UNIVERSITY OF SOUTH ALABAMA

Policy No:

Responsible Office: Office of Research Compliance and Assurance

Last Review Date: June 2021

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Data and Safety Monitoring Board

1. Purpose

An independent Data and Safety Monitoring Board (DSMB) will be convened to assess the progress of a clinical study, the safety data, and critical efficacy endpoints (if appropriate) and provide recommendations to the PI. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. The DSMB will review cumulative study data from all participating sites to evaluate safety, study conduct, and scientific validity and data integrity of the study.

2. Applicability

Not all studies require the use of a DSMB. All studies should be evaluated by ORCA and the IRB to determine the need for a DSMB based on the study design, risk to patients, funding agency, and other concerns. A study with any of the following criteria should utilize a DSMB:

- Multi-site clinical trials with interventions that entail greater than minimal risk(s) to participants
- If the trial is evaluating mortality or another major endpoint, such that inferiority of one treatment arm has safety as well as effectiveness implications.
- Any research done in an emergency setting where the informed consent requirement is waived.
- All phase III clinical trials with the exception of behavioral and nutritional studies
- Phase I or II trials that involve blinding
- The trial includes vulnerable population and is greater than minimal risk
- When it would be ethically important for the trial to stop early if the primary question addressed has been definitively answered, even if secondary questions or complete safety information were not yet fully addressed.
- When there is prior information suggesting the possibility of serious toxicity with the study treatment
- Studies that do not meet the above criteria, but are required by the funding source to be reviewed by a DSMB

The DSMB Chair or the Office of Research Compliance and Assurance can be contacted if there are questions on the need for a DSMB.

3. Definitions

Data Safety and Monitoring Board (DSMB): a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from one or more ongoing clinical trials. The DMC advises the sponsor regarding the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial.

Data Safety and Monitoring Plan (DSMP): a specific plan, developed by the local principal investigator (PI), that outlines how study progress will be monitored throughout the course of the research to ensure the safety of subjects as well as the integrity and confidentiality of data.

Institutional Review Board (IRB): an administrative body established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of the institution with which it is affiliated.

Office of Research Compliance and Assurance (ORCA): an Office that works with research oversight committees, boards and offices responsible for specific components of research compliance to ensure compliance with all regulatory requirements related to research activity. The office is responsible for monitoring regulatory changes and recommending institutional responses to ensure compliance, and the oversees development and implementation of policies, procedures, programs and educational activities which satisfy federal, state and institutional regulations governing the conduct of research.

Quorum: the minimum number of members of an assembly or society that must be present at any of its meetings to make the proceedings of that meeting valid.

4. Policy Guidelines

4.1 Composition of the DSMB

The Committee will be composed of at least five members (inclusive of the DSMB Chair). The DSMB should include experts in or representatives of the fields relevant to the protocol. Biostatisticians should also be present on the DSMB.

Quorum – A quorum will occur when half plus one of the established members are present. Without a quorum a meeting will not be held.

If a member misses a meeting, the Chair should ensure the member is available for the subsequent meeting. If a member misses a second meeting, the Chair should ask the member about his or her ability to remain on the DSMB. If a third meeting is missed, the member will be replaced.

A vice-chair will be appointed to fill in for the Chair should he/she become unavailable or otherwise cannot fulfill the responsibilities of the Chair.

4.2 Independence of the DSMB

It is essential that the judgment of members of the DSMB not be influenced by factors other than those necessary to maintain subject safety and to preserve the integrity of the study. Persons who have an apparent financial, intellectual, or other interests with a drug, device, or procedure should not be a DSMB participant for the evaluation of that investigational product. Independence is essential to ensure

that DSMB members are objective and capable of an unbiased assessment of the study's safety and efficacy data.

No DSMB or consultant may participate in any DSMB review of any project in which he/she has a conflict of interest, except to provide information requested by the DSMB. Examples of such conflicts of interest could include: a member of the DSMB who serves as an investigator or sub-investigator on research under review by the DSMB, or a member who holds a financial conflict of interest in a sponsor or product under study. DSMB members with a conflict of interest are recused and not counted towards quorum, whether or not the recused member remains present in the room. This is recorded in the DSMB meeting minutes

At least annually, DSMB members must disclose all pharmaceutical companies, biotechnology companies, and CROs in which they hold financial interest. The University Conflict of Interest form must be used by members to disclose all consultancies (direct or indirect) with pharmaceutical companies, biotechnology companies, and CROs.

The Chair will be responsible for deciding whether consultancies or the disclosed interests of the members materially affect their objectivity. Members of the DSMB will be responsible for notifying the DSMB Chair and the ORCA office of any changes of interest in pharmaceutical companies, biotechnology companies, or CROs, including consultancies. In such cases, the DSMB meeting minutes will document the disclosure of the potential conflict of interest and the outcome of the discussion (e.g., abstention of member from voting, recusal from discussion). The Chair will decide whether any of these relationships results in a conflict of interest which would preclude involvement on the DSMB. Members of the DSMB who develop potential or significant perceived conflicts of interest will be asked to resign from the DSMB. In the event that the Chair has a conflict of interest, the responsibilities of the Chair will be given to the Vice-Chair.

4.3 Responsibilities of the DSMB

4.3.1 Objectives

The primary objective of the DSMB is to monitor the safety of the interventions and the validity and integrity of the data from the clinical study. Additionally, the DSMB will evaluate the pace of recruitment and will make recommendations to the IRB regarding the continuation, modification, or termination of any or all arms of the study.

4.3.2 General Responsibilities

The general responsibilities of the DSMB are:

- To evaluate, on an ongoing basis, the accumulating safety assessments to ensure the ongoing safety of study subjects
- To consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study

- To review all documents submitted to the DSMB for review
- To review the conduct of the study, including protocol violations
- To review data on participant recruitment, accrual, and retention, as well as assessments of data quality, completeness, and timeliness
- Protect the confidentiality of the study data and the DSMB discussions
- To make recommendations to continue, modify, or terminate the study

4.3.3 DSMB Chair Responsibilities

The following responsibilities are those of the DSMB Chair:

- Serves as a voting member
- Serves as the primary contact person for the DSMB
- Reviews and approves the Charter
- Ensures that those involved in the day-to-day management of the study are excluded from DSMB voting procedures
- Discusses DSMB recommendations with PI and IRB and appropriate members of the project team as appropriate
- Approves selection of DSMB members in consultation with the Vice President for Research and Economic Development
- Reviews conflict of interest information and has authority for actions taken based on findings of conflicts

4.4 Principal Investigator Responsibilities

The following activities are the responsibility of Principal Investigator:

- Provides DSMB regularly scheduled reports 2 weeks prior to scheduled meetings
- Provides ad hoc reports requested by the DSMB in a timely manner
- Be available to be present for open sessions as requested by the DSMB
- Disseminate the DSMB recommendations to the IRB and funding source
- Provide the DSMB verification that their recommendation has been shared with all appropriate parties
- Submit any protocol amendment that may affect the Data Safety Monitoring Plan, eligibility criteria, endpoints, or objectives to the DSMB prior to implementation.
- Maintain data from all participating sites
- Perform functions outlined in the approved DSMP

4.5 Office of Research Compliance and Assurance (ORCA) Responsibilities

The following activities are the responsibility of ORCA or, as clarified herein, its designee(s):

- Takes and maintains minutes from Open Sessions
- Communicates the DSMB recommendation(s) to the PI, as appropriate
- Polls for and arranges DSMB teleconferences
- Posts appropriate review materials for DSMB members

- Disseminate documents to DSMB prior to the scheduled meeting
- Maintain confidentiality of documents submitted for DSMB review, Open Session minutes, and DSMB correspondence
- Distributes Open Session minutes to DSMB members
- Facilitates the meetings, assists in the development of the agenda, and ensures that the meeting minutes and recommendation(s) are appropriately documented

4.6 Meeting of the DSMB

4.6.1 Charter Meeting

The first meeting of the DSMB for each new protocol will be a Charter Meeting. This meeting will formally establish the DSMB and begin to acquaint the DSMB members with the protocol or types of protocols that this DSMB will be charged with monitoring. It affords the DSMB an opportunity to recommend final revisions to the Data Safety Monitoring Plan, Protocol, statistical analysis, etc.

The PI must be present of the Open Session of Charter Meeting.

DSMB approval must be received prior to any study related activities.

At the beginning of the DSMB meeting, the Chair will initiate the charter session of the meeting, which will include calling the meeting to order and assuring a duly constituted Board.

Meeting objectives will include:

- The introduction of the DSMB members and an establishment of qualifications for quorum.
- A review of the protocol and DSMP to offer feedback as necessary
- Establishment of meeting frequency based on the risk profile, recruitment rate, protocol design, etc.
- Confirmation and recording of any conflict of interest, if applicable.

4.6.2 Protocol and Data Review Meetings

Each protocol and data review meeting will consist of two sessions: Open Session and Closed Session.

4.6.2.1 Open Session

This will begin with an introductory session that includes introductions, roll call, assurance of a quorum, a reminder about the confidential nature of the proceedings and corresponding documentation, and a review of conflict of interest for all DSMB members.

Following the introductory session, the DSMB will move into the open session. Attendees will include the DSMB members, voting and ex officio members, the lead investigator and other study staff personnel, and ORCA staff members. This session may also be open to other investigators, representatives for industrial collaborators, and representatives from the Food and Drug Administration (FDA) as appropriate.

The open session will serve as a general study update. The PI must present the study status and known relevant findings at this session. Others with specific safety experience or concerns may also be called upon to present. The session will provide a forum for an exchange of information among the various groups involved in the conduct of the study. It will afford the DSMB members an opportunity to question the project team about the study and to seek additional information deemed relevant to the data review. Discussions may include progress of the study, including adverse events, disease status of participants, comparability of groups with respect to baseline factors, protocol compliance, site performance, quality control, and timeliness and completeness of follow-up.

Only masked data will be reviewed and/or discussed during the open session. Data from all participating sites must be included in the information submitted to the DSMB.

4.6.2.2 Closed Session

Following the open session of the meeting, a closed session involving the DSMB members will be held to review grouped safety data, discuss findings, develop recommendations, and obtain agreement on voting. During this session, any issues related to subject safety will be discussed. Requests by DSMB Members for the unmasking of data may be made at this time. Interim efficacy analysis planned a priori will be addressed in closed session. Data from all participating sites must be included in the information submitted to the DSMB.

4.6.3 Unscheduled Meetings/Reports

Unscheduled meetings can be requested by any party with the responsibility of overseeing the study. Requests can be made to the DSMB Chair, PI, or ORCA office. The Chair, in collaboration with ORCA, will schedule any unplanned meetings.

The DSMB may request special reports on an as needed basis.

4.6.4 Voting

In order for a motion to be approved, it shall receive the approval of a majority of the members (i.e., half plus one) present at the meeting provided a quorum exists. The voting process proceeds as follows: The Chair may entertain a motion and a second that the DSMB take a certain action regarding a given protocol. After a motion has been made and seconded, there should be an

opportunity for discussion before a vote is taken. Those members present for the vote should be recorded as either voting for, opposed or abstained.

4.7 Communication

4.7.1 Reports to the DSMB

- Associated SAEs and AEs of special interest will be provided to the DSMB one week prior to each scheduled meeting or as requested by the Board. AEs and SAEs of special interest will be determined by the DSMB at the Charter Meeting.
- All deaths regardless of reliability
- Study status reports will be provided to the DSMB at least one week prior to each scheduled meeting.
- Any deviation from the approved Data Safety Monitoring Plan will be communicated by ORCA to the DSMB Chair for guidance.
- Closeout reports are required to the DSMB when the study closes regardless if the study completed or ended prematurely.

4.7.2 DSMB Minutes

The DSMB meetings may be audio taped for the purpose of documenting meeting minutes. Once the Chair approves the minutes, the tapes will be destroyed.

The ORCA representative will prepare the draft meeting minutes of the open session and closed session forward to the DSMB Chair for review within one (1) week following the DSMB meeting. Minutes of the open session will describe the proceedings.

4.7.3 DSMB Actions/recommendations

Following the closed session, a brief summary that describes the individual findings, overall safety assessment, and DSMB recommendations will be approved by the Chair. The ORCA office will distribute to the appropriate Investigator within one week of the meeting.

The DSMB can recommend to IRB that the current study continue without modification, continue with specified modifications, discontinue one or more arms of the study, or halt or modify the study until more information is available.

4.8 Revisions to the Charter

A draft of the Charter will be provided to the DSMB prior to the interim meeting. During the interim meeting, the Charter will be reviewed and revised as needed. The Chair will approve all changes to the Charter. The version date will be displayed as a footer on all pages.

As needed, the Charter may be revised after the interim meeting, with the Chair providing sign-off. Changes to the Charter will be clearly delineated in a document, and this document will be associated with the new version.

4.9 Completion of DSMB Activities

The DSMB will remain active until written notification is received from ORCA office that the study has completed.

The Investigator will notify the Office of Research Compliance Office when a study closes. The Investigator will prepare a report summarizing all data and will present it to the DSMB at a convened meeting. These closure requirements will occur regardless of if the study is completed or ends prematurely.

4.10 Document Retention

The DSMB members will maintain a copy of any relevant correspondence, meeting packets, DSMB reports, and meeting minutes in a secure area prior to the meeting occurrence.

5. Procedures

5.1 Charter Review by the DSMB

5.1.1 Submission of Materials for Charter Review
Submit the following materials to Office of Research Compliance and Assurance (ORCA) by emailing Stefanie White at swhite@southalabama.edu.

- Protocol
- Informed Consent
- Data Safety Monitoring Plan (if separate from the Protocol)
- FDA IND or IDE letter (if applicable)

5.1.2 The ORCA will work with the DSMB members to schedule a convenient date and time to hold the charter meeting.

5.1.3 After the DSMB meeting, an ORCA representative will draft the minutes and a letter to the PI. The DSMB Chair is required to review the minutes and the letter to PI.

5.1.4 The letter to the PI will be sent to the PI and any applicable parties.

5.1.5 The PI is responsible for submitting a copy of the letter to the IRB of record per the IRB's reporting requirements.

5.2 Interim Review by the DSMB

5.2.1 Submission of Materials for Interim Meetings

Submit the following materials to Office of Research Compliance and Assurance Protocol

- Informed Consent
- DSMB Report for Open Session
- DSMB Report for Closed Session if applicable

5.2.2 The ORCA will work with the DSMB members to schedule a convenient date and time to hold the interim meeting.

5.2.3 After the DSMB meeting, an ORCA representative will draft the minutes and a letter to the PI. The DSMB Chair is required to review the minutes and the letter to PI.

5.2.4 The letter to the PI will be sent to the PI and any applicable parties.

5.2.5 The PI is responsible for submitting a copy of the letter to the IRB of record per the IRB's reporting requirements.

5.3 Closure by the DSMB

5.3.1 The Investigator will notify the Office of Research Compliance that their study is closing .

5.2.2 The ORCA will work with the DSMB members to schedule a convenient date and time to hold a closeout meeting.

5.2.3 The Investigator will submit a summary of all data regardless of if the study completed or ended prematurely.

5.2.4 After the convened DSMB meeting, the ORCA will send the Investigator an administrative letter demonstrating that the study is no longer being reviewed by the DSMB.

6. Enforcement

The Data Safety Monitoring Board has final authority to approve or disapprove activities involving the data safety monitoring plan. The responsible parties for oversight and enforcement of this policy are:

- Policy Oversight – Data Safety Monitoring Board
- Policy Enforcement – Office of Research Compliance and Assurance.

7. Related Documents

Below is a list of any applicable policies, procedures, document templates and web links that relate to this policy and help implement the policy.

7.1 Related Regulations and/or Policies

- FDA Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees.
- 21 CFR 50.24(a)(7)(iv)

7.2 Other Related Documents and/or Procedures

- DSMB Report Form- Multisite- Open Session
- DSMB Report Form- Multisite- Closed Session
- DSMB Report Form- Single Site- Open Session
- DSMB Report Form- Single Site- Closed Session