SafeBoosC III steering group committee meeting the 9th of September 2019

Present: Adelina Pellicer, Ebru Ergenekon, Monica Fumagalli, Gunnar Naulaers, Jakub Tkaczyk, Gerhard Pichler, Simon Hyttel-Sørensen, Jonathan Mintzer, Janus Jakobsen, Gabriel Dimitriou, Tomasz Szczapa, Gorm Greisen, Mathias Lühr Hansen

Apologies: Cornelia Hagmann, Gene Dempsey

Missing: Cheng, Olivier Claris, Siv Fredly, Ana Vilan, Anne Marie Heuchan

News from Rigshospitalet, Copenhagen

Web-based training and certification status

Training opened up 20th of June 2019 at www.trialeducation.info. The full training program is now available in English, Chinese, Turkish, Spanish and German. Czech, French and Polish versions will also come. So far, 20 sites have sent us the number of doctors and nurses on the delegation and training log and have gotten access to the training program. 175 doctors and nurses have started training. We plan to monitor and report certification rates for each site at 0, 1, 3 and 6 months after beginning of randomisation. Investigators who have participated in the development of the training program, will be invited to participate.

Randomisation status

First patient was randomised 27th of June at Rigshospitalet. 16 patients have been randomised and 3 Spanish, 1 Danish and 1 Czech site have started to randomise. 40 departments have REB/RB approval

Status on trial preparations from national coordinators

Adelina Pellicer – Spain

Seven out of 14 participating NICUS have ethics approval, and three have started to randomise. Adelina will contact the remaining NICUs regarding their future interest in SafeBoosC participation. Some delays are to be expected, due to issues and misunderstandings regarding the collaboration agreement. Adelina has obtained funding to cover GCP monitoring, but not patient insurance, which was not a requirement by the ethical committee.

Ebru Ergenkon - Turkey

Have received funding to cover local GCP and other expensen. Five units will participate and most have signed the collaboration agreement/EU contract

Gabriel Dimitriou– Greece

Four sites will participate, all have gotten ethics approval. The collaboration agreements will be signed by the PI's but due to legal regulations it is delayed. Patient insurance will be covered by individual sites. A question was raised regarding if patient insurance was necessary. Gorm clarified that it is not required by the trial and that the clinical responsibility lies with the local PI - it is up to the individual sites to decide on insurance.

Gerhard Pichler - Austria

Participating with one NICU. Insurance is necessary, since their ethics committee sees this study as a device trial. They have ethics approval and insurance. The contract is currently with the legal department.

Gunnar Naulers – Belgium

Participating with five units. Many centers in Belgium are running the BeNeDuctus trial and therefore cannot participate in SafeBoosC. They are expected to receive funding; however this requires that liability checks are performed at each site. Gunnar will partake in this inspection. The approval from the ethical committee is not going to be long, they can submit once funding is officially obtained. The local GCP center will be responsible for the monitoring.

Jakub Tkaczyk – Czech Republic

Two units will participate, one is already randomising. Regarding the other center, the collaboration agreement is in the process and they are waiting on the ethics approval. Will start training staff soon. It is not required to insure their patients and the GCP visit will be done by local people – they expect to start randomising during autumn.

Jonathan Mintzer - US

Initially had 25 interested sites, but due to lack of funding, there are now 10 sites. 7 of these sites are able to proceed without funding. Three have submitted for IRB approval. The remaining 4 are all planning submission soon but are working on getting a contract with Masimo, but this is a longer process due to each center must have their own contract with Masimo, and the negotiations are rather slow with the representative – the remaining three sides cannot proceed at an institutional level without funding for the trial and have applied for this, but this may take months.

Some centers are afraid that they cannot cover the costs of GCP monitoring. However, they are trying to find a pragmatic solution. Realistically 5-7 sites will be randomising within the next months. Gorm shares his experience from Copenhagen, where one nurse internally is doing the GCP monitoring and is using her clinical working hours to do this, which has solved the Copenhagen GCP issue.

Monica Fumagalli – Italy

6 participating NICUs. Ethical approval has been obtained in Milano, but the other centres are still waiting for approcal. Collaboration agreements must be translated into Italian and this delays the process a bit. GCP monitoring is expensive in Italy, and they are therefore going for a similar solution as in Copenhagen.

Simon Hyttel-Sørensen – Denmark

Rigshospitalet has been randomizing since June Two others NICU's are finalizing documents and waiting for NIRS monitors from OxyPrem. The fourth site is unsure whether they will proceed. Hopefully within the next couple of months, three NICUs will be randomising.

Thomaz Szczapa– Poland

Ethics approval has been obtained in Poznan, covering all eleven Polish sites. Collaboration agreements are being prepared. The Polish centers expect to use Oxyprem, and five sites have already made an agreement with Oxyprem. GCP is not funded, so they will use a paramedic with GCP training to do the monitoring. Polish staff are currently training, and apart from the web-based training program, they will train their staff with traditional classroom teaching. Planning a national meeting for all PI's in November, where Gorm and Mathias will also participate.

Janus Jakobsen (Copenhagen Trial Unit) – it is very important that we acknowledge that the monitoring might be harmful. As trialists it is essential to be transparent when communicating with patients about not knowing if this intervention is harmful. Gorm elaborates on this, clarifying that it is essential that we stress that we don't know the outcome of this.

Consent - Spain has obtained ethical approval for deferred consent and three out of four of their infants are randomised with deferred consent. Czech Republic also has obtained approval for deferred consent. An ancillary study will be conducted collecting data on the consent methods used in SafeBoosC.

Copenhagen funding and investigator meeting

The application to Elsass foundation was turned down, thus Copenhagen hare still lacking money. However, this will not affect trial conduct – and they will continue to apply to other funds. The Steering Committee

was asked about their view on planning another investigator meeting in Copenhagen and the value of this. Adelina (Spain) expresses that these meetings are very helpful and that she finds it important to keep this tradition. This is the way to move forward with the project and a great stimulation.

Indian participation in SafeBoosC

Five Indian sites want to participate in the trial. They have no experience with NIRS but very eager to learn. Mathias has had meetings with three NICU's, who state that they can be ready within six months and will be using OxyPrem. They mentioned however, that they have a higher mortality rate than what we have based the power calculations on. Janus Jakobsen clarifies that this will only strengthen the power of the trial. There is also an issue regarding loss to follow-up, due to parental early discharge of the baby. This is due to, that hospital costs are expensive and some parents cannot afford it. Even though the loss to follow-up may be equivalent in the two arms, missing data presents a large problem to the planned sensitivity analysis as well as addressing the missing data in best-worst and worst-best case scenarios. All of this is described in the Statistical Analysis Plan. A question was raised that if the loss to follow-up rate was too high, they could possibly be included in a sub-study, but Janus Jakobsen clarifies that this is not a possibility. Gorm expresses his interest in including India in SafeBoosC and how it may strengthen the external validity of the trial. Many important arguments were voiced regarding the inclusion of India, and Mathias will now proceed with investigating the numbers of early withdrawal and loss to-follow up.