must be submitted by the deadline provided by the CTRS.*

- a. *If the study staff is unable to submit the report by the deadline, the PRMS office requires notification before the deadline. The DSMC may provide a one-time deadline extension.*
- b. *If the Review is submitted past the deadline without prior notification, it will be considered a study violation and will require reporting to the UNMC IRB. The DSMC will provide an extended deadline.*
- c. *If the Review Form is not submitted by the extension provided by the DSMC, the SRC will be notified, and the trial may be placed on accrual hold until the DSMC has reviewed and approved the Scheduled Review.*

Please see APPENDIX 4: Tips completing a scheduled review in full.

D. PHASE III INVESTIGATOR-INITIATED INSTITUTIONAL TREATMENT STUDIES:

In accordance with the National Cancer Institute's (NCI) policy, each National Institute of Health (NIH)-supported Phase III study must have a study-specific data and safety monitoring committee or board (DSMC/B). The Principal Investigator may elect to use the Cancer Center's DSMC as the DSMC/B for their Phase III study. Data provided for each arm of these clinical research study/ies will be reviewed while maintaining the blinding of the study arms, if applicable. Interim analyses for major study endpoints will be performed as outlined in the study. Blinding of the study arms, if applicable, will be maintained during the interim analyses. The DSMC may request un-blinding of study arms or other study adjustments if the incidence or severity of adverse events differs significantly between study arms.

If the PI chooses to utilize the Cancer Center's DSMC as the DSMC/B for their Phase III study, it is the responsibility of the UNMC PI to distribute the Cancer Center's DSMP and DSMC Policies and Procedures to all participating institutions and to ensure adherence to the Adverse Event Reporting Guidelines by all participating institutions.

If the PI does not choose to utilize the Cancer Center's DSMC as the DSMC/B for their Phase III study, the composition and review procedures of the study -specific DSMC/B must be approved by the Cancer Center Associate Director for Clinical Research.

If the DSMC/B at a participating site is approved as the monitoring board for AEs and SAEs, the participating site must agree in writing to: 1) forward their AE DSM reports to the DSMC at regularly planned intervals consistent with the DSMC review schedule; and 2) to fully report all SAEs to the DSMC

VI. SERIOUS ADVERSE EVENT (SAE) REVIEW

The DSMC reviews all SAEs occurring on trials monitored by the committee. Principal Investigators are responsible for fully reporting all SAEs as outlined in the study and in the Cancer Center's Institutional DSMP. The DSMC requires SAEs be fully reported to the PRMS Office *within 7 days* of

the PI of study staff becoming aware of the SAE. These events are also incorporated into each protocol safety review/adverse event scheduled review submitted to the DSMC.

A. DEFINITION OF A SERIOUS ADVERSE EVENT

An Adverse Event is serious and requires full reporting when the patient outcome meets one of the definitions listed below per Code of Federal Regulations 312.32: (per NCI AE Guidelines Section 2.1.22)

1. **Death**
2. **A Life-Threatening adverse drug experience**
3. **Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours)**
4. **A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**
5. **A congenital anomaly/birth defect**
6. **Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21CFE 312.32; ICH E2A and ICH E6).**

NOTE Regarding Studies Conducted at Multiple Sites: It is essential that all **internal and external** AEs and SAEs on studies sponsored by UNMC and conducted at multiple institutions be monitored by the DSMC or a single board specifically designed for the individual study.

For Investigator Initiated-institutional Institutional or Multi-institutional studies with UNMC as the study source (i.e. sponsor), the UNMC PI is responsible for reporting all Internal and External AEs and SAEs as outlined in the study.

B. DEFINITION OF A FULLY REPORTED SAE

Full reporting of an SAE to the DSMC is complete upon submitting the following documents for review:

- The UNMC DSMC SAE Assessment form or equivalent form summarizing the SAE;
- A blinded copy of all patient source documents related to the SAE;
- A blinded copy of the subject's most recently signed Informed Consent Form (ICF).

C. REPORTING SERIOUS ADVERSE EVENTS

Any Internal AE meeting one or more of the definitions of SAE outlined in Section IV.B above **regardless of whether or not it meets the UNMC IRB's requirements for reporting** must be fully reported to the DSMC.

Please see APPENDIX 5: Tips for Submitting SAEs in full

****Note to Study Staff:** Failure to fully report an SAE, as required, will be considered a study violation and may be reported to the Associate Director for Clinical Research.

****Note to Study Staff:** Please see attached instructions for completing a Serious Adverse Event Assessment form and submitting the required documentation.

VII. REVIEW OF DOSE COHORT CHANGES ON PHASE I STUDIES

DSMC approval is *not* required prior to a change in the study's dose level; however, the PI must notify the DSMC upon making the change by completing and submitting the Dose Level Change Report (<http://www.unmc.edu/cancercenter/clinical/prms.html>) for review at the DSMC's next regularly scheduled meeting.

VIII. REVIEW OF INTERIM ANALYSES (IA) or INTERIM REVIEW (IR)

Clinical research study/ies monitored by the DSMC may contain stopping rules for excessive toxicity or lack of efficacy. Whenever an IA is performed to ensure no study defined stopping rules have been met, a copy of the analysis must be forwarded to the DSMC. The DSMC will acknowledge receipt of the IA and discuss the results at its next regularly scheduled meeting.

****Note to Study Staff:** Failure to complete a scheduled IA or IR per protocol and submit to the DSMC will result in notification to the SRC and may lead to the study being placed on hold until the IA is reviewed and approved by the DSMC.

IX. SUBMISSION DEADLINES

The DSMC submission deadline is sent annually to all study staff with the list of scheduled reviews for the year. Please contact the PRMS Office at 402.559.4969 for a list of submission deadlines. Submissions to the DSMC must be made directly to the Cancer Center PRMS Office at prmsoffice@unmc.edu. Please note: all New Investigator-Initiated projects will be offered a pre-review to be completed by the PRMS Office Team. If the study-staff chooses to have a pre-review done, the submission *must be provided* to the PRMS Office two-weeks prior than the standard deadline for all other submissions.

A list of scheduled meetings and DSMC submission deadlines is available from the Cancer Center PRMS Office or the PRMS Website at <http://www.unmc.edu/cancercenter/clinical/prms.html>.

X. CLINICAL RESEARCH STUDY TERMINATION and CONCLUSION of DSMC REVIEW

PIs are responsible for notifying the DSMC of study termination or completion. Submit notification directly to the Cancer Center PRMS Office at prmsoffice@unmc.edu.

Review of the study, scheduled review of AEs and review of SAEs by the DSMC will continue as long as research subjects are considered to be at-risk for study-associated toxicity.

XI. REVIEW PROCEDURES

A. ASSIGNMENT OF REVIEWERS

The following are reviewed by one member eligible to review:

- Regularly Scheduled AE Reports
- Fully reported SAEs

The following are reviewed by all members eligible to review:

- New protocols
- Changes to the Adverse Event Reporting Guidelines and Toxicity section
- Changes to the Stopping Rule section
- Changes to the Interim Analyses

If expedited review of a Fully Reported SAE is required, the DSMC Chair may conduct the review or assign the review to a member of the DSMC. However, the result of the review by the full DSMC at the next regularly scheduled meeting.

B. CONFLICT OF INTEREST POLICY

New protocols, AEs, and SAEs will not be assigned to DSMC members who function as principal or secondary investigator on the study. DSMC members with a conflict of interest will recuse themselves from the meeting room during the discussion and voting for any issue on studies on which they serve as a principal or secondary investigator.

In addition, DSMC members will recuse themselves from discussion and voting to avoid any conflict of interest (personal, financial, ethical). A selected member will act as Chair if the Chair must recuse himself/herself to avoid a conflict of interest.

XII. REVIEW OUTCOMES

Review results (including recommendations for change) are communicated to the PI and Study Staff in writing. The results are reported to the SRC, and the SRC will incorporate these observations into the SRC review process.

A. Review of New Clinical Research Studies and/or Changes to Previously Reviewed Sections Pertaining To Adverse Event Reporting Guidelines and Toxicity, Stopping Rules and Interim Analyses

Review results will be categorized as one of the following:

- a. Approved**
- b. Approved with Note to PI or Study Staff**
- c. Additional Information Required/Clarification Requested:** The information is requested directly from the PI and Study Staff in a formal letter from the DSMC. The PI *must reply in writing* for the study to be reviewed at the following DSMC



meeting by the full board.

- d. **Tabled:** The information is requested directly from the PI and Study Staff in a formal letter from the DSMC. The PI *must reply* in writing for the study to be reviewed at the following DSMC meeting by the full board.
- e. **Further Clarification Requested:** The information is requested directly from the PI and Study Staff in a formal letter from the DSMC. The PI must reply in writing for the study to be reviewed at the following DSMC meeting by the full board.
- **Now Approved, PI Response Acceptable:** The investigator will be notified in writing with a copy to the SRC and the IRB.

B. Review of AEs and SAEs:

Review results will be one of the following:

- **Approved/No study and/or operational changes required:** The investigator will be notified in writing with a copy to the SRC and the IRB.
- **Additional information required/Clarification Requested:** The information will be requested directly from the investigator or through the DSMC. The investigator will be notified in writing with copies to the SRC, the IRB, and the Audit Committee. *Clerical changes/corrections may be approved by the DSMC Chair or Vice Chair.
- **Minor study and/or operational changes recommended:** The investigator will be notified in writing with a copy to the SRC and the IRB.
- **Major study and/or operational changes recommended/Tabled:** This recommendation generally results from the identification of significant concerns for the safety of research participants by the DSMC. The investigator, the Chair of the SRC, and the Associate Director for Clinical Research will be notified immediately both verbally and in writing regarding DSMC concerns with a copy to the IRB. The SRC and/or the Associate Director for Clinical Research may decide to temporarily suspend accrual to the study pending acceptable changes.
- **Now Approved, PI Response Acceptable:** The investigator will be notified in writing with a copy to the SRC and the IRB.

XIII. REPORTING RESULTS OF DSMC REVIEW

The DSMC will communicate the results of all reviews and recommendations regarding changes to the study or study conduct to the PI in writing. Written communications to the PI are signed by the DSMC Chair. If the DSMC Chair is a named investigator on the study being reviewed, communication will be signed by a member of the DSMC in attendance at the DSMC meeting. Minutes from the DSMC meetings are submitted to the Cancer Center's SRC, Audit Committee, and the UNMC IRB for informational purposes.

APPENDIX 1: DSMC POLICIES AND PROCEDURES FOR STUDIES BEING CONDUCTED AT MORE THAN ONE SITE WITH UNMC AS THE STUDY SOURCE (i.e. Sponsor)

I. PURPOSE:

The Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC) is assigned the responsibility of monitoring the safety of all research participants in clinical research studies sponsored by the Fred & Pamela Buffett Cancer Center (FPBCC) members, as outlined in the UNMC Eppley Cancer Center revised Institutional Data and Safety Monitoring Plan, Version 4.0, dated September 21, 2020.

In addition to the policies outlined in the Cancer Center's DSMC Policies and Procedures, **the following policies apply to all cancer-related Investigator-initiated Institutional and Multi-institutional treatment studies sponsored by UNMC and/or its Associated Locations and being conducted by at least one additional participating site.**

II. DEFINITIONS:

A. UNMC ASSOCIATED LOCATIONS

UNMC/NMC Associated Locations include, but are not limited to, the Bellevue Medical Center, Village Pointe Medical Center, NE Orthopedic Hospital, and UNMC/NMC Clinics. Children's Hospital and Medical Center is NOT included.

B. PARTICIPATING SITE/S

The previous definitions of "Affiliate" and "Participating" sites are no longer valid. All sites other than UNMC/NMC and Associated Locations are now considered "Participating" sites. This includes Children's Hospital and Medical Center.

III. CLINICAL RESEARCH STUDIES REQUIRING DSMC REVIEW:

All cancer-related Investigator-initiated Institutional and Multi-institutional treatment studies sponsored by UNMC and/or its Associated Locations fall under the purview of the DSMC. These clinical research study/ies must be monitored by the DSMC or a board specifically designed for the individual study. The level of monitoring is determined by the type of study and potential risks.

IV. DSMC RESPONSIBILITIES:

A. Responsibilities of the UNMC Principal Investigator (PI) and Coordinator:

1. Conducts continuous review of data and subject safety.
2. Ensures all AEs and SAEs are reported to the Cancer Center's Protocol Review and Monitoring System (PRMS) Office and to the UNMC IRB as specified in Section 9.0 of the currently approved study document (or the equivalent adverse event reporting).
3. Distributes the DSMP to the Participating Site/s and ensures adherence to the Adverse Event Reporting Guidelines by all participating institutions.



4. Conducts an initial site visit prior to opening a study to accrual at a Participating Site.
5. Provides ongoing guidance and direction, as needed, to the Participating Site Investigator/Consenting MD and Coordinator regarding study specific data and subject safety.
6. Submits study, data collection and adverse event report forms to the FPBCC Audit Committee (AC), Data and Safety Monitoring Committee (DSMC), and Scientific Review Committee (SRC) for approval.
7. Provides the approved study, data collection, and adverse event report forms to the Participating Site.
8. Ensures all study specified adverse events from Investigator-initiated Institutional Pilot, Phase I, Phase II, and Phase III studies are reported on standard adverse event reporting forms directly to the PRMS Office and separately to the IRB.

B. Responsibilities of the Participating Site Investigator/Consenting MD and Coordinator:

1. Conducts continuous review of data and subject safety at the Participating Site.
2. Ensures all adverse events are reported to the UNMC PI as specified in Section 9.0 of the currently approved study document (or the equivalent adverse event reporting section).
3. Acts as liaison between the DSMC and the Participating Site Investigator and/or Consenting MD as needed.
4. Following the completion of the DSMC review, ensures appropriate follow-up and/or changes are completed as requested by the DSMC.

C. Responsibilities of the Cancer Center PRMS Office:

1. Provides ordination/training to the Participating Site Coordinator prior to opening a study to accrual at Participating Site regarding Audit, DSMC, or SRC policies and procedures. Provides ongoing guidance and direction, as needed, to the Participating Site Coordinator.
2. Communicates in writing the study's adverse event summary and the results of the DSMC review of the study to the SRC and the Associate Director of Clinical Research.
3. Forwards the DSMC's recommendations regarding changes to the study or study conduct to the Associate Director of Clinical Research for action.
4. Sends notification of the impending DSMC review to the UNMC PI and Study Coordinator at least 30 days prior to the scheduled DSMC review date.

V. DSMC MONITORING OF MULTI-INSTITUTIONAL STUDIES WHERE UNMC IS THE LEAD SITE (i.e. Study Source or Sponsor):

- A. Clinical research studies for all Multi-institutional studies with one or more participating sites and with UNMC as the lead site and study source (i.e. sponsor) must clearly outline the reporting requirements and procedures for all participating site/s.
- B. Study sections pertaining to these reporting requirements and procedures must be approved by the DSMC prior to SRC review and approval.
- C. The following issues must be addressed within the study for Multi-institutional studies with participating sites:



1. The study may state the DSMC Committee or Board at a participating site will monitor all AEs and SAEs on-site. However, this designation, along with the reporting procedures at the participating site/s, must be approved by the DSMC.
2. If the DSMC/B at a participating site/s is approved as the monitoring board for AEs and SAEs, the participating site/s must agree in writing to: 1) forward their AE DSM reports to the DSMC at regularly planned intervals consistent with the DSMC review schedule; and 2) to fully report all SAEs to the DSMC.
3. The UNMC PI and/or their designee will be responsible for: 1) incorporating the AE/SAE data received from participating site/s into one DSMC Worksheet for all participating sites; 2) submitting the combined worksheet to the DSMC at regularly scheduled intervals; and 3) ensuring all SAEs for all participating sites are fully reported and submitted to the DSMC.

VI. INSTITUTIONAL REVIEW BOARD:

If a participating site does not have their own Institutional Review Board (IRB), the UNMC IRB will be the IRB of record for clinical research study/ies sponsored by UNMC and conducted by at least one additional participating site.

VII. DSMC DOCUMENTATION:

All DSMC documentation will be maintained in the Cancer Center PRMS Office (i.e. minutes, letters). In addition, copies of all DSMC related documents will be maintained at the Participating Site.

VIII. INTRANET AND OPEN FORUM COMMUNICATIONS:

Current DSMC Policies and Procedures may be accessed on the intranet at <http://www.unmc.edu/cancercenter/clinical/prms.html>. Periodic open forums are scheduled with study coordinators and PIs to communicate and clarify DSMC policies and procedures and obtain feedback to streamline and facilitate the DSMC review process.

Please note: With the large number of IITs currently under the purview of the PRMS office, efficiencies in our internal processes must be created to optimize our workflows. Moving forward, all questions which arise outside of the open forums regarding Audit and DSMC must be submitted via email OR a meeting must be scheduled. Please send a meeting invite (including conference room number) to the Clinical Trials Regulatory Specialist to discuss any questions you may have regarding Investigator-Initiated Protocols.

Please note: the Clinical Trials Regulatory Specialist will only answer questions regarding PRMS Committee policy and/or reporting requirements as defined in the approved protocol and reserves the right to redirect questions to be asked of the IIT Office, Study Staff or Principle Investigator.

Questions requiring immediate assistance must be submitted via email with a **high** priority status.

APPENDIX 2: DSMC SUGGESTED STANDARD SRC PROTOCOL LANGUAGE

The DSMC approves the following required language be used for Single-Site, Investigator-Initiated Protocols. The PI is responsible for adding the necessary information for protocol specific toxicities, adverse events, and serious adverse events. The protocol will not be approved by the DSMC without the required Toxicity and Adverse Event Reporting language.

The following applies ONLY to DSMC requirements. Additional information may be necessary.

9.0 TOXICITY AND ADVERSE EVENT REPORTING GUIDELINES

This protocol will comply with monitoring and adverse event reporting requirements of the UNMC/Fred & Pamela Buffett Cancer Center Data Monitoring plan. The protocol will adhere to the institutional and FDA guidelines for the toxicity reporting.

All patients will be closely followed for toxicity from the time of informed consent until 30 days after last administration of study medication. ***Please note this time-frame is a minimum. If the PI prefers a longer time-frame the duration may change.***

Adverse events will be assessed by reports from subjects to their physician/Investigator and by physical examinations. Per NCI guidelines, serious adverse events (SAEs) and adverse events (AEs) will be graded and toxicity assessed using the revised NCI CTCAE version 5.0. AEs and SAEs will be followed until resolution, baseline or grade 1 or less levels.

SAEs should be followed until resolution, death, or until no further improvement is reasonably expected. Deaths occurring within 30 days of study treatment regardless of relationship will be reported to the UNMC DSMC.

9.1 Definitions

Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

An elective surgery or procedure that is scheduled to occur during a study will not be considered an AE if the surgery or procedure is being performed for a pre-existing condition and the surgery or procedure has been planned before study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., the surgery is performed earlier than planned), then the deterioration of the condition for which the elective surgery or procedure is being done will be considered an adverse event.

Any worsening of a pre-existing condition or illness is considered an AE. Laboratory abnormalities and changes in vital signs are considered to be AEs if they result in discontinuation from the study, necessitate

therapeutic medical intervention, meet protocol specific criteria and/or if the investigator considers them to be adverse events.

Unexpected Adverse Event

An unexpected AE is any adverse drug event that is not listed in the current labeling/Investigator's Brochure. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

Serious Adverse Event

A serious adverse event is one that at any dose (including overdose) and regardless of causality that:

1. **Death**
2. **A Life-Threatening adverse drug experience**
3. **Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours)**
4. **A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**
5. **A congenital anomaly/birth defect**
6. **Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21CFE 312.32; ICH E2A and ICH E6)**

9.2 Adverse Event Reporting and Definitions Per University of Nebraska Medical Center, IRB and Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC)

This protocol will adhere to all institutional guidelines for adverse event reporting. Adverse events will be evaluated using the NCI Common Terminology Criteria for Adverse Events (CTC-AE) version 5.0.

9.2.1 IRB REPORTING

Please see IRB Reporting Requirements

9.2.2 Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC) Reporting

In its initial review, the DSMC will make a recommendation for the frequency of DSMC monitoring based on an assessment of risk associated with study-associated therapy, per the DSMC policy. Reporting of the following will be done in accordance with DSMC guidelines:

- All Serious adverse events (SAEs) and toxicity reporting will be reported to the DSMC
- All adverse events grade 3 or higher (expected or unexpected, regardless of attribution) will be reported to the DSMC

Attribution of AEs: The likelihood of relationship of the AE to the study drugs will be determined by the investigator based on the following definitions:

Not related: The subject was not exposed to the study treatment or another cause is obvious.

Probably not related: The AE is most likely explained by another cause, and the time of occurrence of the AE is not reasonably related to the study treatment.

Possibly related: Study treatment administration and AE occurrence reasonably related in time, and the AE is explained equally well by causes other than study treatment, or treatment administration and AE occurrence are not reasonably related in time, but the AE is not obviously a result of other causes.

Probably related: Study treatment administration and AE occurrence are reasonably related in time, and the AE is more likely explained by study treatment than by other mechanisms.

Definitely related: There occurrence and timing of the AE are clearly attributable to the study treatment.

All SAEs and AE reporting will be completed using DSMC approved forms. Detailed policy and procedures for this section may be reviewed at: <http://www.unmc.edu/cancercenter/clinical/prms.html>

9.3 Auditing

Auditing is a systematic and independent examination of trial-related activities and documents to determine:

- whether the evaluated trial-related activities were conducted
- the data were recorded, analyzed, and accurately reported, according to the protocol, to the sponsor's SOPs, GCP, and applicable regulatory requirement(s).

Auditing is a Quality Assurance, one point process during the trial.

This study will undergo audit on at least a semi-annual basis by the UNMC Fred & Pamela Buffett Cancer Center Audit Committee.

Detailed policy and procedures for this section may be reviewed at: <https://www.unmc.edu/cancercenter/clinical/prms.html> .



APPENDIX 3: TIPS FOR COMPLETING ADVERSE EVENT REPORTING WORKSHEET

Every subject consented and will have a line on the AE Reporting worksheet whether or not any AEs are reported.

Off treatment dates must be added to the AE Reporting Worksheet within 7 days of the Subject stopping treatment.

Disease progression must be noted in the comments section of the AE Reporting Worksheet.

APPENDIX 4: TIPS FOR COMPLETING A SERIOUS ADVERSE EVENT ASSESSMENT FORM IN FULL

I. Submitting an SAE for protocols dated up to -19 and for use by participating sites submitting to the IIT Office:

1. The SAE must be submitted on the most current version of the Serious Adverse Event Assessment Form available on the PRMS website. Failure to use the most recent form will be an automatic Decline to Review from the PRMS Office and the complete submission will require re-submission.
2. Handwritten submissions will not be accepted by the PRMS Office. All fields must be completed electronically with the exception of the name, date and signature fields. Failure to complete the form electronically will be an automatic Decline to Review from the PRMS Office and the complete submission will require re-submission.
3. *See below for a blank practice form.* Please open each comment box for a helpful tip on how to complete the section.

****Note to Study Staff:** Failure to fully report an SAE, as required, will be considered a study violation and may be reported to the Associate Director for Clinical Research.

****Note to Study Staff:** Please see attached instructions for completing a Serious Adverse Event Assessment form and submitting the required documentation.

II. Submitting an SAE for protocol dated -20 moving forward:

1. The SAE must be submitted via CTMS. Please refer to the Quick Guide located in OnCore CTMS Training Resources in the Subject Management section.

<https://www.unmc.edu/cctr/clinical-trials/ctms-training/training-resources/>

2. Training must be completed prior to submitting SAEs via CTMS. Contact the PRMS Office at prmsoffice@unmc.edu to schedule a training session.

Serious Adverse Event Assessment Form

Only for Non Investigator-Initiated Trials

IRB# Click or tap here to enter text.

PI: Click or tap here to enter text.

TITLE: Click or tap here to enter text.

Only for UNMC Investigator Initiated Trials

For all IIT Trials: All Serious Adverse Events (SAEs), regardless of severity or relationship, require reporting to the DSMC via the PRMS Office with seven (7) days of the Study Staff's knowledge.

IRB# Choose an item.

PI: Choose an item.

TITLE: Choose an item.

Report date: Click or tap to enter a date. _____

All Serious Adverse Events (SAEs), regardless of severity or relationship, require reporting to the PRMS Office with seven (7) days of the Study Staff's knowledge.

Subject ID (DO NOT use MRN): Click or tap here to enter text. Site: Click or tap here to enter text.

Date of Event: Click or tap to enter a date.

Date of Report: Click or tap to enter a date.

Description of Event:

Click or tap here to enter text.

1. Event: Click or tap here to enter text. Grade: Choose an item.
 - a. Attribution: Please circle one
 - Unrelated** – AE is *clearly not* related to the intervention
 - Unlikely** – AE is doubtful related to the intervention
 - Possible** – AE is maybe related to the intervention
 - Probable** – AE is likely related to the intervention
 - Definite** – AE is *clearly* related to the intervention
 - b. Expected (currently in ICF): Yes No
 - c. Does the event require a change in the ICF? Yes No
 - d. Serious: Yes No

Comments: Click or tap here to enter text.

2. Event: Click or tap here to enter text. Grade: Choose an item.
 - a. Relationship: Choose an item.
 - b. Expected (currently in ICF): Yes No
 - c. Does the event require a change in the ICF? Yes No

d. Serious: Yes NoComments: [Click or tap here to enter text.](#)

3. Event: [Click or tap here to enter text.](#) Grade: Choose an item.
- a. Relationship: Choose an item.
- b. Expected (currently in ICF): Yes No
- c. Does the event require a change in the ICF? Yes No
- d. Serious: Yes No

Comments: [Click or tap here to enter text.](#)

In the case of more than three (3) SAEs, please contact the PRMS Office and you will be sent a copy of the form with the number of events you require.

Site PI or Consenting MD is required to assess, grade an attribute each SAE on this form.

Submit the completed form and all supporting documentation related to the event to the UNMC PRMS Office. If a MedWatch form was completed for these events, please include it in the submission.

Printed name of person completing report

Date

Printed Name Site PI/Consenting Sub-I

Signature of Site PI/Consenting Sub-I

Date

-----UNMC Only-----

Printed name of UNMC Principal Investigator

Signature of UNMC Principal Investigator

Date

UNMC Clinical Research Support Administrative Reporting Review:FDA: Yes No N/AUNMC IRB: Yes No N/ADSMC: Yes No N/A