GLIDE Trial
Data and Safety Monitoring Board Charter

Title of Study: GLIDE Trial
Protocol Date: DD/MMM/YYYY
NCGM IRB Approval Number: XXX
Principal Investigator: XXX
Coordinating Center: Center for Clinical Sciences, National Center for Global Health and Medicine

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Abbreviations

CCS	Center for Clinical Sciences
CRB	Certified Review Board
DSMB	Data Safety and Monitoring Board
IRB	Institutional Review Board
NCGM	National Center for Global Health and Medicine
PI	Principal Investigator
PMDA	Pharmaceuticals and Medical Devices Agency

1. Data Safety Monitoring Board (DSMB) Overview

- Study Name: XXX
- Study Design: XXX
- Phase: XXX

Description

- An independent Data Safety Monitoring Board (DSMB) will be established for this study to review accumulating study data and to monitor the safety of all subjects enrolled.
- The DSMB will be coordinated by NCGM CCS.
- The DSMB will be independent from the sponsor, investigators and regulatory agencies.
- The purpose of this charter is to define the roles and responsibilities of the DSMB, delineate qualifications of the membership, describe the purpose and timing of meetings, provide the procedures for ensuring confidentiality and proper communication, and outline the content of the reports.
- The charter will be approved by the DSMB members as attested to by the signature of the DSMB chair.

Membership

- Members will disclose conflicts of interest and will be cleared of significant conflicts of interest and potential conflicts of interest in accordance with provisions in this charter.
- DSMB members will sign confidentiality agreements covering DSMB activities.
- Composition of membership will be at least two physicians with expertise in the area pertaining to the study and at least one biostatistician.

Reporting

- Data reviewed by the DSMB will be provided by NCGM biostatisticians and database management team.
- Issues and recommendations identified by the DSMB will be provided to NCGM CCS, NCGM IRB and any other IRBs overseeing the study by the DSMB chair in accordance with this charter.
- Details of closed session deliberations will be considered privileged and not subject to disclosure except as required by law.

2. Study Overview/Summary

(Paste the synopsis here; include primary and secondary objectives)

3. DSMB Roles and Responsibilities

This DSMB will:

- Meet periodically to review aggregate and individual subject data related to safety, scientific validity, data integrity and overall conduct of the study.
- Assess the performance of overall study operations, rate of participant recruitment, and any other relevant issues as necessary.
- Review factors that might affect the study outcome or compromise the confidentiality of the study data.
- Review factors external to the study such as scientific or therapeutic developments that may impact participant safety or the study.
- Review specific interim analyses for efficacy as stipulated in the study protocol.
- Provide recommendations to continue or terminate the study depending upon these analyses if applicable.
- Communicate other recommendations or concerns as appropriate.
- Operate according to the procedures described in this charter and all procedures of the DSMB.
- Follow conflict of interest guidelines as detailed below (see DSMB Membership).
- Comply with confidentiality procedures as described below (see Confidentiality).
- Maintain documentation and records of all activities as described below.

To appropriately manage conflict of interest:

- No member of the DSMB should have direct involvement in the conduct of the study.
- Members should disclose any conflict of interest to ensure that members do not have serious scientific, financial, personal, or other conflicts of interest related to the conduct, outcome, or impact of the study.
- Members will sign a non-conflict of interest statement in regard to this study which will be on file. Conflicts of interest and/or potential conflicts of interest will be reduced to the greatest extent that is consistent with assembling a highly competent DSMB. Any questions or concerns that arise regarding conflicts of interest will be addressed by the DSMB chair with input from other DSMB members as necessary.
- Please see Appendix A for the sample of the DSMB invitation letter. All DSMB ad-hoc members will sign a Conflict of Interest Statement (Appendix B) at the time they are invited to join the DSMB.

4. PI Roles and Responsibilities

The PI will directly or through delegation:

- Assure the proper conduct of the study.

- Assure collection of accurate and timely data (monitoring and data management).
- Compile and report SAEs to the DSMB.
- Promptly report potential safety concern(s) to the relevant IRBs and, if required, to the DSMB. All SAEs will be routinely reported to the DSMB at each planned meeting.
- Prepare summary reports of relevant data for the DSMB.
- Provide an independent facilitator for presentation of results during DSMB meetings if requested by the DSMB.
- Communicate with regulatory authorities, IRBs, and investigators, in a manner that maintains integrity of the data, as necessary. This communication is not the responsibility of the DSMB.
- Provide funding for the study and DSMB, if required.

5. Membership

The DSMB will consist of 3 members, of which 2 have had previous experience of study conduct and design. The DSMB members are selected by the study management team.

As characteristic qualifications, members will:

- Work professionally and meet qualifications for their respective professions (e.g., specialty physicians, statistician, epidemiologist, etc.).
- Comply with accepted practices of their respective professions.
- Be independent from the sponsor, IRBs, regulatory agencies, PI, site investigators, steering committee membership, advisory board membership, clinical care of the study subjects, or any other capacity related to study operations.

Although each DSMB member will be expected to serve for the duration of the study, in the unlikely event that a member is unable to continue participation, the reason will be documented and a replacement will be selected.

6. Meetings

Projected Schedule of Meetings

Timeline	Data Review by	Type of Data
Once first 50 patients enrolled	*DSMB chair, statistician, and/or physician expert*	*Protocol violations, serious adverse events, enrolment summary (by site) and tables for primary and secondary endpoints compared by treatment arm (if open-label)*
When follow-up is completed on first XXX patients	*Entire DSMB*	*Same as above, by treatment arm*

Upon completion or termination of study	*Entire DSMB*	*Same as above, by treatment arm*

Meeting Format

DSMB meetings will generally be conducted by teleconference and coordinated by the study management team. A quorum, defined as all 3 members being present, will be required to hold a DSMB meeting. Critical decisions of the DSMB should be made by unanimous vote. However, if this is not possible, a majority vote will decide. For convenience, decisions may be made by email correspondence if a suitable teleconference cannot be arranged.

A facilitator (e.g., statistician involved with report preparation) may attend the DSMB meetings as a non-voting member in order to facilitate data presentation and follow-up reporting, unless deemed not necessary by the DSMB. The meetings will include both open and closed sessions.

The open session may be attended by representatives of the sponsor and/or study investigators. Data presented in the open session may include enrolment data, individual adverse event data, baseline characteristics, overall data accuracy and compliance data or issues, and other administrative data. Minutes of the open session will be recorded by the Research Coordinator from study management team. Minutes will be finalized upon signature of the chair and maintained by NCGM CCS in accordance with applicable statutory regulation.

The closed session will be restricted to the DSMB members, a facilitator, and an independent recorder. Data which may compromise the integrity of the study (e.g., comparative data) will be analyzed and discussed only in the closed session. The minutes of the closed session will be recorded by an independent person. Minutes from the closed session will be recorded separately from the minutes of the open session and stored securely by the DSMB chair. Closed session minutes, finalized by signature of the chair, will be maintained in confidence and retained until discarded in accordance with applicable statutory regulation.

The DSMB will approve written minutes that include the names of the attendees, the topics discussed by the DSMB and describe its individual findings, overall safety assessment and recommendations. The rationale for recommendations must be included if appropriate.

7. Study Review Criteria

Guidance for the conduct of efficacy analyses, and guidelines / stopping rules will be established prior to the DSMB's first evaluation of data.

Effectiveness Analyses

The primary effectiveness endpoint is XXX. The DSMB will review the interim analyses of effectiveness measures after enrolment and follow-up of approximately 50 and XXX patients. The intention-to-treat (ITT) analysis approach, supported by the per-protocol approach, will be adopted to make inference on the possible superiority of the treatment arm, compared to the control arm, in terms of the primary effectiveness endpoint. The proportions of XXX (with 95% confidence intervals) in the two study arms will be calculated.

Logistic regression with 'treatment group' as the only covariate will be employed to draw inference on the possible superiority of the intervention treatment compared to the control treatment. The odds ratio and absolute risk differences (with 95% confidence intervals) will be calculated with the control arm as the reference group. Appropriate parametric or non-parametric statistical techniques will be employed to analyze the data for secondary effectiveness endpoints of the study. *(Outlines of statistical plans for secondary effectiveness endpoints.)* All secondary analyses will be based on ITT population.

Basic statistics in the study report will include information on missing values for all relevant study variables. A summary of baseline patient characteristics with totals and proportions (%) for categorical variables, and minimum, maximum, inter-quartile ranges and standard deviations for continuous variables will be presented.

The stopping rule would be a statistically significant difference in primary outcomes between the two therapies at a level of $P<0.001$ (Peto rule).

Consideration of External Data

The DSMB will also consider data from other studies or external sources during its deliberations, if available, as these results may have a profound impact on the status of the patients and design of the current study.

Safety analyses

All SAEs and deaths will be reported in detail to the DSMB to ascertain whether any compromise to patient safety has occurred by inclusion in the study. Any significant differences in SAEs between the two groups will be assessed by the DSMB as a potential stopping requirement.

8. Guidelines for Reports

Monitoring for Safety

The primary charge of the DSMB is to monitor the study for patient safety. Formal DSMB safety reviews will occur as specified above.

Monitoring for Effectiveness

The DSMB will monitor effectiveness outcomes to determine relative risk/benefit, futility, or for early termination. DSMB effectiveness reports will occur as specified.

Monitoring for Study Conduct

The DSMB will review data related to study conduct. Data to be reviewed and listed in the DSMB reports includes: enrolment rates over time, time from last patient enrolled to date of report (indication of delay between treatment or follow-up and reporting), summary of protocol violations, completeness of treatment and follow-up visit data, and follow-up duration for the population included in the report.

Data Flow for Adverse Events

The DSMB will carefully monitor adverse events periodically throughout the duration of the study. The investigators will be expected to report Serious Adverse Events (SAEs) directly related to the study drug to the IRBs within 24 hours of knowledge of the event. These events will then be reported to the DSMB at each interim analysis.

Preparation of Reports to the DSMB

The study management team at NCGM CCS will prepare and distribute reports to the DSMB. The reports will be delivered electronically approximately 14 days prior to the date of each DSMB meeting.

In order to provide the maximum amount of information to the DSMB, the analyses will employ the most recent data (recognizing limitations thereof) available at the time of the analysis. Requests for additional data by the DSMB members will be made to the DSMB chair or their designee.

The DSMB will review the data coded by treatment arm and discuss the analyses during the closed portion of the scheduled meeting. *Unblinding of the treatment arm will be conducted by a designated study statistician and information will only be shared during the closed portion of the meeting. Unblinding will not be required as this is an open-label study.*

DSMB Communication of Findings and Recommendations

Following each meeting and within 14 days of the meeting, the chair will send findings and recommendations of the DSMB to the PI in the form of a DSMB recommendation letter (Appendix C). The recommendation letter will only contain the minimum information necessary to convey the DSMB decisions and comments, avoiding extraneous study details where possible.

These findings and recommendations can result from both the open and closed sessions of the DSMB. If these findings include serious and potentially consequential recommendations that require immediate action, the chair will also promptly notify the PI by phone.

PI Response to DSMB Findings and Recommendations

The PI will review and respond to the DSMB recommendations. The recommendations of the DSMB will not be legally binding but require professional consideration by the recipients. If the DSMB recommends continuation of the study without modification, no formal response will be required. However, if the recommendations request action, such as a recommendation for termination of the study or modification of the protocol, the DSMB will request that the PI provide a formal written response stating whether the recommendations will be followed and the plan for addressing the issues.

It is recognized that the PI may need to consult with regulatory agencies or other consultants before finalizing the response to the DSMB. Upon receipt, the DSMB will consider the PI's response and will attempt to resolve relevant issues, resulting in a final decision. Appropriate caution will be necessary during this process to avoid compromising study integrity or the ability of the PI to manage the study, should the study continue. The PI will agree to disseminate the final decision to the appropriate regulatory agencies, IRBs, and investigators within an appropriate time.

In the unlikely event of irreconcilable differences, especially regarding study termination or other substantial study modifications, the DSMB may decide to discontinue monitoring the current study and disband. This decision will be communicated to all investigators, study coordinators and the IRBs.

Public disclosure of the PI's final decision or DSMB recommendations will be at the discretion of the PI. The DSMB will not make any public announcements either as a group or individually.

9. Closeout

This study may be terminated under a variety of circumstances including, but not limited to, termination for significant differences in efficacy, safety issues as per protocol or DSMB monitoring guidelines. Responsibilities of the DSMB with regard to closeout will be to review the final study report to ensure study integrity. The DSMB may recommend continuing action items to the PI based upon the final review.

10. Confidentiality

All data provided to the DSMB and all deliberations of the DSMB will be privileged and confidential. The DSMB will agree to use this information to accomplish the responsibilities of the DSMB and will not use it for other purposes without written consent from the DSMB chair. No communication of the deliberations or recommendations of the DSMB, either written or oral, will occur except as required for the DSMB to fulfil its responsibilities. Individual DSMB members must not have direct communication regarding the study outside the DSMB (including, but not limited to the investigators, IRBs, regulatory agencies) except as authorized by the DSMB.

11. Amendments to the Charter

This DSMB charter can be amended as needed during the course of the study. Information to be included as amendments will be any modifications or supplements to the reports prepared for the DSMB, as well as amendments to other information addressed in this charter. All amendments will be documented with sequential version numbers and revision dates, and will be recorded in the minutes of the DSMB meetings. Each revision will be reviewed and agreed upon by both the PI and the DSMB. All versions of the charter will be archived in accordance with this document.

12. Archiving of Activities and Related Documents

All DSMB documentation and records will be retained by NCGM CCS until discarded in accordance with the statutory guidelines or for a time period of 5 years after completion of the study, whichever is longer. Access to archived data will be controlled by NCGM CCS which will release the information only as specified in this charter or as required by law.

DSMB Charter Approval

DSMB Chair	*Qualifications:*
Name:	
Signature:	Date: (DD/MMM/YYYY)

Other DSMB Members:	*Qualifications:*
Name:	
Signature:	Date: (DD/MMM/YYYY)
	Qualifications:
Name:	
Signature:	Date: (DD/MMM/YYYY)

Principal Investigator Signature:

Name:

Date: (DD/MMM/YYYY)

Appendix A: DSMB Invitation Letter Template

Date (DD/MMM/YYYY)
Title and Name
Position and Institution
Address

Dear Dr. XXX:

Invitation to serve on the Data Safety Monitoring Board (DSMB) for the GLIDE Trial

NCGM is initiating a new clinical study (the GLIDE Trial). The study aims to evaluate the clinical efficacy and safety of XXX versus standard of care for YYY. The study synopsis can be found in the DSMB Charter.

An independent DSMB is required for this study in accordance with the IRB regulations. The role of the DSMB is to ensure unbiased assessment of safety, study conduct, and progress during interim analyses, as well as to provide recommendations on continuation, modification or termination of the study.

We would like to invite you to be part of the DSMB for the study. Roles and responsibilities of the DSMB include:

- Attendance in at least three review meetings (after the first 50, XXX and all subjects have completed the YY-day study period or as determined by DSMB);
- Evaluation of the study design and protocol;
- Review of accumulative data on participant enrolment, demographic and baseline characteristics, protocol deviation(s), data quality, safety data, and efficacy data.

If you accept this invitation, you will have to confirm that you do not have any financial disclosure or conflict of interest with any of the organizations or institutions involved in the study. Should you require any additional information, please do not hesitate to contact the DSMB secretaries at NCGM CCS (XXX, YYY). We hope you will accept the invitation to be part of the DSMB for the GLIDE Trial.

Kind regards,

XXX
Principal Investigator
National Center for Global Health and Medicine

Appendix B: Financial Disclosure and Conflict of Interest Statement

DSMB Member:
Institution:
Position:

The avoidance of any perception that members of a Data Safety Monitoring Board (DSMB) may be biased in some fashion is important for the credibility of the decisions made by the DSMB and for the integrity of the study. Possible competing interest should be disclosed to study management team. Please complete the following section and return to the DSMB secretaries at NCGM CCS.

1. The following situations may pose a possible Conflict of Interest:
   - Stock ownership in any commercial companies involved
   - Stock transaction in any commercial company involved (if previously holding stock)
   - Consulting arrangements with the sponsor
   - Frequent speaking engagements on behalf of the intervention
   - Career tied up in a product or technique assessed by study
   - Hands-on participation in the study
   - Involvement in the running of the study
   - Emotional involvement in the study
   - Intellectual conflict e.g. strong prior belief in the study's intervention arm
   - Involvement in regulatory issues relevant to the study procedures
   - Investment (financial or intellectual) in competing products
   - Involvement in the publication

2. Please check the applicable item below.

   ☐ I do not have any of the above interests to report

   ☐ I have the following (or attached) interests to report:

   _____

3. I will notify DSMB promptly if a change occurs in any of the above during the tenure of my responsibilities, or I discover that an organization with which I have a relationship meets the criteria for a conflict of interest.

4. I am aware of my responsibilities for maintaining the confidentiality of any non-public information that I receive or become aware of through this activity, and for avoiding using such information for my personal benefit, the benefit of my associates, or the benefit of organizations with which I am connected or with which I have a financial involvement.

5. Acceptance of this invitation to serve on the DSMB confirms that I do not have any financial or other interest with any of the collaborating or competing pharmaceutical firms or other organizations/institutions involved in the study that constitute a potential conflict of interest.

_____

Signature Date (DD/MMM/YYYY)

Appendix C: DSMB Recommendation Letter Template

Confidential
Meeting date:
Time:
Attendees:

On <date>, the DSMB met by teleconference to review the data on safety and efficacy of XXX involving <#> patients with YYY enrolled in the GLIDE Trial.

On the basis of the data on safety and efficacy of the intervention arm reviewed at this meeting, we recommend the following:

1. Continuation of the study according to the current version of the protocol <protocol version number and date> with no changes.

or

2. Continuation of the study according to the current version of the protocol <protocol version number and date>, but with the changes outlined below.

a. XXXXXXXXXXXXXX.
b. XXXXXXXXXXXXXX.

or

3. Termination of the study for the following reasons:
a. XXXXXXXXXXXXXX.
b. XXXXXXXXXXXXXX.

We expect our next review of data to be on <provide date and time>.

Regards,

_____

DSMB Chair Signature Date (DD/MMM/YYYY)