Minutes from SafeBoosC III Steering Committee Meeting – 23rd of November 2020

Attendees: Hans Fuchs, Gunnar Naulaers, Jonathan Mintzer, Janus Jakobsen, Monica Fumagalli, Tomasz Szczapa, Jakub Tcakzyk, Simon Hyttel-Sørensen, Ana Vilan, Eugene Dempsey, Mathias Lühr Hansen, Gorm Greisen, Marie Rasmussen, Christian Gluud

Apologies: Cornelia Hagmann, Adelina Pellicer, Saudamini Nesargi, Siv Fredly

Absent: Guoquiang Cheng, Gerhard Pichler, Gabriel Dimitriou, Ebru Ergenekon, Anne Marie Heuchan

Trial status update from Copenhagen - Mathias
Overall, the trial is progressing well. Currently, 59 centres are open for randomisation. Centres from the UK, Ireland and Norway, as well as additional US centres are expected to start randomising within the next couple of months. The randomisation rate has been stable during the past three months (average 2.02-2.19 patients per day from September through November) and more than 600 patients have been randomised. At this pace, we will reach our sample size in the beginning of 2022. Data completion is also good. Reminders on data completion will be sent out more frequent the next two months, due to the planned first interim analysis, which will be conducted in February.

Updates on trial execution, by national coordinators

Jonathan Mintzer – United States
The Cerebral Palsy Alliance Research Foundation (CPARF) grant has been awarded with 175.000 USD. Therefore, an additional 5-6 US centres will be able to participate. Jonathan expect that at least four additional US centres will be up-and-running before March 2021.

Hans Fuchs – Germany
Five participants have been randomised in Freiburg. No additional German centres will participate.

Jakub Tzackub – Czech Republic
One centres is randomising in a good tempo, and the other centres is finally progressing with trial preparations, as the bureaucratic issues seems to have been solved.

Monica Fumagalli – Italy
Three centres are open for randomisation and two have already randomised. A fourth centre in Rome is expected to open for randomisation soon.

Simon Hyttel-Sørensen – Denmark
All four centres are open and have all randomised participants

Ana Vilan – Portugal
One centre from Porto is expected to participate. However, they still need to complete a few trial preparation tasks. Furthermore, they do not have many preemies in these times.

Tomasz Szczapa – Poland
Seven centres are currently are open for randomisation, whereof four have randomised participants.

Ireland – Gene
Cork is expected to start randomising in the near future, and two more centres are expected to follow.

Gunnar Naulers
All six centres are open for randomisation whereof five have randomised participants

Gorm reminds the steering committee that we are still conducting the ethics study. To our knowledge, the SafeBoosC-III trial is the first in neonatology to utilize different consent methods across participating countries. The objective of the study is to describe the decision process made by investigators and review committees and furthermore to describe and analyse concerns or complaints that may arise during the trial. Therefore if investigators run into problems in relation to the consent procedure, raised by clinicians or parents, they are encouraged to inform us.

When will we close the door for new hospitals and how 3.0 - Gorm
Currently, 10-15 sites are expected to start randomisation within the next 3-4 months. Therefore newly randomising centres may not be able to randomise as many participants as required per the protocol (30 patients). Janus (CTU) points out that there may arise statistical problems, when having many small sites providing few outcomes (death or severe brain damage).

Enough members (n=12, >50%) of the steering committee (n=22) are present to constitute a quorum. The members votes in favour of not including any new centres that are not already a part of the SafeBoosC-III consortium. However, if new centres are added to the US participating list due to the newly granted CPARF funding, such new centres will be accepted.. Furthermore, centres which are preparing to participate will be adviced to start randomising no later than end of March 2021.

Protocol amendments – when? (Protocol version 1.2.3) – Gorm and Mathias
Small but not substantial amendments are needed in the protocol. Since these are minor, the protocol will be resubmitted once all centres are randomising, i.e. after 1st of April 2021.

SafeBoosC IIIx
Gorm, Mathias and Marie presented a possible future trial – the SafeBoosC-IIIx trial. The objective of this trial is to evaluate the benefits and harms of clinical care with access to cerebral NIRS in order to reduce cerebral hypoxia during mechanical ventilations, compared to clinical care without access to cerebral NIRS monitoring in neonates. Inclusion criteria is gestational age more than 28+0 weeks, postnatal age less than 28 days and requiring any type of mechanical ventilation. The hypothesis is that the intervention will decrease a composite outcome of death or survival with moderate to severe neurodevelopmental impairment at two years of age.

The steering committee discussed several aspects of this study design which raised several concerns. First of all, the population will be very heterogenous although they all have a common risk of brain injury. Secondly, concerns were raised regarding participants undergoing surgery, since this aspect will require involvement of the pediatric anesthesia department in participating

centres. A potential problem could also be a shortage of devices, since some centres don't have more than two NIRS devices, however OxyPrem is interested in continuously supporting centres with oximeters. Simon Hyttel-Sørensen also proposed the idea of conducting a threshold trial, where patients would be randomised to different hypoxic thresholds. The Steering Committee agreed that preparations towards a new possible trial should proceed and therefore, the planning will continue. More details will be presented on the next meeting in January.

The SafeBoosC-III app – Marie

An app for clinicians involved in the randomisation and care of participants in SafeBoosC-III has been developed. It is meant as a convenient handbook to answer trial related questions such as eligibility criteria, hypoxic thresholds and contact information for the emergency randomisation.. No user registration is required and furthermore, no data is collected from the app. It is already available for Android, by searching for SafeBoosC in Google Play. Once it is available in App Store, the steering committee will be notified and will be given two weeks to review the app, before it is distributed to the rest of the investigators.

The COVID-19 EP study – Marie

The study investigating the admissions of extremely preterm infants during the COVID-19 lockdown in 46 NICUs of the SafeBoosC consortium, has been submitted to PlosOne. There was no significant difference between the number of EP infant admissions during the three most rigorous lockdown months of the COVID-19 pandemic in the spring of 2020, compared to the corresponding three months in 2019 (n=428 versus n=457 respectively, p=0.33). There were no significant changes within individual geographic regions, and no significant association between the level of lockdown restrictions and change in the number of EP infant admissions (p=0.334). The study is available on the preprint server MedRxiv:
https://www.medrxiv.org/content/10.1101/2020.10.02.20204578v1