Secondary and ancillary studies for the SafeBoosC-III trial

Minutes from the meeting on the 24th of March 2022 at 20:00 CET

Attendees: Gorm Greisen, Marie Rasmussen, Gene Dempsey, Adelina Pellicer, Berndt Urlesberger, Dario Gallo, Elzbieta Rafinska-Wazny, Gunnar Naulaers, Hans Fuchs, Janus Jakobsen, Christian Gluud, Jonathan Mintzer, Kosmas Sarafidis, Liesbeth Thewissen, Luis Arruza, Mariana Baserga, Maria Gomes-Chiara, Marta Teresa, Miguel Alsina, Monica Fumagalli, Afif El-Khuffash, Tomasz Szczapa

Welcome and introduction

Gorm stated the difference between a secondary, ancillary and local study:

Secondary study: SafeBoosC-III data

Ancillary study: SafeBoosC-III data + additional data

Local study: no SafeBoosC-III data (but SafeBoosC-III participants)

The studies will be presented today and discussed today and the Steering Committee will take a vote for approval on the 28th of March.

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

Proposal:
Automated analysis of transient desaturations of the NIRS signal may aid prediction of IVH in extremely preterm infants. Further investigation of these transients, their association with peripheral saturations and an understanding of the physiology underlying the frequent cerebral desaturations observed in patients is required. To validate these findings on an independent validation data set and further characterise the significant desaturation events it is proposed to test the predictive models in a larger, multi-centre cohort of extremely preterm infants. Thus, Cork extend their invitation to other centres to participate in this post hoc analysis. Secure data transfer systems would be established to permit safe transfer of anonymised NIRS data. It is estimated that NIRS data from 100 patients (12.5%) would be required to test the robustness and establish the accuracy of the predictive models.

Discussion:
It is asked whether a specific NIRS device is needed. Many centers use Oxyprem, but this is not the device used in Cork. Gene says he needs to check with the engineer. Some centers may only have a frequency of data points every 30 seconds, which is fine to participate. It is good if the saturation is recorded as well, but not a criterium. They will not correct for saturation changes. Gorm says its possible to do a power calculation for the predictive values. It is asked whether data analysis could be done decentralised to easy data management. A possibility is to draw a new data management contract, to get a subset of the pseudoanonymised data from Copenhagen so the statistic could be done in Cork.

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

Proposal:
Treatment based on NIRS monitoring for extremely preterm infants during the first 72 hours of life will decrease the mean white matter abnormality score at 40-44 weeks of postmenstrual age. This ancillary study aims to 1) Evaluate the impact of NIRS monitoring on the white matter evaluated through brain MRI validated scores (Kidokoro WM injury Score) at 40-44 weeks of PMA and 2) Evaluate the impact of NIRS monitoring on intraventricular and cerebellar hemorrhage evaluated through brain MRI at 40-44 weeks of PMA compared with cranial US until 36 weeks of PMA.

Discussion:

More centers are welcome to join the study if they perform routine MRI at term age. Some Polish, Greek and Italian centers also do term MRI. Monica argues that it was a challenge to analyse the MRIs in SafeBoosC-II (where MRI was part of the data collection and readings were done centrally) because of the difference in scanners and image quality. It may be possible to make an extra module in OpenClinica where the MRI scores would be reported. Furthermore, it may require new parental consent to conduct this study in some countries.

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

Proposal:

This study sets out to investigate the pressure-flow cerebral autoregulation (CAR) by coherence and transfer function gain in the infants with available data randomized to NIRS monitoring. The hypothesis is that during transition in extremely preterm infants, the pattern of the cerebral autoregulation curve will be significantly different in infants with an adverse outcome (any IVH, cerebellar haemorrhage, PVL on CUS) compared to infants with a normal outcome (normal CUS).The secondary hypothesis would be to compare different mathematical models for cerebral autoregulation to define the better method.

Discussion:

It is clarified that the data needed, apart from the SafeBoosC-III data, for this study is continuous rScO2 values with sample frequency 1/30 Hz or higher, continuous SaO2 values with sample frequency 1/30, continuous S/M/D ABP values with sample frequency 1/30 Hz or higher, all three within the in first 72 hours after birth. Two samples a minute are required as a minimum. Some other centers may have this information, but it is proposed that an invitation is sent to all centers in the consortium, to ask if anyone has gathered this data. Furthermore, it is asked what kind of

matemathical models will be compared, as many algorithms are used locally. Liesbeth clarifies that it should be possible to include local algorithms.

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

Proposal:

Mechanical ventilation (MV) has been associated with reduced cerebral blood flow as compared to breathing spontaneously in preterm infants. This may suggest a smaller margin of safety against cerebral ischaemic hypoxia. In preterm infants, peri-and intraventricular and cerebellar haemorrhage is relatively common in the first week of life, whereas ultrasound scanning later in the clinical course may show cystic periventricular leucomalacia, post haemorrhagic ventricular dilatation, and cerebral atrophy. Mechanical ventilation, particularly mechanical ventilation for many days, may contribute to this. We hypothesize that the risk of a diagnosis of late brain injury is twice as high in infants who was mechanically ventilated compared to those who were not. Given the expected distribution of variables in the dataset, the statistical power to detect this at $p<0.05$ is likely to be above 95%.

Discussion:

It is argued, that there is very little data to interpret the pathophysiology of late brain injury (only variables of mechanical ventilation yes/no and days of mechanical ventilation are collected). Gorm clarifies that the aim is not to investigate the pathophysiology. Furthermore, it is suggested if it is possible to do a subgroup analysis with respect to the mode of mechanical ventilation, however we unfortunately do not have data on this.

Meta-analysis of General Movement Assessments(GMA) conducted in neonates included in SafeBoosC-III

The hypothesis of the ancillary study is that surviving preterm neonates in the experimental group show better results in Global-GMA at term age compared to surviving neonates in the control group. The protocol is available at safeboosc.eu (SafeBoosC-III → Secondary and ancillary studies). This ancillary study has already been approved by the steering committee but if any center does GMA assessments at term age, and are interested to join, please contact Gerhard Pichler, Graz (gerhard.pichler@medunigraz.at)