Minutes from the SafeBoosC Steering Committee Meeting the 28th of March 2022

Present: Tomasz Szczapa, Monica Fumagalli, Adelina Pellicer, Maria Vestager, Cornelia Hagmann, Gerhard Pichler, Markus Harboe Olsen, Gabriel Dimitriou, Jakub Tcakzub, Siv Fredly, Janus Jakobsen, Christian Gluud, Cornelia Hagmann, Anne Marie Heuchan, Eugene Dempsey, Saudamini Nesargi, Gunnar Naulaers, Gabriel Dimitriou, Marie Rasmussen, Mathias Lühr Hansen, Gorm Greisen

Apologies: Hans Fuchs, Jonathan Mintzer

Absent: Guoqiang Cheng, Ebru Ergenekon, Simon Hyttel-Sørensen

Trial status update from Copenhagen

We completed recruitment on December 16th 2021 with a total of 1601 randomised participants across 70 centers. Of the 1601, 20 participants withdrawed by parents/ never gave consent and for two participants from one centre, data cannot be obtained since the centre withdrawed from the trial after the two randomisations. Therefore, 1579 partipants are eligible for data entries. For the end of monitoring, SAR and follow up form, all eligible participants have had data entries complete. For the blinded follow up form, 1572 participants have had data entries completed and we expect that data entries will be completed for the remaining participants, before the deadline 1st of April. For GCP reports, all but five have been received and approved, and it is expected that the remaining five reports will be received within the next few days. On the 7th of April, the last data quality monitoring report will be conducted, and the 15th of April will be the deadline for completion of inquiries arisen from the data quality monitoring.

Secondary publications

The secondary and ancillary studies were presented and discussed on the 24th of March. The minutes will be uploaded to safeboosc.eu shortly. Tonight, a decision on the secondary study shall be taken and the next steps for the ancillary studies must also be taken.

Mechanical ventilation and late brain injury in the SafeBoosC-III trial, an ancillary study
Gorm Greisen, Copenhagen, Denmark

18 members of the steering committee are present (>50%, total n=22) which is enough to consistitute a quorum. Fourteen present members vote in favor of the proposal and the secondary analysis on mechanical ventilation is therefore approved.

SafeBoosC-III MRI at term age, a secondary study, Miguel Alsina, Barcelona, Spain

It is argued, that there may not be enough power to detect a relevant, and realistic difference if only the two Spanish centres (Clinical-Maternitat in Barcelona and Joan de Deu in Barcelona) will participate. A strength in the current study set-up (with only two participating sites) is, that the 50 patients included from the two centers in Barcelona have their term MRIs done in the same scanner and are assessed by the same people. It is proposed that if more centers are to be invited, there should be specific scanner requirements. It is argued that the possible inter reader difference may even out between groups, due to the nature of randomisation. The same is done for the cerebral ultrasound assessments, but white matter injury on MRI may not be as well defined as pathology on ultrasound readings are. Therefore, it may be a problem with readings done locally. However it would be hard to imagine a feasible study with central reading. This was done in SafeBoosC-II and was challenging. Miguel will be contacted with these comments and asked to make a decision regarding to keep it locally in Barcelona or involving other centers.

Quantification of flow-pressure cerebral autoregulation in extremely preterm infants, a secondary study, Liesbeth Thewissen, Leuven, Belgium

Not many centres have collected the necessary data to participate in this study. Adelina may have data, and might be able to contribute. Gene may also be able to contribute with data from the HIP trial. Gunnar suggest to build a database with anonymous data, managed from Belgium. Gunnar and Lisbeth will work on extending the protocol with a data management plan and will reach out to investigators with an invitation to participate in the study.

Early cerebral desaturation events and intraventricular haemorrhage in extremely preterm infants, a secondary study, Eugene Dempsey, Cork, Ireland

The same issues as discussed with the cerebral autoregulation study above, are raised here. Additional ethics approval may be required, as well as new parental consents. This will differ from country to country. Gene will reach out to other centers and propose a data management plan.

Secondary bayesian analysis of the SafeBoosC-III trial – Markus Harboe Olsen

Markus initiated his presentation with explaining the difference between frequentist statistics, which is the statistical methods that most trials use, and Bayesian statistics. In short, frequentist statistics tests the effect of the intervention in a dichotomized matter, i.e. benefit/harm (p-value<0.05) or no effect (p-value>0.05), while bayesian statistics tests the probability of benefit and harm for a number of predefined effect sizes.

Markus also shares an example from The COVID STEROID 2 Randomized Trial (https://jamanetwork.com/journals/jama/fullarticle/2785529), where the frequentist analyses showed that the intervention did not benefit (p-value >0.05), but the bayesian analyses showed larger probability of benefit than the probability of clinical important harm (https://link.springer.com/article/10.1007/s00134-021-06573-1).

It is discussed why this secondary Bayesian analysis was not included in the original SAP, which of course would have been preferred. Furthermore, it is highlighted that NEJM encourages researched to use Bayesian statistics.

All present members voted in favor of the proposal and the Bayesian analysis, which is therefore approved.

The SafeBoosC-III follow up study

In eight centers, one or more participants thave reached two years of corrected age, and seven of them have initiated data entries in OpenClinica. A total of 29 participants have had their data entered in OpenClinica, and 26 families have completed the parental questionnaire. We are planning an ancillary study with Deirdre Murray and her start-up company Liltoda. They have developed a touchscreen application called CogniTOT to detect developmental delay in young children. It is a non-verbal, tablet-based test requiring minimal training of the assessor and has been validated in children from multilingual homes. It has been tested in multiple cohorts, but never in a multinational setting such as the SafeBoosC-III follow up study. We are working on the data management contracts and hereafter an invitation will be sent out to all investigators.

Bo Mølholm Hansen and Anne Mette Plomgaard are both supervisors of Marie's PhD and have contributed substantially to the design and protocol of the SafeBoosC-III follow up study. It is therefore proposed that they are included as co-authors for the publications of the follow up study.

All present members vote in favor of including Bo and Anne Mette as co-authors and it is therefore approved.

The SafeBoosC-IIIv trial

Maria explains that we are still in the process of applying for funds to cover the central trial costs. We plan to apply for the Innovation Fond once again, and expect that the application – this time – will be strengthened by the good process in SafeBoosC-III. In additional, we have also applied for smaller grants and will receive the decisions late summer/early fall.

Investigator meeting in May 2022

Mathias explains that the deadline for registration is 1st of April and therefore, all investigators who have not already registered or declined participation, should do so.

Meeting ended at 21:33 (93 minutes).

Marie and Mathias