Charter for the Independent Data Monitoring and Safety Committee (DMSC) of the pragmatic randomised clinical trial SafeBoosC III

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Revision history

Version	Author	Date	Changes
1.0	Mathias Lühr Hansen Gorm Greisen Janus Christian Jakobsen Christian Gluud	18.03.2019	Initial version
1.1	Mathias Lühr Hansen Gorm Greisen Janus Christian Jakobsen Christian Gluud	23.09.2020	• Change in the timing of the only preplanned interim analysis. • Specification that only the biostatistician will have access to the microdata provided by the Coordinating Center • Removal of the data point 'randomisation date" • Specification on when data is considered lost to follow-up • Section on anonymous data • Addition of text regarding information and data confidentiality of the DMSC • Adding that primary outcome should be monitored and not just mortality

Introduction

This Charter defines the primary responsibilities for the independent Data Monitoring and Safety Committee (DMSC) of the pragmatic randomised clinical trial SafeBoosC III, its relationship with other trial components, its membership, and the purpose and timing of its meetings, all based on the good clinical practice (GCP) guidelines. The SafeBoosC III trial protocol is found on the web page of the trial (https://www.rigshospitalet.dk/english/departments/juliane-marie-centre/department-of-neonatology/research/SafeboosC-III/Sider/the-protocol.aspx) and the detailed statistical analysis plan is published [1]. The Charter also provides the procedures for ensuring confidentiality and proper communication, outline the content of the open and closed reports, and provides a proposal for the statistical monitoring guidelines to be implemented by the DMSC.

Primary responsibilities of the DMSC

The DMSC will be responsible for safeguarding the interests of the trial participants as well as potential future trial participants by assessing the benefits of and harms from the interventions during the trial. The DMSC will provide recommendations about stopping or continuing the trial to the Steering Committee (SC) of SafeBoosC III. A central responsibility of the DMSC is to contribute to enhancing the integrity of the trial. Results from other clinical trials or investigational plans in the same field can be weighted into the DMSCs recommendations, but any external information shall be assessed carefully.

The DMSC will be advisory to the SC. The SC will be responsible for promptly reviewing the DMSC 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 DMSC are required to keep all information and data obtained from the coordinating centre confidential throughout the entire process, as well keeping any results from the safety monitoring confidential.

One interim analysis is pre-planned and shall take place after one third of the trial participants (n=533) have been randomised. The timing and prevalence of additional interim analyses will be decided solely by the DMSC. The DMSC is planned to meet physically or communicate via telephone conference (TC) or mail, in order to evaluate the analysis of the SafeBoosC phase III trial. The DMSC may additionally meet or communicate via TC whenever they decide, or contact each other by e-mail, in order to discuss the safety of the trial participants.

The sponsor has the responsibility to report to the DMSC the overall number of participants with the primary outcome (mortality or severe brain injury), serious adverse events (SAEs), and severe adverse reactions (SARs) per intervention group under code. The DMSC can request, at any time during the trial, reporting of these outcomes.

The recommendations of the DMSC regarding continuing, changing the design, or stopping of the trial should be communicated without delay to the SC of the SafeBoosC III trial. Then the SC has the responsibility to inform as fast as possible, and no later than five working days, all investigators of the trial and the departments, including participants in the trial, the recommendation of the DMSC and the SC decision hereof.

Members of the DMSC

The DMSC is an independent multidisciplinary group consisting of two clinicians and a biostatistician that, collectively has experience in the management of premature newborns and in the conduct, monitoring, and analysis of randomised clinical trials.

DMSC members

Andrew Whitelaw

Emeritus Professor of Neonatal Medicine, University of Bristol, Neonatal Neuroscience level D, St Michael's Hospital, Bristol, United Kingdom

James Boardman

Professor of Neonatal Medicine, Centre for Clinical Brain Sciences, MRC Centre for Reproductive Health, Queen's Medical Research Institute, Edinburgh, United Kingdom

Theis Lange

Associate Professor, Section of Biostatistics, Department of Public Health, Copenhagen University, Copenhagen, Denmark

Conflicts of interest

Such conflicts may be financial, scientific, or regulatory in nature. The DMSC membership has been restricted to individuals free of conflicts of interest.

Any DMSC members who develop significant conflicts of interest during the course of the trial, should resign from the DMSC.

DMSC membership is to be for the duration of the clinical trial. If any members leave the DMSC during the course of the trial, the SC shall appoint the replacement(s) in agreement with the remaining members of the DMSC.

Proper communication

To enhance the integrity and credibility of the trial, procedures will be implemented to ensure the DMSC has sole access to evolving information from the clinical trial, regarding comparative results of the primary outcome and safety data, aggregated under code by treatment group (0,1). An exception will be made to

permit access to the data manager, who will be responsible for serving as a liaison between the database and the DMSC.

At the same time, procedures will be implemented to ensure that proper communication is achieved between the DMSC and the trial SC, sponsor, and investigators. To provide a forum for exchange of information among the various parties, who share responsibility for the successful conduct of the trial, a format for open report and closed report will be implemented. The intent of this format, is to enable the DMSC to preserve confidentiality of the comparative safety results, while at the same time providing opportunities for interaction between the DMSC and others who have valuable insights into trial-related issues.

Closed session

Sessions involving only DMSC members will be held to allow discussion of confidential data from the clinical trial, including information about the benefits and harms of the interventions. In order to ensure that the DMSC will be fully informed in its primary mission of safeguarding the interest of the participants and of potential future participants, the DMSC will be blinded in its assessment of outcome data. However, the DMSC can request unblinding from the SC. Datasets on the primary outcome, SAEs, SARs, and follow-up status will be provided by the data manager of the coordinating data centre, The Copenhagen Trial Unit.

Closed report

Closed report will include analysis of the safety aspects (primary outcome, SAEs, and SARs). This closed report will be prepared by the DMSC biostatistician, based on the data he obtains from the data manager of the coordinating data centre. Only the biostatistician will have access to the anonymized microdata as provided by the coordinating data center.

The closed reports should provide information that is accurate. The reports should be provided to the additional DMSC members approximately three days prior to the date of their meeting or TC.

Minutes of the DMSC meetings

The DMSC will prepare minutes of their meetings. The closed minutes will describe the proceedings from all DMSC meetings, including the listing of the DMSC's recommendations. Because it is likely, that these minutes may contain unblinded information, it is important that they are not made available to anyone outside the DMSC.

Open report

Based on their closed meetings and closed reports, the DMSC will provide the SafeBoosC SC with open reports with 1) recommendations regarding continuation of the trial; 2) recommendations for breaking the blind for the DMSC; and 3) if the DMSC wishes to continue the trial, their wishes to assess data the next time. This open report should not disclose the suspected intervention in the two intervention groups. The open report is only for the eyes of the SC and the contents should not be disclosed to anyone else outside the SC.

Recommendations to the Steering Group

The DMSC will make a recommendation to the SC to continue, change, hold, or terminate the trial. This recommendation will be based primarily on safety considerations and will be guided by statistical monitoring guidelines, defined in this Charter. If the DMSC recommends change, hold, or termination of the trial, a virtual face to face meeting between the DMSC and the SC should be held, in which the DMSC explains its recommendation, based on the dataset provided by the data manager.

If the DMSC requests breaking of the blind, the SC can ask the data manager of The Copenhagen Trial Unit to inform the DMSC of the nature of the two intervention groups.

The SC is jointly responsible with the DMSC for safeguarding the interests of participating participants as well as potential participants and for the conduct of the trial. Recommendations to amend the protocol or

conduct of the trial made by the DMSC, will be considered and accepted or rejected by the SC. The SC will be responsible for deciding whether to continue, change, hold, or stop the trial based on the DMSC recommendations.

The DMSC will be notified of all changes to the trial protocol or conduct. The DMSC concurrence will be sought on all substantive recommendations or changes to the protocol or trial conduct prior to their implementation.

Statistical monitoring guidelines

The variables below are defined in the SafeBoosC-trial protocol. The SafeBoosC trial has many listed outcomes. For the two groups, the DMSC will evaluate data on:

The DMSC will be provided with these data from the Coordinating Data Centre as:

- Number of participants randomised
- Number of participants randomised per intervention group (0,1)
- Number of participants stratified per stratification variable per intervention group (0,1)
- Number of events (mortality or severe brain injury, SAEs, and SARs) in the two groups (0,1)

Based on evaluations of these outcomes, the DMSC will decide if they want further data from the Coordinating Data Centre, and when next to perform analyses of the data.

For analyses, the data will be provided in one file as described below.

Based on the analyses of the primary outcome and the safety variables, the DMSC is suggested to use Lan-DeMets sequential monitoring boundaries. For the calculation of the sequential monitoring boundaries for benefit or harm on the primary outcome, the required sample size should be based on an assumed proportion

of 34% in the control group (Pc); a relative risk reduction of 22%; an alpha of 5%; and a beta of 10%. The Copenhagen Trial Unit's software Trial Sequential Analysis can calculate the required sample size (1600 participants) as well as the monitoring boundaries. For the individual components of the primary outcome and for the safety outcomes, the statistical limit to guide its recommendations regarding early termination of the trial for harms, is recommended also to be conservative.

Conditions for transfer of data from the Coordinating Data Centre to the DMSC

The DMSC shall be provided with the data described below in one file.

The DMSC will be provided with a comma separated data file, containing the data defined as follows:

1. Row 1 contains the names of variables (to be defined below)
2. Row 2 to N (where N-1 is the number of participants who have entered the trial) each contains the data for one participant
3. Column 1 to p (where p is the number of variables defined below) each contains in row 1, the name of a variable and in the next N rows, the values of this variable

The values of the following variables should be included in the dataset:

1. The randomisation code – the DMSC is not to be informed on what intervention the groups received
2. All-cause mortality or severe brain injury
3. All-cause mortality
4. Severe brain injury
5. Serious Adverse Events
6. Serious Adverse Reactions
7. Lost to follow-up indication

Anonymised data

As no information on 'Participant ID' or 'Site' will be included in the dataset provided to the DMSC, data is considered anonymised. Furthermore, data points have been chosen according to the 'privacy by design' principle, i.e. only the most necessary data points will be included in the dataset and available to the DMSC.

Listing of data points in the proposed dataset:

Abbreviations:

R: Randomisation form

E: End of monitoring form

S: Severe Adverse Reactions form

F: Follow-up form

B: Blinded follow-up form

- R9_randomisationgroup: This yields the value "K" or "F", which is coding for the randomisation outcome
- S01a_sarspecific (type of SAR): "0" is severe skin damage, "1" is critical displacement of endotracheal tube threatening the life of the infant, "2" is critical displacement of endovascular line threatening the life of the infant, "3" is mismanagement while trying to improve respiratory status, "4" is mismanagement while trying to improve cardiovascular status, and "5" is mismanagement while trying to improve oxygen transport.
- E12_parentsdiscontinuepriorinformedconsent: "1" is yes, "0" is no
- E12b_parentswithdrawpermissiontousefuturedata: "1" is yes, "0" is no
- E12D_parentsdiscontinuedeferredconsent: "1" is yes, "0" is no
- E12Dd_parentsdeclinepermissiontousefuturedata: "1" is yes, "0" is no
- F01_followupdate: date for follow-up in dd-mm-yyyy format
- F08_respsupp36weeks (supplemental oxygen or CPAP requirements at 36 weeks postmenstrual age or discharge): "1" is yes, "0" is no

- F09_nec (necrotising enterocolitis stage II or III): "1" is yes, "0" is no
- F10_rop (retinopathy of prematurity stage III or higher): "1" is yes, "0" is no
- F11_sepsis (Late onset sepsis (>72 hours of age) as treatment with antibiotics for at least five days): "1" is yes, "0" is no
- F12_death (death before 36 weeks postmenstrual or discharge): "1" is yes, "0" is no.
- BF01_ivh (Intraventricular haemorrhage grade 3 or 4): "1" is yes, "0" is no
- BF02_cpvl (cystic periventricular leukomalacia): "1" is yes, "0" is no
- BF03_phvd (post-haemorrhagic ventricular dilatation): "1" is yes, "0" is no
- BF04_cerebhaem (cerebellar haemorrhage): "1" is yes, "0" is no
- BF05_cerebatroph (cerebral atrophy): "1" is yes, "0" is no

Mapping of proposed dataset to current dataset

1. The randomisation code: the value of R10_randomisationgroup
2. All-cause mortality:
    a. If value in field F12_death is 1, the participant is considered dead before 36 weeks postmenstrual age or discharge
    b. If value in field F12_death is 0, the participant is considered alive at 36 weeks and/or at discharge
3. Severe brain injury:
    a. If value in field BF01_ivh OR field BF02_cpvl OR field BF03_phvd OR field BF04_cerebhaem OR field BF05_cerebatroph is 1, the participant has had a severe brain injury
    b. If value in field BF01_ivh AND field BF02_cpvl AND field BF03_phvd AND field BF04_cerebhaem AND field BF05_cerebatroph is 0, the participant did not have a severe brain injury
4. Severe adverse events:

a. If value in field F08_respsupp36weeks is 1, the participant has had a severe adverse event
b. If value in field F09_nec is 1, the participant has had a severe adverse event
c. If value in field F10_rop is 1, the participant has had a severe adverse event
d. If value in field F11_sepsis is 1, the participant has had a severe adverse event
e. If value in field F12_death is 1, the participant has had a severe adverse event
f. If value in field B01_ivh is 1, the participant has had a severe adverse event
g. If value in field B02_cpvl is 1, the participant has had a severe adverse event
h. If value in field B03_phvd is 1, the participant has had a severe adverse event
i. If value in field B04_cerebhaem is 1, the participant has had a severe adverse event
j. If value in field B05_cerebatroph is 1, the participant has had a severe adverse event

5. Severe adverse reactions

a. If value in field S01a is 0, 1, 2, 3, 4, or 5, the participant has had a severe adverse reaction
b. If there is no value in field S01a, the participant has not had a severe adverse reaction

6. Lost to follow-up indications

a. If no value in field F01_followup data, the participant will be considered lost to follow-up
b. If value in field E12_parentsdiscontinue is 1 AND if value in field E12b is 1, the participant will be considered lost to follow-up
c. If value in field E12D_parentsdiscontinue is 1 AND if value in field E12Dd is 1, the participant will be considered lost to follow-up