SafeBoosC III September newsletter and Minutes from jENS meeting

Dear investigators

Welcome to the September version of the SafeBoosC III newsletters as well as Minutes from the SafeBoosC meeting at jENS in Maastricht. It contains important information, so please read it carefully.

Status on funding
We are still applying for money (275,000 Euro) to cover expenses to Copenhagen Trial Unit (data management and statistics), future investigator meetings in Copenhagen and salary for Mathias' fourth year as trial manager. Elsass foundation, which granted us, 350,000 Euro to kickstart the trial, declined our latest application – they told us that we could apply again, when some of the expenses were covered elsewhere. We have therefore sent funding applications to MTHP-foundation, Lundbeck foundation and Sven Andersen foundation and expect answers during the fall.

Status on contracts
The process of getting the collaboration agreement approved by legal departments, seems to be time consuming in some hospitals. Thus, only 11 NICUs have been able to sign and return the collaboration agreement up until now. We therefore urge you to start the process of getting the collaboration agreement approved in your hospital, as soon as possible.

2nd SafeBoosC Investigator Meeting in Copenhagen, January 2020
The invitation for the second SafeBoosC III investigator meeting in Copenhagen from 23rd to 24th of January, has been sent out. As for the first meeting, we can cover local costs but not travel expenses. For more information on the agenda as well as practicalities, please see the invitation:

https://www.rigshospitalet.dk/english/departments/juliane-marie-centre/department-of-neonatology/research/SafeboosC-III/Documents/invitation-for-2nd-investigator-meeting.pdf

Deadline for registration will be 1st of of December.

Participation of Indian NICUs
In the beginning of September, we received a declaration of interest from Indian NICUs, and at the latest steering committee meeting, their participation was approved by voting. Saudamini Nesargi from St Johns Medical College Hospital in Bangalore will be national coordinator. She is now in the process of recruiting Indian sites as well as applying for ethics approval. A warm welcome!

Certificate for completion of web-based training is ready!
A certificate for completion of the SafeBoosC online training program is now available and will be sent out to all staff members that have completed the relevant training modules.

OpenClinica does not support mobile devices
Since validation of data entries into the eCRF does not work on mobile devices, we have decided to disable access to OpenClinica through mobile devices, including tablets. This is done to avoid accidently wrong data entries (for example entry of a 10 gram birthweight, which is normally not possible due to validation measures)

Layer of protection between sensor and the babies' skin can affect StO_2 values
In June we tested the effect of not removing the white cover from an adhesive INVOS neonatal sensor, when measuring cerebral StO_2, in a blood-lipid phantom. We found that the hypoxic threshold decreased by 3% when the cover was kept on the sensor, and we suspect that other layers of protection could have a similar, or even larger effect. Thus, we recommend all investigators to avoid protection layers between the sensor and the skin. We expect the results to be published in "Advances in Experimental Medicine and Biology".

Update of trial documents since August

- SOP: list of data needed for eCRF entry (https://www.rigshospitalet.dk/english/departments/juliane-marie-centre/department-of-neonatology/research/SafeboosC-III/Documents/sops/list-of-data-needed-for-ecrf-entry-050919.pdf)

Minutes of SafeBoosC meeting at jENS, September 19th, 2019

Attendees
We forgot to circulate an attendees list during the meeting. Therefore, the list below is constructed from the pre-meeting attendee list. We were happy to see the large number of last-minute drop-ins and apologize to those not mentioned below.

Attendees: Karen Tanja, Marianne Hauf, Manuel Schmid, Jan Miletin, Afif El Khufash, Gunnar Naulaers, Gitte Hahn, Gorm Greisen, Marie Rasmussen, Mathias Lühr Hansen, Gitte Zachariassen, Karen Fairchild, Lina Chalak, Miguel Alsina, Adelina Pellicer, Isabel De Las Cuevas, Ruth Del Rio Florentino, Heike Rabe, Siv Fredly, Hallvard Martin Reigstad, Merih Cetinkaya, Angelika kontou, Maria Farini, Virgilio Carnielli, Jan Sirc, Roland Hentschel, Sotiris Fouzas.

A status on randomisation and preparations
Mathias started the meeting by updating the attendees on randomisations and preparations. So far, 20 babies have been randomised across five NICUs (three from Spain, one from Denmark and one from Czech Republic). An additional 38 NICUs have obtained REB/IRB approval. Despite the present randomisation rate being under the trend line (randomising 1600 babies in 24 months), the active sites are randomising with a rate as we had hoped for.

Mathias explained that this trend was also seen in SafeBoosC II, but that the randomisation rate increased after the first four months (fig 2). However, the enrolment period was also extended from 12 to 18 months (50%) which we want to avoid for SafeBoosC III.

A status on web-based training and monitoring of certification rates
Marie Rasmussen updated the attendees on the fact that 21 NICUs have been given access to the training program, 175 staff members have started training and the modules are available in English, German, Spanish, Chinese and Turkish, with more languages to come. Marie explained that she is in the process of monitoring certification rates and will do this continuously for the next 12 months. She plans to write a manuscript on the process of training and certification and will invite the investigators who have developed the training modules to participate.

Experience with randomising babies
Rigshospitalet, Copenhagen, Denmark – Gitte Hahn
Gitte explained that in Copenhagen, randomisation opened mid-June and so far, nine babies have been randomised. They are using prior informed consent, since the use of deferred consent was not allowed. The Ethics Committee decided that the enrolment window of six hours was sufficient to obtain prior consent. However, they accepted that only one parental signature was enough. This has simplified the consent process and so far, the enrolment window of 6 hours has not been an issue. Only one parental couple have declined participation.

La Paz, Madrid, Spain - Adelina Pellicer
Adelina explained that five babies have been randomised in La Paz since randomisation opened mid-July. She further elaborated that, due to their experience from SafeBoosC II, implementation of SafeBoosC III has been easy. Staff members are especially keen about the pragmatic design of SafeBoosC III. Regarding consent, La Paz can use all three methods (prior informed consent, deferred consent, opt-out). As in

Copenhagen, only one parent needs to sign the consent form. So far, only prior informed consent has been used. A question was raised on how La Paz deals with running multiple trials simultaneously. Adelina responded that so far, there are no competing trials and when this situation occurs, babies will be randomised in SafeBoosC using deferred consent if necessary.

Hospital Clinic de Barcelona (Maternitat(, Spain – Miguel Alsina
Clinic de Barcelona have randomised three babies since randomisation opened in the beginning of July. Miguel explained that preparations have been easy, due to the hard work and preparations done in La Paz. As in La Paz, Clinic de Barcelona can use all three consent methods. So far, they have used deferred consent and no issues have been raised by parents. Miguel mentioned that since they have less experience with NIRS than La Paz, it has taken some effort to implement the intervention in their NICU. However, most staff have completed the web-based training and certification, which have been very helpful.

Institute for the Care of Mother and Child, Prague, Czech Republic - Jan Sirc
Jan Sirc explained that since randomisation opened less than two weeks ago, the first baby has been randomised. They can use deferred consent as well. Jan also mentioned that they use INVOS monitors and have received local funding from Medtronics. However, this funding cannot be used to cover equipment.

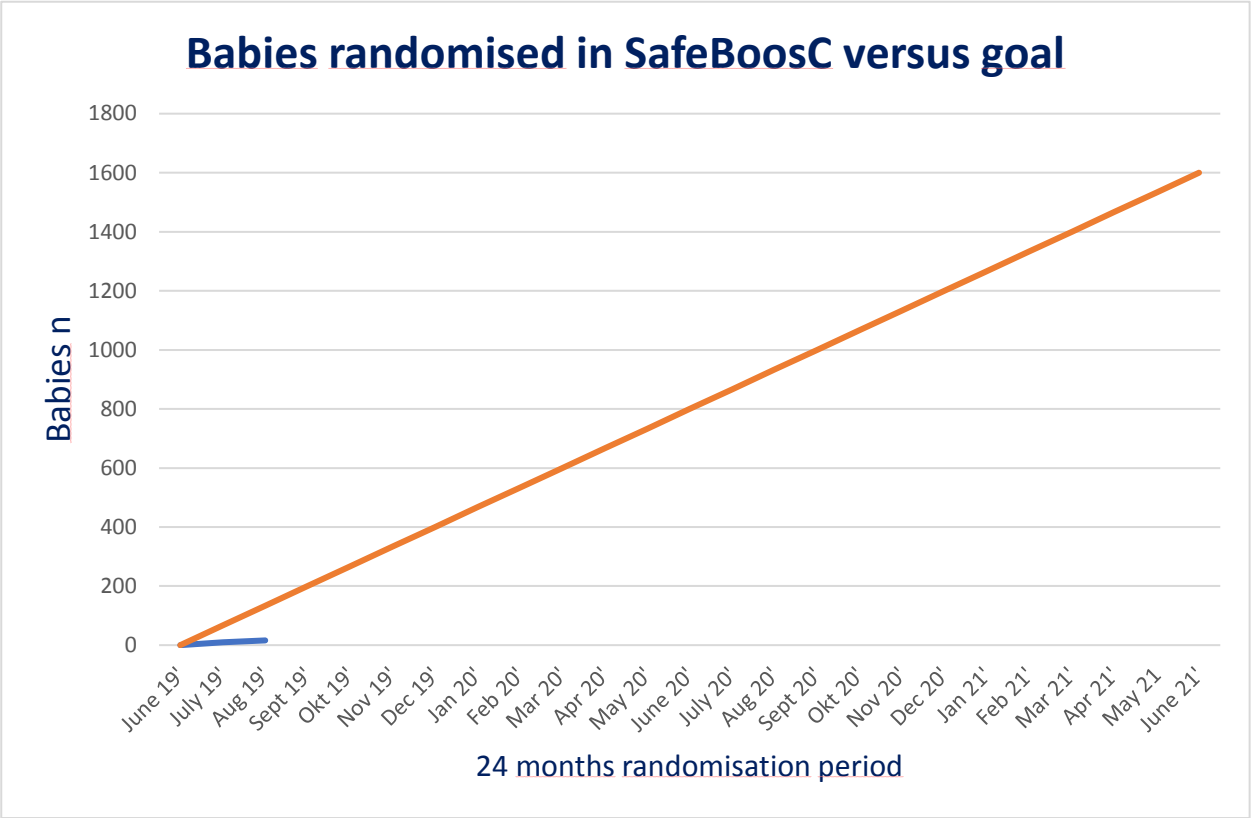
Discussions regarding trial preparations
A question was raised whether organisations/foundations who have funded and supported individual countries and NICUs will be mentioned in the final publication. Gorm answered, that all funding for SafeBoosC will be mentioned in the publication, including local sponsoring.

At last, Gorm mentioned that patient insurance – if needed – should be covered by local money, since Copenhagen cannot cover local expenses. Even more important, the interventions are based on cerebral oxygenation monitoring as well as other clinical information and decided by the local clinical staff. Thus, it does not really make sense that Copenhagen cover indemnity for such decisions. It is different from traditional drug trials where all study procedures are at the control of the sponsor. He also mentioned that SafeboosC is not a device trial in the strict sense, since only devices that are approved for clinical use are used, thus insurance might not be necessary. It is not necessary in Copenhagen.

Regarding data, Gorm also mentioned that Copenhagen will be data controllers once data is entered into OpenClinica, but NICUs can get a copy of their own data at any time. For that purpose, and for the purpose of giving data access to the GCP monitors, a data management contract is needed between Copenhagen and hospitals in non-EU countries. This is paradoxical in the sense that it is about that hospital's own data.

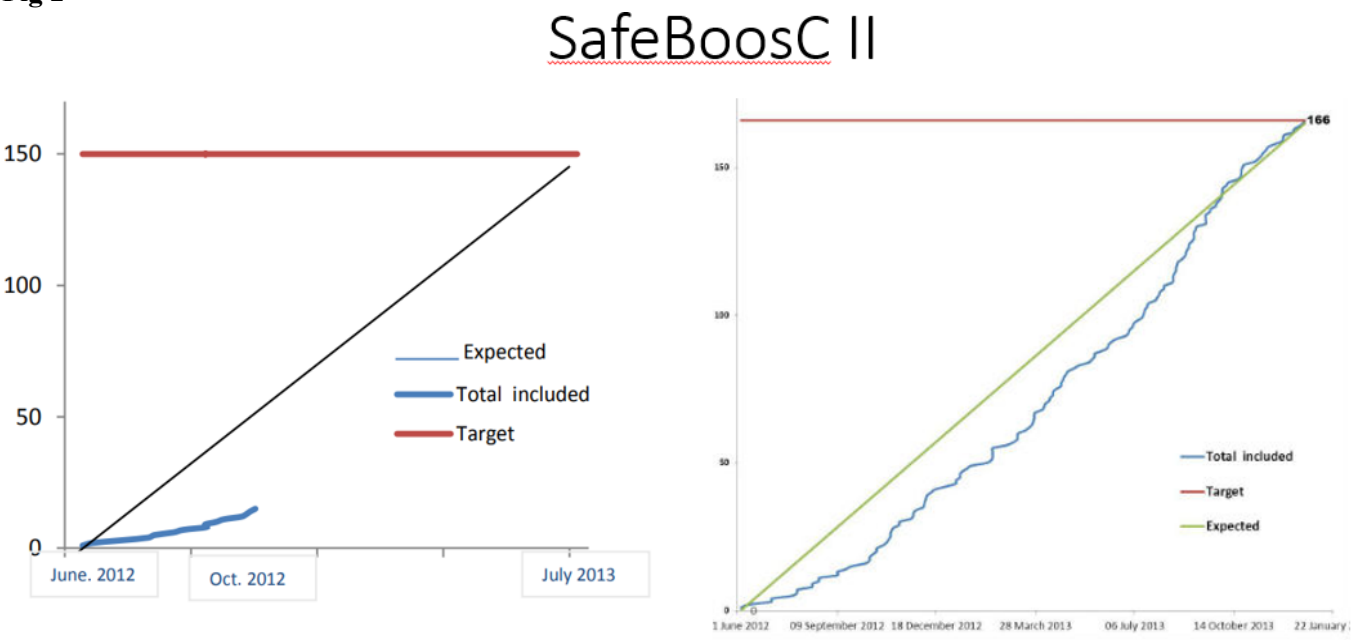
Any other business.
As there were no more comments or questions, the meeting ended before schedule, permitting some informal group discussion, before the participant went back to the surrounding jENS conference.

Fig 1



Orange line is the trend line for randomising 1600 babies within 24 months. Blue line is the present randomisation rate.

Fig 2



To the left: black line is the trend line for randomising 150 babies within one year. The blue line is the present randomisation rate after four months into the enrolment period.

To the right: green line is the trend line for randomisation 166 babies over 18 months. The blue line is the randomisation from the beginning and until the end of enrolment for SafeBoosC II.