Data and Safety Monitoring Committee (DSMC) Charter

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TABLE OF CONTENTS

1 PURPOSE

The purpose of the Robert H. Lurie Comprehensive Cancer Center (RHLCCC) Data and Safety Monitoring Committee (DSMC) is to provide oversight for clinical research activities for all Lurie Cancer Center (LCC) Investigator-Initiated trials, and other clinical trials operating under the LCC Data and Safety Monitoring Plan (DSMP). The goal is to ensure the safety of participants, the integrity of research data, and compliance with the IRB-approved protocol.

The DSMC will also ensure clinical research activities adhere to all rules, regulations, and guidance set forth by the Food and Drug Administration (FDA), National Cancer Institute (NCI), the International Council of Harmonisation's (ICH) Good Clinical Practice (GCP), the IRB of record, and institutional standard operating procedures (SOPs).

This charter will outline administration and procedures for ensuring such oversight by the DSMC and applies to clinical research conducted at LCC, its satellite sites, and any sites participating on a trial under this plan. It is used in conjunction with the DSMP.

The DSMC is an independent committee within the Lurie Cancer Center's (LCC) Protocol Review and Monitoring System (PRMS).

2 MEMBERSHIP

The LCC's Deputy Director appoints committee members in consultation with the DSMC Chairs. The composition of the committee is described below. Committee membership is maintained in a separate membership roster.

2.1 LEADERSHIP

The DSMC includes one (1) Chair and one (1) Co-chair.

2.2 MEMBERS

Membership consists of one (1) panel of 5-9 core voting members, as well as rotating departmental and ad hoc members assigned to specific meetings as needed. The panel includes multidisciplinary representation from Northwestern Medicine's medical oncology, radiation oncology, surgical oncology, pediatric oncology, medical social sciences, biostatistics, and investigational pharmacy. Ad hoc reviewers may be used for designated review purposes as needed. Ad hoc reviewers will vote only on protocols they review.

2.3 Non-Voting Members

The panel has administrative support through the Quality Assurance (QA) and Compliance teams. Other non-voting members representing clinical research interests may attend meetings but are not considered voting members.

3 Procedures and Administration

3.1 Meetings

3.1.1 Panel Meetings

The DSMC meets once a month at regularly scheduled times. Additional meetings may be called with agreement of the Chairs as needed. Minutes will reflect member attendance, studies and items discussed, any requests for additional information, and decisions.

3.1.2 DSMC Preparation Team Meetings

The DSMC preparation team – consisting of the DSMC Chair(s), as well as members of the Compliance and QA teams – meets bi-monthly to review administrative updates, the upcoming agenda, with an initial review of incoming safety or compliance concerns, incoming data/statistical analyses, studies up for progress reviews, or other outstanding issues. Occasionally, actions may be taken, or determinations may be made outside of panel or sub-committee meetings, in which case these are documented in the following month's agenda as having been reviewed in an ad-hoc capacity.

3.1.3 DSMC Sub-Committee Meetings

The DSMC Sub-Committee for Audits, or Audit Sub-Committee (ASC), meets at least quarterly to conduct a review of audits conducted under the DSMP. The sub-committee consists of the ASC Chair and Co-chair, and a subset of voting members representing various oncology specialties. The ASC conducts first patient, for-cause, and comprehensive audits as described in the DSMP.

Audits are typically focused on trials assessed as high-risk (although moderate and minimal risk trials may undergo for cause or periodic audits if appropriate) and will be audited according to the plans listed in the DSMP. Studies and sites are subject to audit upon IRB approval, and typically start at the time of opening to accrual. A study may be exempt from an audit if there are no identified patterns of non-compliance previously identified, enrollment has concluded, or study is preparing for closure.

Audits are conducted as required following a modified version of the NCI's Clinical Trials Monitoring Branch Auditing Guidelines. This includes overall audit ratings of:

- Acceptable with no follow-up
- Acceptable with follow-up required
- Unacceptable with follow-up required

All audits are reported to the full DSMC for final approval and acknowledgment or additional actions.

3.2 COMMITTEE SUPPORT

The LCC employs seven to ten (7-10) Quality Assurance (QA) staff members who provide ongoing oversight and monitoring of Investigator Initiated Trials as determined by the DSMP. The QA team also provides administrative support for the DSMC which includes:

- Maintaining meeting schedule and reserving necessary resources
- Creating meeting agendas, materials, and minutes
- Generating DSMC review outcome letters and processing responses
- Facilitating communications between the DSMC, ASC, SRC, study team, as well as with other components of the LCC Research Oversight System (ROS)

The LCC also employs four to five (4-5) compliance staff members who provide support in addressing overarching compliance issues and serving as a resource to research teams. Each compliance staff member has a different area of focus, with at least 1 member supporting the Audit Subcommittee (ASC). This compliance team member is responsible for:

- Audit scheduling
- Assigning auditors for each audit
- Initial compilation of audit findings and reports
- Creating meeting agendas, materials, and minutes
- Generating ASC review outcome letters and processing responses, including proposed corrective and preventative action plans (CAPAs)
- Facilitating communications between the ASC and DSMC, study team, as well as with other components of the LCC Research Oversight System (ROS) such as the SRC and Disease team (DT)s

At least 1 member also supports participating site management for Investigator-Initiated Trials that fall under the DSMP.

Consortium trials that are managed and/or monitored outside of the Lurie Cancer Center but utilize the Lurie Cancer Center DSMC may also have representatives from other CROs to present materials, generate outcome letters, and communicate with the study team.

3.3 QUORUM

Quorum for DSMC meetings is defined as three (3) core voting members, including at least one (1) biostatistician and one (1) Chair or Co- chair. An ad hoc reviewer may count towards quorum if in attendance. If quorum is not met for a panel meeting, studies for review may still be presented; essential review documents will then be routed for electronic review to the rest of the panel. If needed, the review outcome may be finalized in the next DSMC preparation meeting.

Quorum for ASC meetings is defined as one (1) core voting member, which must include as least one (1) Chair or Co-chair. If quorum is not met for a panel meeting, studies for review may still be presented; essential review documents will then be routed for electronic review to the rest of the panel.

3.4 APPOINTMENTS

Appointments are for 3-year terms with auto renewal. Attendance will be recorded at each panel meeting. Members are expected to attend at least 75% of the meetings annually. Attendance is reviewed annually with the DSMC Chair(s), and any concerns or membership needs are brought to the monthly Research Oversight Committee (ROC) meeting for discussion with LCC leadership.

3.5 CONFIDENTIALITY

Discussions that occur within DSMC are confidential and are not disclosed except as outlined in this charter. DSMC decisions are communicated to the respective PI and study team, as appropriate, but specific details related to the details of the discussion or persons involved in the discussion are disclosed. Formal DSMC action letters are also communicated to the respective DT leaders and the SRC. Meeting minutes are considered confidential. Any materials shared or distributed with the DSMC are considered confidential.

3.6 CONFLICT OF INTEREST

Members will be recused from any discussions on studies for which they serve as Principal Investigator.

4 ONGOING STUDY MONITORING

The DSMC is tasked to monitor Investigator-Initiated Trials under the DSMP according to their phase and risk level. Any areas of concern may include notification to the other Research Oversight Committees.

4.1 TRIAL PROGRESS

SRC recommendations regarding IITs are shared with the QA team during the annual DT portfolio review process conducted by the SRC. While not a direct DSMC responsibility, concerns about accrual identified during review of progress reports are communicated to SRC for review and action, via Semi-Annual Reports, as needed.

4.1.1 Semi-Annual Reports

DSMC reviews the progress of all clinical trials monitored by the committee through review of semi-annual reports. The semi-annual reports include summary information for and any recommendations on accrual, adverse events, and compliance issues. These are prepared by the assigned QAM and distributed to the PI and study team(s) for input as needed. The DSMC may make recommendations regarding accrual, safety and toxicity, protocol compliance, and data compliance which may require responses or corrective action plans from the PI and study team as appropriate.

Such recommendations regarding accrual concerns will be communicated to the SRC.

Semi-Annual reports are generated every 6 months from the date the trial opened at the lead institution. The DSMC will review all reports until the trial is closed to accrual, all patients are off treatment and completed their safety follow up period, and there is reasonable expectation that no further safety events or compliance concerns will be identified.

Semi-Annual reports will be provided to the IRB at the time of Continuing Review, unless reportable new information is identified or recommended in the report, in which case the report should be submitted in the IRB-required timeframes for RNI.

4.1.2 FDA Annual Reports

The DSMC will be provided a copy of all FDA Annual Reports upon submission to the FDA. Information contained in these reports should not greatly differ from that in the Semi-Annual Progress Report.

The DSMC will review all reports until the IND/IDE is withdrawn with the FDA.

Reports will be generated by the assigned QAM.

4.2 Safety Review

The DSMC assesses participant safety by reviewing adverse events, serious adverse events, or other events of clinical interest, UPIRSOs, as applicable. The DSMC should also ensure timely and appropriate reporting to any oversight authorities (IRB, FDA, etc.).

The Principal Investigator (PI) and study team are responsible for ensuring all events are reported per protocol (i.e. to the funding sponsor or other institutions).

4.2.1 Serious Adverse Events (SAEs)

Any serious adverse events or events meeting expedited reporting criteria per protocol and are reported to the assigned QAM are subject to review at the next available DSMC meeting. The DSMC will review all SAEs or events meeting expedited reporting criteria until the trial is closed, and as needed per protocol design.

If limited information is available in the report, it is still presented at the next available DSMC meeting, but any change in SAE term, grade, or relationship to study agent will require re-review.

Possible DSMC actions after review of safety data may include:

- Acknowledgement of the event
- Request for clarifications or recommend updates to an internal report which will be re-reviewed at the next panel meeting
- Recommend reporting the event to the IRB or FDA, as applicable.

4.2.2 External Safety Reports or Action Letters

The DSMC will review any external safety reports which the PI determines are reportable according to the Management of External Safety Reports policy. In addition, all action letters which impact studies operating under the DSMC will be reviewed. The DSMC may recommend reporting the event to the IRB along with updates to the study consent.

4.2.3 Safety Reviews, Interim Analysis, Dose Escalation Reviews

The DSMC reviews all potential dose limiting toxicities (DLTs) for dose escalations and safety run-in reviews. In addition, the DSMC reviews critical efficacy endpoints for interim analyses or stopping criteria as defined by the protocol. The study assigned statistician will review these independently.

For safety run-in and dose escalation trials, the DSMC will review safety data prior to the requested dose escalation of the applicable cohort(s)/arm(s). The DSMC will continue to review safety data until the safety run-in is complete or the MTD is established, as needed per protocol design.

The PI is responsible for ensuring all data is entered and queries addressed in a timely manner to ensure proper review. After monitoring is completed and there are no identified safety data missing, the QAM will export all adverse event/toxicity information entered into the case report forms.

The QAM will highlight any events that were identified by the investigator as meeting DLT criteria. The QAM will also pre-screen other events that may potentially meet DLT criteria.

For interim analyses and review of stopping criteria, the QAM will compile a report containing all data needed to confirm whether the critical efficacy endpoint or stopping criteria has been met.

These reports will be presented at a DSMC panel meeting, unless an urgent determination is needed. The study assigned statistician will also review the data summary report and make their recommendation per protocol design.

The results of any interim analysis will be communicated to the study team, including the study statistician.

4.3 COMPLIANCE

The DSMC will ensure the investigator and study teams adhere to the protocol and all rules and regulations.

The Principal Investigator (PI) is responsible for ensuring all deviations are reported per protocol.

4.3.1 Deviations

All deviations are reviewed by the assigned QAM and presented at the next available DSMC preparation meeting. At the preparation meeting, a determination may be made that the deviation can be closed from further review if it does not meet or have the potential to meet Reportable New Information (RNI). The QAM may also request additional information from the study team. The DSMC will review all deviations or compliance concerns until the trial is terminated.

If an individual or group of deviations meets or has the potential to meet RNI, it is recommended for additional review at the next available DSMC meeting according to the Protocol Deviations and Reportable New Information policy. Of note, deviations may also be reviewed in summary or re-

reviewed as a periodic group if a pattern is seen to emerge or repeat occurrences are noted on a monitoring visit.

The definition of RNI will be subject to the IRB of record, but generally speaking, if there are serious or continuous non-compliance that poses an increased risk to patient safety or the study design, the DSMC may require further action. The DSMC may request additional information from the study team, close out the deviation from further review, recommend corrective action by the study team, recommend reporting to the IRB of record, or recommend suspension of enrollment.

4.3.2 Audit Reports

The DSMC will review audit reports, with a particular focus on items related to continued non-compliance, patient safety, and data integrity. The DSMC will review all reports until the trial is terminated. This will include both internal audits and any external audits for a study under DSMC purview.

4.4 Data Integrity

The DSMC will monitor trials for data integrity as it relates to any of the aforementioned categories, to ensure validity and completeness.

4.4.1 Data Set Reviews

The DSMC reviews any requests for data release in accordance with the Quantitative Data Sciences Core (QDSC) Data Release Policy and the DSMC Data Release Policy. The DSMC will review all data requests until the trial is terminated.

DSMC decisions are dependent on trial design, trial status, type of data being requested for release. Such determinations are communicated back to the PI and statistician.

Study suspension may take place in addition to any of the other DSMC recommendations or actions.

5 Levels of DSMC Review

5.1 Urgent Review

Urgent DSMC is reserved for DSMC items that require a DSMC decision prior to the next full panel meeting. Situations which may require urgent DSMC review are:

- Screening deviations that do not affect eligibility (e.g. out of window baseline procedures) will be reviewed according to DSMC Waivers and Deviations Policy
- Protocol deviations which may require immediate DSMC action (e.g. study suspension or prompt IRB reporting)
- Safety reviews, interim analysis reviews, or dose escalation reviews for studies where there are patients waiting to urgently enroll in the study once the review is completed

Urgent DSMC review will take place via email. All DSMC members are asked to respond with their decision, however, due to the time-sensitive nature of these requests, action may be taken with chair approval.

5.2 Full Panel Review

The majority of DSMC items will be reviewed at a full panel DSMC meeting. These items will be considered reviewed if presented at a DSMC meeting which achieved quorum. Any DSMC decisions will be documented in the meeting minutes by the QA team. Any items for which the DSMC requests follow-up will be returned to either a future DSMC preparation or full panel DSMC meeting.

5.3 Administrative Review

DSMC items which are unlikely to require a DSMC decision may be administratively reviewed by the DSMC. Examples of such items include:

- IND annual reports
- Semi-annual reports without DSMC recommendations

Items which may be administratively reviewed will be sent to DSMC members for individual review prior to the full panel DSMC meeting. Review will be confirmed at the start of the full panel DSMC meeting and an opportunity to further discuss any concerns regarding the administrative items will be provided.

6 DSMC Recommendations

- Approved/Proceed without response: study may proceed with no additional requests.

- Proceed with modification or response required: enrollment may continue but the PI must respond to DSMC concerns within the specified timeframe. Lack of response or an unsatisfactory response may result in study suspension.
- Study Suspension: enrollment is immediately suspended but existing subjects may continue protocol treatment and follow-up. The study may reopen once the Principal Investigator has provided a satisfactory response to DSMC concerns regarding toxicity, data integrity, or study conduct. In rare circumstances the DSMC may recommend suspension including suspension of active treatment for existing subjects. Study team is responsible for notifying the IRB of record of any suspensions/closures, as appropriate.
- Study Closure: recommendations for study closure due to unacceptable toxicity or data integrity issues. If a study is determined by the DSMC to require closure due to unacceptable toxicity, the study will first be promptly suspended to further enrollment pending notification to and confirmation from the SRC (who has sole authority to close trials within the LCC research oversight system). Upon SRC confirmation, the study will then be permanently closed to accrual and all enrollment activity must cease. NOTE: further guidance regarding current subjects on active treatment or follow-up should be discussed and documented and may require reporting to the IRB or other regulatory authorities, as appropriate. Studies with compliance or data integrity issues may also be recommended by DSMC for closure to further accrual, but subjects may remain on study intervention per the discretion of the DSMC. These recommendations will also be submitted to the SRC for confirmation and review of impact to the scientific validity of the study. Study team is responsible for notifying the IRB of record of any suspensions/closures, as appropriate.
- Site Closure: For multi-center trials, closure of a site due to substandard performance.
- Other Appropriate Action: DSMC may recommend additional actions which may include, but are not limited to, suspension of an Investigator's portfolio, of a program, or changes to policy, procedures, and protocols.

The applicable support team member will distribute any outcome report to the PI and study team as soon as possible following DSMC decision, and no later than 2 weeks following DSMC decision; these may be communicated via email or may in some cases come as a formal DSMC Action Letter (as discussed in the DSMC meeting). Any updates to study status will also be documented in the CTMS. Other actions will be administratively reviewed by other Research Oversight Committees, such as SRC, as needed.

Any requests for information must be received by the designated response date in the outcome letter. Any responses from the PI and study team will then be reviewed by DSMC at the next

available meeting, or sooner, as appropriate. If the DSMC determines a response to be satisfactory, a final outcome letter or email may be sent to the PI and study team.

Investigators who disagree with the DSMC recommendations to suspend or close a trial may appeal in writing to the DSMC within 30 days of receipt of notice. However, the study should remain suspended/closed per DSMC directive during the appeal process. If the DSMC upholds a recommendation for study suspension/closure, there will be no further appeals.

7 APPENDICES

7.1 ASSOCIATED DOCUMENTS

- Data and Safety Monitoring Plan
- DSMC Roster
- NU IIT DSMC Waivers and Deviations v 2.0 28Sep2016
- NU Policy, Current Clinical Trial Data Release Policy- Quantitative Data Sciences Core (QDSC) Eff 01 Aug 2018-352717
- DSMC SOP 3_DSMC Data Release Policies and Processes v4.1 06Nov2018 Final
- Cancer Center SOP, Current R-SM-204 Management of External Safety Reports Eff 27 Mar 2017
- Cancer Center SOP, Current R-SM-204 Management of External Safety Reports,Clarification Eff 04 Dec 2017
- Cancer Center SOP, Current R-SM-204 Management of External Safety Reports,Clarification for NU IITs Eff 17 Jan 2023
- Cancer Center SOP, Current 110 Protocol Deviations and Reportable New Information Eff 22 Dec 2020
- SRC Charter