Charter for the Data Safety Monitoring Committee of the STEPCARE-trial

ClinicalTrials.gov no. NCT05564754

1. Introduction

The present charter will define the primary responsibilities of the Data Safety Monitoring Committee (DSMC), its relationship with other trial components, its membership, and the purpose and timing of its meetings. The charter will also provide the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DSMC, and an outline of the content of the open and closed reports that will be provided to the DSMC.

2. Primary responsibilities of the DSMC

The DSMC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DSMC will provide recommendations about pausing, stopping or continuing the trial to the trial Steering Group through the Chair/Chief investigator of the STEPCARE-trial. To enhance the integrity of the trial, the DSMC may also formulate recommendations relating to the selection/ recruitment/ retention of participants, their management, improving adherence to protocol specified regimens and retention of participants, and the procedures for data management and quality control. Of note the DSMC shall safeguard the interest of the participants and their primary focus is thus to evaluate recruitment of participants, outcomes, and complications. As the degree of adherence to protocol and protocol violations are difficult to assess in a pragmatic trial with broad instructions, this part of the DSMC responsibility will mainly consist of distinct features, such as separation between groups. The day-to-day assessment of adherence regarding eligibility, timing of interventions, data entry, neurological prognostication etc. will be the responsibility of the trial management group. The DSMC will be advisory to the steering group. The steering group will be responsible for promptly reviewing the DSMC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in trial conduct are required.

The DSMC is planned by protocol to meet physically or by video at regular intervals and to evaluate the planned interim analysis of the STEPCARE-trial. The DSMC may additionally meet whenever they decide, contact each other by telephone or e-mail to discuss the safety for trial participants. The trial Chair/Chief investigator has upon request the responsibility to report monthly to the DSMC chair, the overall number of serious adverse events. The DSMC may request at any time during the trial the distribution of events, including outcome measures and serious adverse events, according to intervention groups. The recommendations of the DSMC regarding stopping or continuing should be communicated without delay to the steering group of the STEPCARE trial. The steering group has the responsibility to inform as fast as possible, and no later than 48 hours, all investigators of the

trial and the departments including patients in the trial the recommendation of the DSMC and the steering group decision hereof.

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3. Members of the DSMC

The DSMC is an independent multidisciplinary group consisting of clinicians, trial methodologists and a biostatistician that, collectively, has experience in the management of ICU patients and in the conduct, monitoring and analysis of randomized clinical trials.

Paul Mouncey (Chair)
Kathy Rowan (Chair mentorship) David Harrison Timothy Walsh Joyce Yeung

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There will be an independent statistician that will be the liaison between the trial and the DSMC. The independent statistician will have access to the trial electronic case record form and provide the DSMC with analyses according to the plan below.

Michael Bailey, Monash University, will be the independent statistician. The independent statistician is not part of the DSMC and may not take part in their recommendations.

The DSMC will have the right to recommend additional members to act on the DSMC or observe the DSMC work. This could be members of the public, patients, and trainees. The DSMC chair communicates with the trial chair/chief investigator regarding additional members.

4. Conflicts of interest

DSMC membership has been restricted to individuals free of conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. Any DSMC members who develop significant conflicts of interest during the trial should resign from the DSMC. DSMC membership is to be for the duration of the clinical trial. If any members leave the DSMC during the trial, the steering group will appoint (a) replacement(s) after discussion with the acting DSMC.

5. Meeting schedule and data reporting

The DSMC will meet at least every 12 months and may decide to meet more often as tailored to the need of the trial. Two weeks before a DSMC meeting the Chair/Chief investigator will deliver a governance report to the DSMC. Data delivery and analyses will be

undertaken by the independent statistician and sent to the DSMC before every formal interim analysis, and when the DSMC requests.

6. Formal interim analysis meeting

Formal interim analysis meetings will be held to review data relating to treatment efficacy, patient safety, and quality of trial conduct. The members of the DSMC will meet when outcome results at 30 days after randomization of 500 participants have been obtained.

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Subsequent analyses/meetings will be decided by the DSMC, but a minimum of three interim analyses shall be conducted.

7. Proper communication

To enhance the integrity and credibility of the trial, procedures will be implemented to ensure the DSMC has access solely to evolving information from the clinical trial regarding comparative results of efficacy and safety data, aggregated by treatment group (MAP_X/ MAP_Z; FEV_X/ FEV_Z; SED_X/ SED_Z). An exception will be made to permit access to the independent statistician who will be responsible for serving as a liaison between the database and the DSMC. At the same time, procedures will be implemented to ensure that proper communication is achieved between the DSMC and the trial investigators. To provide a forum for exchange of information among various parties who share responsibility for the successful conduct of the trial, a format for open sessions and closed sessions will be implemented. The intent of this format is to enable the DSMC to preserve confidentiality of the comparative efficacy results while at the same time providing opportunities for interaction between the DSMC and others who have valuable insights into trial-related issues. The steering group will be responsible for monitoring if other relevant trial results are published during the STEPCARE trial period that may influence the decision to continue or terminate the trial. The chair/chief investigator of STEPCARE will send all relevant trial results within seven days after publication to inform the DSMC.

8. Closed sessions

Sessions involving only DSMC members will be held to allow discussion of confidential data from the clinical trial, including information about the relative efficacy and safety of interventions. To ensure that the DSMC will be fully informed in its primary mission of safeguarding the interest of participating patients, the DSMC will be blinded in its assessment of safety and efficacy data. However, the DSMC can request unblinding from the steering group.

9. Open reports

For each DSMC meeting, open reports will be provided available to all who attend the meeting. The reports will include data on recruitment and baseline characteristics, and pooled data on eligibility violations, completeness of follow-up, and compliance. The

independent trial statistician will prepare these open reports in collaboration with the trial management.

10. Closed reports

Closed reports will include analysis of the primary outcome measure, the secondary outcome measures except quality of life, and serious adverse events including unexpected serious adverse events. These closed reports will be prepared by the independent statistician in a manner that allow them to remain blinded. The format for these reports should be agreed by the DSMB and reports should be provided to DSMC members at least three days prior to the date of their meeting.

11. Minutes of the DSMC Meetings

The DSMC will prepare minutes of their closed meetings. The closed minutes will describe the proceedings from all sessions of the DSMC meeting, including the listing of recommendations to the steering group. Because it is likely that these minutes may contain unblinded information, it is important that they are not made available to anyone outside the DSMC (until randomization has stopped and the blinded analysis has taken place). The trial management group will prepare minutes from the open meetings.

12. Recommendations to the steering group

After the interim analysis meeting, the DSMC will make a recommendation to the steering group to continue, hold, or terminate the trial within a maximum of 10 working days. This recommendation will be based primarily on safety and efficacy considerations and will be guided by statistical monitoring guidelines defined in this charter and the trial protocol. The recommendation will be in a written format that could be sent to relevant authorities, grant providers, or ethical committees. The steering group is jointly responsible with the DSMC for safeguarding the interests of participating patients and for the conduct of the trial. Recommendations to amend the protocol or conduct of the trial made by the DSMC will be considered and accepted or rejected by the steering group. The steering group will be responsible for deciding whether to continue, hold, or terminate the trial based on the DSMC recommendations. The DSMC will be notified of all changes to the trial protocol or conduct. The DSMC concurrence will be sought on all substantive recommendations or changes to the protocol or trial conduct prior to their implementation.

13. Statistical monitoring guidelines

The STEPCARE Trial is based a 2x2x2 factorial design with three main comparisons (SED_1/ SED_2; FEV_1/ FEV_2; MAP_1/ MAP_2), i.e., participants will be randomized to eight intervention groups. The trial is conducted under the general assumption of no significant interaction effects between the trial interventions, i.e., it is planned to analyze and report the trial results in three separate main publications. To assess if it is reasonable to assess each of the three comparisons separately, the DSMC should as a first step assess if there is

evidence for interaction effects on outcomes. The outcome parameters are defined in the STEPCARE-trial protocol. To avoid a potential delay after a decision to stop the trial, the plan is to perform short-term follow-up assessments (outcomes occurring during the primary hospital stay) on all main outcomes (all-cause mortality, poor functional outcome, and serious adverse events). If it is concluded that there are no significant interaction effects on outcomes, for each of the three comparisons the DSMC will evaluate data on:

• The primary outcome measure - all cause mortality at 6 months or mortality during primary hospital stay for those participants who have not reached 6 months.

• The secondary outcome measure - poor functional outcome (mRS 4 to 6) within 30 days and at 6 months.

• Serious adverse events including unexpected serious adverse events – during intensive care unit stay until day 7.

The DSMC will be provided with these data from the independent statistician as:

• a. Number of patients randomized
• b. Number of patients randomized per intervention group (MAP_X/ MAP_Z; FEV_X/ FEV_Z; SED_X/ SED_Z)
• c. Number of events, according to the outcomes, in the intervention groups (for each comparison)

Based on evaluations of these outcomes, the DSMC will decide if they want further data from the trial management and when next to perform analysis of the data. For analyses, the data will be provided in one file as described below.

Based on the analyses of the primary outcome measure and serious adverse events, the DSMC will use Lan-DeMets group sequential monitoring boundaries (boundary for benefit, harm, and futility) as the statistical limit to guide its recommendations regarding early termination of the trial. These boundaries will be specified in the statistical analysis plan prior to the interim analysis being conducted. The DSMC should also be informed about all unexpected serious adverse events occurring in the eight groups of the trial.

The DSMC may also be asked to ensure that procedures are properly implemented to adjust trial sample size or duration of follow-up to restore power, if protocol specified event rates are inaccurate. If so, the algorithm for doing this should be clearly specified.

14. Conditions for transfer of data from the trial database to the DSMC

The DSMC will be provided with a an analysis report from the independent statistician who has access to the trial database. The report will include but not be limited to data on the number of initiated sites, participants screened and randomized at each site, primarily blinded data on numbers allocated to the two groups of the three interventions, separation between the intervention arms, intensive care unit survival, 30 day, survival, 6 month

survival and functional outcome, and adverse events. A list of unexpected serious adverse events in verbatim and adjudicated by the trial management team will also be provided.

A mock report for the data transfer will be decided by the DSMC, the trial management group and the independent statistician. This report will not be part of the charter but will be included in the minutes as a working document.

Charter signed:

Paul Mouncey (Chair of the DSMC): 

Date: 25/07/2023

Niklas Nielsen (Chair, Chief investigator, STEPCARE): 

Date: 25/07/2023

Janus Jakobsen (Trialist, STEPCARE): 

Date: 25/07/2023