Minutes from SafeBoosC III Steering Committee Meeting – 22nd of March 2021

Attendees: Hans Fuchs, Gunnar Naulaers, Jonathan Mintzer, Janus Christian Jakobsen, Monica Fumagalli, Tomasz Szczapa, Jakub Tkaczyk, Eugene Dempsey, Christian Gluud, Adelina Pellicer, Anne Marie Heuchan, Cornelia Hagmann, Gerhard Pichler, Maria Vestager, Mathias Lühr Hansen, Gorm Greisen, Marie Rasmussen

Apologies: Saudamini Nesargi, Siv Fredly

Absent: Guoquiang Cheng, Ana Vilan, Simon Hyttel-Sørensen, Ebru Ergenekon, Gabriel Dimitriou

Trial status update from Copenhagen - Mathias

Overall, the trial is progressing well. Currently, 67 centres are open for randomisation. Ten additional sites are still preparing to participate. It is expected that at least 70 centres will randomise participants, eventually. Norway, The UK and Ireland have been opened for randomisation and the two latter have already randomised participants. As of the 18th of March 2021, 891 patients have been randomised. The randomisation rate has increased again. If the current randomisation rate persists, we will reach our sample size of 1600 participants before the end of 2021.

The Data Monitoring and Safety Committee have conducted the first interim analysis based on data from 560 patients and concluded that the trial should continue, and that no further interim analysis is needed. Furthermore, there are have been no severe adverse reactions reported.

Janus (CTU) suggests that we start planning what conferences the trial results should be presented on.

Trial execution status by national coordinators was skipped due to a long meeting.

Discussion and decision making on ROP classification
We relied on the classical staging (= pre-threshold CRYOROP) when planning SafeBoosC-II and -III. But more and more ophthalmologists now use the ETROP criteria. Several PI's have supported that this a real problem. As early ROP treatment may prevent the disease to develop into stage 3, which we have used as the criteria for ROP until now, the steering committee have decided to add a second coding of retinopathy of prematurity (ROP) in OpenClinica on treatment/no treatment.

This should not mean much extra work for future patients but requires that the PI add data regarding ROP-treatment for all participants, where the follow-up form has already been

completed. Data up to 36 weeks PMA may only be used. We will monitor completion of this additional data entry point during the monthly data completion monitoring report. We will add the change to the protocol and use the additional data in a sensitivity analysis.

Enough members (n=13, >50%) of the steering committee (n=22) are present to constitute a quorum. The members vote in favour of this proposal.

Gunnar suggests to add the same data point (ROP treatment yes/no) to the SafeBoosC-III two year follow-up eCRF. This will be discussed later.

Discussion and decision making on blinded outcome assessment and co-authorships in the two-year follow-up study

As discussed previously, the SafeBoosC-III two year follow up will rely on routine clinical data as well as parental questionnaires. Blinding of the clinical examinations is not possible, but it is unlikely that these clinicians will be biased regarding the SafeBoosC allocation group. We suggest that the PI should delegate the review of the clinical files of the child to a competent colleague who would then perform the data entries in OpenClinica blinded. This would require that each NICU should develop a blinding procedure to be approved centrally. The PI would be given a regular co-authorship and the blinded 2-year outcome assessor would be given a non-byline authorship. This would mean that their name would not appear in the byline, but would be stated in acknowledgements and would furthermore appear in a PubMed search. We believe this is a pragmatic approach that would strengthen the quality of the follow-up study.

Enough members (n=13, >50%) of the steering committee (n=22) are present to constitute a quorum. The members vote in favour of this proposal.

For more information on authorships please see the following manuscript from JAMA: doi:10.1001/jama.2017.19341

Information on problem - and decision – regarding entry of follow-up dates later than 36 weeks PMA

Following the last central data monitoring meeting, we discovered that for 103 babies, the follow-up date was registered to be after 36+0 weeks of postmenstrual age. In the majority of the 103 registered cases, the registered follow-up date is only a little later than 36+0 weeks PMA and primarily due to one of the following issues:
1) date of last weighing is used as follow-up date or
2) the investigator has used the date where he/she sat on the computer and entered data from the clinical files i.e. not when the baby reached 36 weeks PMA.
In both situations, we have reports from investigators that only data up until 36+0 weeks PMA have been used, when entering data on primary and exploratory outcomes. Therefore, we have decided not to do any further regarding the already entered data. However, OpenClinica has been revised, so that it is no longer possible to enter a follow-up date later than 36+0 weeks PMA.

Update on the SafeBoosC-IIIv trial

Data from national coordinators supports the hypothesis that there is a population of newborns that would meet the inclusion criteria of the SafeBoosC-IIIv trial. Therefore, the steering committee agrees that the planning of the trial should continue and funding applications will be submitted while the protocol is being developed. Since 3000 infants shall be randomised the steering committee is urged to reach out to colleagues from other countries, to expand the consortium. The synopsis will be available shortly on www.safeboosc.eu

Some national coordinators share a concern regarding obtaining funding for protocol insurance, which is required in Ireland, the UK, China and India.

Collaboration agreement

As of right now the collaboration agreements between the local centres and Copenhagen terminate in April 2021. All present members (n=13) of the steering committee vote in favour of extending the collaboration agreements. We will discuss with the lawyers in Copenhagen how to make this as simple as possible. Possibly, an extension could include the two year follow up study.

No further business