Minutes from the SafeBoosC Steering Committee Meeting the 26th of June

Present: Ebru Ergenekon, Jonathan Mintzer, Hans Fuchs, Adelina Pellicer, Gorm Greisen, Mathias Lühr Hansen, Marie Rasmussen, Siv Fredly, Christian Gluud, Tomasz Szczapa, Gabriel Dimitriou, Simon Hyttel-Sørensen, Monica Fumagalli, Janus Christian Jakobsen, Gerhard Pichler, Saudamini Nesargi, Gunnar Naulaers, Jakub Tkaczyk

Apologies: Maria Vestager

Absent: Guoqiang Cheng, Ana Vilan, Anne Marie Heuchan, Eugene Dempsey

Trial status update from Copenhagen

As of the 18th of September, a total of 1360 babies have been randomised across 72 centres. 69 hospitals have randomised a baby. This corresponds to 2.5 randomised babies per day. The average randomisation rate across the last six months is 2.53 randomised babies per day. If we continue in a similar pace, we will complete recruitment before the end of 2021.

Formal decision regarding co-authorship for Marie Rasmussen, for the publication of the primary outcomes

Enough members of the steering committee were present to constitute a quorum (n>50% of the committee, present: 16/21 members). 16/16 members voted in favour of making Marie Rasmussen a co-author for the publication on the primary outcome results.

Discussion on investigator meeting in Copenhagen/virtual/hybrid – and when?

The model will be the same as previously. Attendees pay for their own transportation and the hotel expenses will be paid by the central trial team. All steering committee members agree that it is important for the collaboration of the trial (and future studies), to have a physical meeting in the near future. Tomasz suggests to make it hybrid, so it is possible to attend both virtually and physically. Also in relation to the constantly change covid policies, this would be a pragmatic solution. It is discussed whether the meeting should be in March/April 2022, focusing on the data completion of the trial and the follow up study, or, if it should be in May/June 2022 with the unblinding of the abstract. A final decision will be made in the fall of 2021.

Discussion on 'SOP: Expected timeline for completion of SafeBoosC-III and submission of manuscript'

A SOP has been made to ensure the results of the trial are published as soon as possible without losing quality along the way. We hope that estimating the dates beforehand will speed up the completion process, so PI's in advance can plan:

1. Completion of data entries
2. Completion of the last GCP report
3. Completion of inquiries from last quality monitoring report

Gorm comments on the possibility of publishing the summary data as soon as the abstracts are unblinded, to ensure transparency and wide distribution, but this will on the respective journals policy. A discussion and decision on this in the steering committee will follow.

Discussion and decisions on SafeBoosC-IIIv

A discussion on the treatment guideline and whether it should be changed for the SafeBoosC-IIIv trial. It is argued that it will be strenuous to adapt it to fit the heterogenous population in relation to the physiology, of the SafeBoosC-IIIv trial, and thereby there should be an overall treatment guideline instead, for the sake of the pragmatic approach of the trial. It is therefore decided that the treatment guideline should stay as it is, i.e. the same as used in SafeBoosC-III.

The protocol is discussed. Some places will not be in equipoise to randomise infants on ECMO. If you are not in equipoise, the infant should not be randomised. Furthermore multiple births will be randomised independently in the SafeBoosC-IIIv trial. This might pose as a problem for parents if the second infant requires mechanical ventilation and is to be included in trial, and does not receive the same treatment as the first infant. It is discussed whether the second infant should be included in the trial then, or be excluded from the trial and receive the same treatment as the first infant. This is not a large problem in the trial, as there will be less twins in this population compared to the SafeBoosC-III trial. Adelina raises a much valid point, that the 24 month follow-up will be a challenge, since these infants are not followed regularly at the hospital. The 24 month outcome (primary outcome) is solely based on parental questionnaires and the importance of keeping in contact with the parents is stressed. We hope that the follow up workflow will be tested rigorously in the SafeBoosC-III FU study, and we will have some experience to learn from, before commence with the SafeBoosC-IIIv trial. Christian gluud suggest that all parents of children who complete the 24 months questionnaire will take part in a draw for a prize.

It is discussed if there should be a time window to initiate cerebral NIRS monitrering after start of mechanical ventilation. The first 48 hours are the most critical hours. The effect may decline thereafter It is decided that it should be possible to initiate cerebral NIRS monitorering within 6 hours, in order to include a participant in the trial.

It is decided that the work with the SafeBoosC-IIIv protocol will continue and the next step will be to finish the protocol paper and seek ethics approval in Denmark. All steering committee members will be invited to co-author this paper, on the condition that they intend to partake in the IIIv trial.

Update on the SafeBoosC-III two-year follow-up study
The first child randomised in the trial will reach two years of corrected age this September from Copenhagen. However, ethical approval is still pending. Five more centers will start following up participants this fall and the three Spanish centers have ethical approval.

The following workflow will be exercised:

1. 3-6 months prior to your first participant turns 2 years of corrected age, Marie will contact you for the following information (for more details see safeboosc.eu and find the SOP on task to complete before commencement of the SafeBoosC-III follow up study)
    - Blinded assessor
    - Blinding procedure

    - Ethics approval
2. Meanwhile Marie will supply you with the following:
    - A patient list with all randomised participants will exact follow up dates and dates for receiving the parental questionnaires
    - Access to the OpenClinica Sandbox, for the blinded assessor to try
    - Information about parental questionnaire with links for parents

How to minimize loss to follow up in the SafeBoosC-III follow up study

Missing data is the largest threat to the follow up study. If we have high amounts of missing data, it will reduce the statistical power, complicate the analysis and make the uncertainty of our results larger. Therefore it is stressed that we try to be proactive about preventing loss to follow up. The following measures are proposed to minimize the amount of missing data:

- As soon as possible, think about what children might be in risk of loss to follow up (for example families with lower socioeconomic status, parents who are foreign born etc)
- Families who move - how do we get the data?
- Use the parental questionnaire
    - Should the clinician call the family and ask them the questions by phone?
    - Should parents be assisted in filling out the questionnaire in the follow-up clinic?

No further business