Minutes from SafeBoosC III Steering Committee Meeting – 25th of January 2021

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

Apologies: none

Absent: Guoquiang Cheng, Cornelia Hagmann, Ana Vilan

Trial status update from Copenhagen - Mathias

Currently, 62 sites are open for randomisation. The number of randomising sites is still increasing. Norway, UK and Ireland are expected to start randomising before the next steering committee meeting. During the last month, the randomisation rate has decreased a bit, which may be due to the Christmas holidays or the second wave of COVID-19. However, the randomisation rate is starting to pick up again. It is expected that at least 70 sites will be randomising per 1st of March 2021. Depending on the randomisation rate, we will reach our sample size of 1600 patients between November 2021 and March 2022.

The first interim analysis will be conducted in February and therefore sites are highly encouraged to prioritise completion of data entries.

Updates on trial execution, by national coordinators

Jonathan Mintzer – United States

The CPARF grant was awarded in November 2020. Furthermore, NIRS sensors to all sites have been sponsored by the industry. Three US sites are randomising and an additional five are preparing to open for randomisation within the next months. All sites have research coordinators working on trial preparations and all IRBs have been submitted. Two sites are expected to start randomising within the next two months, but the remaining sites may need an extra month or two.

Anne Marie Heuchan - United Kingdom

Glasgow is suspected to open up for randomisation this week and Wishaw is expected to follow shortly.

Hans Fuchs – Germany

One participating site. Has not had any eligible patients the last month.

Jakub Tzackub – Czech Republic

One site is randomising in a good tempo, and the other site is close to opening up for randomisation.

Monica Fumagalli – Italy

Four sites are randomising. A fifth site is still waiting for ethical approval, which has been delayed due to COVID-19.

Simon Hyttel-Sørensen – Denmark

Four sites are open and have all enrolled patients.

Gabriel Dimitriou - Greece

Four sites are open for randomisation. Some sites have experienced a decrease in eligible patients.

Tomasz Szczapa – Poland

Seven sites are currently open for randomisation, whereof five sites have randomised patients. Two other sites are close to opening up for randomisation.

Gene Dempsey - Ireland

Cork has just opened for randomisation. Three other sites are hoping to participate as well, hopefully by late March.

Gerhard Pichler - Austria

One site is open for randomisation in Austria. No further will be participating.

Adelina Pellicer - Spain

Eleven sites are open for randomisation. Two additional sites are still preparing for participation. Adelina raises a concern regarding the unequal contributing of randomised patients. This is the case in other countries as well, and will be addressed later.

Gunnar Naulers - Belgium

All six sites are open for randomisation and all have randomised patients.

Ebru Ergenekon - Turkey

Five sites are open for randomisation. Experiencing the same problems as seen in Spain with unequal randomisation. Gazi University hospital have had problems with some deliveries being transferred to other sites. Hopeful to catch up with the randomisation rate.

Siv Fredly - Norway

The site in Oslo is expected to open for randomisation within the next weeks. The site from Bergen is not expected to participate.

Saudamini Nesargi - India

One site is randomising, but have not had many eligible patients. One other site is preparing, but it is uncertain whether or not they will participate due to legal issues regarding the collaboration agreement.

Progress on the SafeBoosC-III two-year follow-up study
Preparations for the SafeBoosC-III two-year follow up study are progressing. The outcome measures will rely on routine follow-up data in combination with the PARCA-R questionnaire. An online platform for the distribution of the PARCA-R questionnaire, in 17 languages, will be developed. Two-year follow-up assessments will begin in the late fall of 2021. The steering committee has agreed that a follow-up percentage of 75% of surviving children is required to obtain co-authorship. The protocol will be circulated in the Steering Committee in February and hereafter an official invitation to participate in the follow-up study will be sent out to all participating sites.

Discussion of the draft synopsis for the SafeBoosC-IIIv trial
The draft synopsis is based on two conditions: 1) recruitment of newborns with respiratory distress, only, rather than all newborns needing mechanical ventilation, and 2) the choice of moderate-or-severe neurodevelopmental impairment as the primary outcome, rather than a continuous measure of neurodevelopment in survivors.
The following points were raised and discussed by the Steering Committee.

Patient group - It was proposed if the patient group should be extended to surgical newborns as well. This may pose as a challenge for many sites, since the anaesthesiologists provide the care for the patient during surgery, and we may not get data during this critical time. A possible solution could be, to simply accept that babies will not be monitored during surgery – the trial focuses on cerebral NIRS monitoring during mechanical ventilation in the neonatal intensive care units. However, with the possible expansion to surgical patients, there might arise a problem with heterogeneity. Janus explains, that if the intervention effect between patient subgroups differs largely, the variance will increase as well, which needs to be taken into account in the sample size calculations and thereby might increase the sample size. Patients with cardiac congenital malformations should be excluded.

Sample size calculations - Many concerns were raised regarding the indicative sample size of 3000 patients in total (which is based on the respiratory distress patient group). If each site includes 10 patients each year, and 80 sites are randomising, this would take roughly 3,5 years. If the patient group were to be expanded to the surgical patients as well, this would be shortened.

Primary outcome - Some concerns were raised regarding the severity of the primary outcome. The primary outcome death and moderate-to-severe neurodevelopmental impairment may not have as high an incidence as first assumed in this patient group.

Equipoise - Adelina argues, that in her site, cerebral oximetry is already standard care for newborns undergoing surgery for diaphragmatic hernia and cardiac congenital malformations. Therefore, her hospital is not in equipoise to randomise these patients. This may also be the case in other sites.

More than 24 hours of ventilation - The rationale behind this proposed inclusion criteria is to exclude the patients receiving ventilation due to surfactant treatment.

Consent - The synopsis proposes that consent should be sought and ideally, cerebral oximetry should start before intubation of the patient. However, a concern was raised regarding the feasibility of this. It was proposed that more patients may be included, if it were possible to seek consent within the first 24 hours of ventilation, as an example.

The Steering Committee agrees that the preparations for the SafeBoosC-IIIv trial should continue. To be able to do so, all members of the committee are asked to provide data on the number of newborns being mechanically ventilated per year, the indication for intubation and if possible, data on survival and neurological outcomes. The members are urged to prioritise this, so preparations can continue on a solid foundation. It is planned to start applying for funding for the new trial within the next months.

No further business