SafeBoosC-III newsletter April 2021

Dear investigators

Welcome to the April 2021 issue of the SafeBoosC-III newsletter.

New answer possibility to the question "When has cranial ultrasound been performed?"
Up until last week, there were four answer possibilities to the question "When has cranial ultrasound been performed" in the eCRF: 1) early cUS (before eight days of life), 2) late cUS (after 35 days of life), 3) both early and late cUS, and 4) the baby was never scanned. This means that if a baby was solely scanned between 8 and 35 days of life, there is no relevant answer possibility. In the beginning of April, an investigator notified us about this issue.

Initially we included the data point on timeliness of cranial ultrasound scans, to try an quantify the quality of the primary outcome, since some brain injury events might be missed, if early or late scans are absent. However, scans between 8 and 35 days are still valuable, and a relevant answer possibility should be available. This is a mistake from our side while designing the eCRF.Therefore, we have added a new answer possibility: "Only cUS between 8 and 35 days of life".

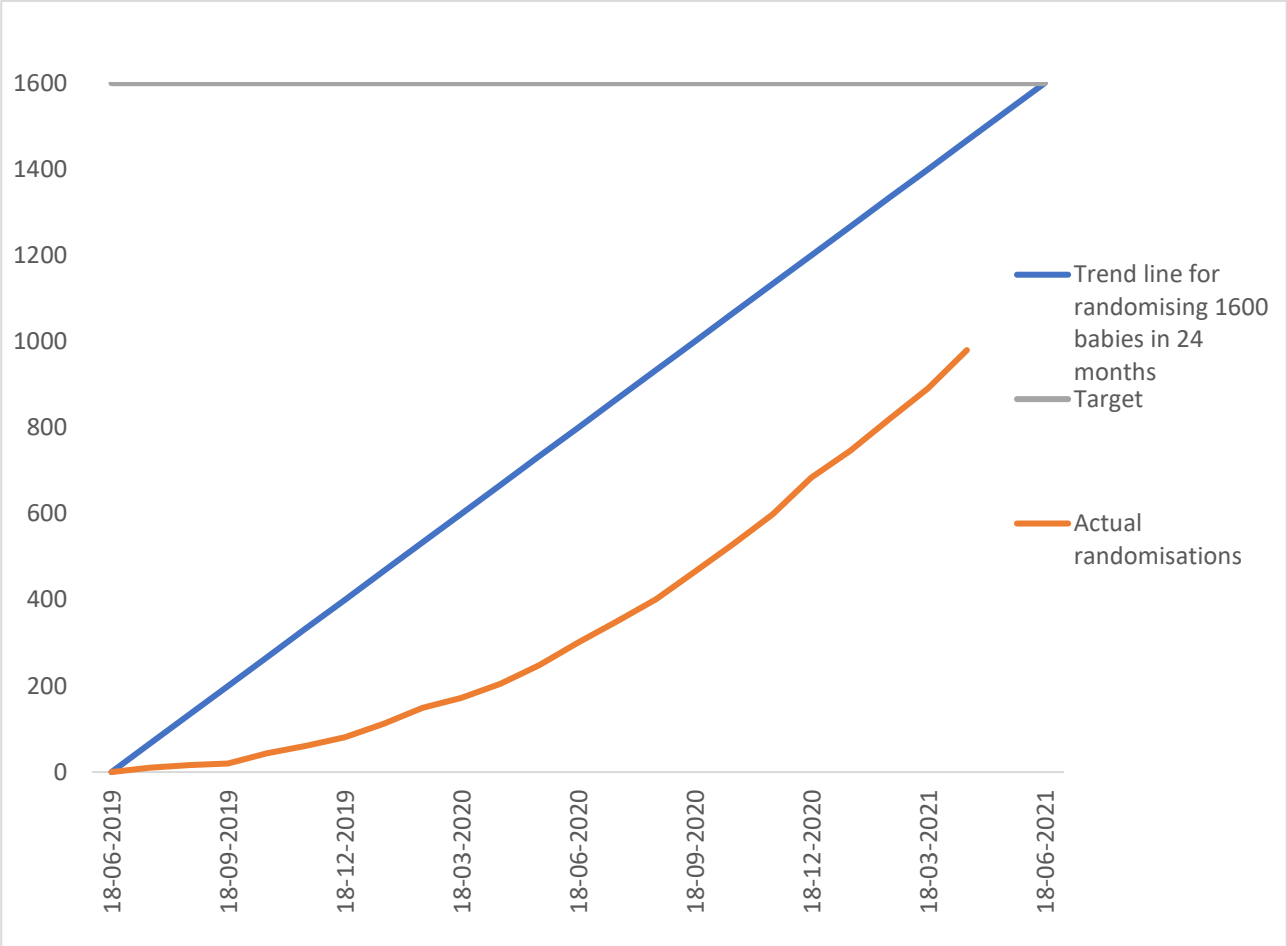
Updated GCP documents
Some investigators reported that it was unclear, if babies that have not reached 36 weeks PMA should be included in the GCP monitoring visits. We would like to clarify that **only** babies that have reached 36 weeks PMA (or died before the data of the monitoring visit), should be included in the monitoring visits. This has been decided since it is not possible to source data verify mortality statu, if the babies are alive and have not reached 36 weeks PMA, since this is time point for outcome assessment. This has now been added to the GCP monitoring plan and report template, available on safeboosc.eu:

https://www.rigshospitalet.dk/english/departments/juliane-marie-centre/department-of-neonatology/research/SafeboosC-III/Sider/good-clinical-practice.aspx

Status on randomisations and trial preparations
As of the 18th of April, a total of 980 babies have been randomised across 68 centres (fig. 1). This corresponds to 2.87 randomised babies per day, which is a significant increase in the randomisation rate when compared to previous months (2.55 in March and 2.35 in February), and the highest rate so far. Furthermore, one new centre has started randomisation. We expect that five more centres will start randomising within the next months.

Based on the randomisation rate across the last three months, we will complete recruitment before the end of 2021.

Figure 1. Randomisations in the SafeBoosC-III trial



In **table 1** below, you will find an overview of the randomisations in each of the 68 centres up until 18th of April 2021. You will also find an overview of the average number of randomisations per month for each centre during the time period, where the hospital has been open for randomisation.

Table 1. Open centres, randomisations and average randomisations per month per centre up until 18th of April 2021.

Country	Centre	Randomised since	Randomisations	Average randomisations per month
Austria	University Hospital Graz	Jun 2020	13	1.3
Belgium	UZ Leuven	Jun 2020	25	2.5
Belgium	Liege Rocourt	Jul 2020	13	1.2
Belgium	Grand Hospital de Charleroi	Jul 2020	6	0.5
Belgium	AZ St. Jan University Hospital Brugge	Sep 2020	9	1.3
Belgium	CHU Tivoli	Sep 2020	11	1.6

Country	Centre	Randomised since	Randomisations	Average randomisations per month
Belgium	Liege Citadelle Hospital	Nov 2020	0	0
Czech Republic	The Institute for the Care of Mother and Child	Sep 2019	48	2.5
Czech Republic	Motol University Hospital	February 2021	1	0.5
China	Children's Hospital of Zhejiang, Hangzhou	Jan 2020	3	0.2
China	Children's Hospital of Fudan University, Shanghai	Jan 2020	35	2.3
China	Hainan Women and Children's Medical Center	Mar 2020	0	0
China	Guangzhou Women and Children's Medical Center	Mar 2020	2	0.2
China	Longgang District Central Hospital of Shenzen	May 2020	7	0.6
China	The People's Hospital of Dehong	May 2020	3	0.3
China	Guangxi Maternal and Child Healthcare Hospital, Nanning	May 2020	6	0.5
China	Xiamen Children's Hospital	May 2020	3	0.3
Denmark	Rigshospitalet	Jun 2019	80	3.6
Denmark	Odense University Hospital	Dec 2019	9	0.6
Denmark	Aalborg University Hospital	Mar 2020	10	0.8
Denmark	Aarhus University Hospital	May 2020	11	1
Germany	Freiburg University Hospital	June 2020	7	0.7
Greece	Ippokrateion General Hospital of Thessaloniki	Oct 2019	26	1.4
Greece	University of Patras General Hospital	Jan 2020	9	0.6
Greece	Alexandra Univ. Hospital	Mar 2020	13	1
Greece	University Hospital of Heraklion	Mar 2020	8	0.6
India	St Johns Medical College Hospital, Bangalore	Jun 2020	3	0.3
Ireland	University Hospital Cork	February 2021	8	4
Ireland	Rotunda Hospital Dublin	Pending	0	0
Italy	Fondazione IRCCS Cà Granda Ospedale, Milano	Nov 2019	33	1.9
Italy	Presidio Ospedaliero S. Anna, Turin	Aug 2020	4	0.5

Country	Centre	Randomised since	Randomisations	Average randomisations per month
Italy	Ospedale Fillipo del Ponte, Varese	Oct 2020	4	0.7
Italy	Fondazione Policlinico Univ. A. Gemelli, Roma	Dec 2020	8	2
Norway	Oslo University Hospital	March 2021	5	5
Poland	Medical Center UJASTEK, Krakow	Jan 2020	28	1.9
Poland	Szpital Uniwersytecki, Kraków	Oct 2020	7	1.2
Poland	Warsaw University of Medical Sciences	Oct 2020	8	1.3
Poland	Poznan University of Medical Sciences	Mar 2020	27	2.1
Poland	Specialist Hospital No. 2 in Bytow	Feb 2020	4	0.3
Poland	Wroclaw Medical University	Apr 2020	0	0
Poland	Jan Biziel University Hospital	Sep 2020	0	0
Spain	H. Univ. Juan XXIII de Tarragona Hospital	Feb 2020	13	0.9
Spain	La Paz University Hospital	Jul 2019	61	2.9
Spain	Hospital Clinic de Barcelona	Jul 2019	38	1.8
Spain	University Hospital 12 de Octubre	Jul 2019	46	2.2
Spain	Hospital de Sant Joan de Deu	Oct 2019	24	1.3
Spain	Hospital Clinico San Carlos	Sep 2019	25	1.3
Spain	Hospital Universitarie Puerta del Mar	Oct 2019	17	0.9
Spain	H. Universitario Marqués de Valdecilla	Dec 2019	14	0.9
Spain	H. U. Virgen de las Nieves, Granada	Jan 2020	6	0.4
Spain	C. U. Universitario de Santiago	Jan 2020	0	0
Spain	Hospital Miguel Servet	Apr 2020	0	0
Spain	Hospital de Cruces	Jan 2021	2	0.7
Switzerland	Zürich University Hospital	Dec 2019	37	2.3
Switzerland	Luzerner Kantonsspital	Jan 2020	31	2.2
Switzerland	Geneva University Hospital	May 2020	8	2.1
Switzerland	Lausanne University Hospital	Sep 2020	14	2
Turkey	Gazi University Hospital	Jan 2020	12	0.8
Turkey	Marmara University Hospital	Jan 2020	24	1.6
Turkey	Uludag University Hospital	Jan 2020	23	1.5
Turkey	Kanuni Sultan University Hospital	Jan 2020	11	n/a

Country	Centre	Randomised since	Randomisations	Average randomisations per month
Turkey	Bilkent Integrated Health Care Campus	Jan 2020	30	2
Turkey	Basaksehir City Hospital	Jan 2021	3	1
United Kingdom	Royal Hospital for Children, Glasgow	Feb 2021	4	2
United Kingdom	NHS Lanarkshire Hospital, Wishaw	March 2021	2	2
United States	University of Utah, Division of Neonatology	Jun 2020	13	1.3
United states	Loma Linda University Hospital	Sep 2020	23	3.3
United States	UT Southwestern Medical Center, Dallas	Oct 2020	3	0.5
Total			980	

Publication on the SafeBoosC-III central data monitoring plan and experience so far
A manuscript based on the central monitoring plan and the results from the first three monitoring meetings have been submitted to BMC Medical Research Methodology. All investigators actively recruiting have been listed as non-author collaborators in the manuscript.

We used this model of recognising the contribution of all of you who have randomised children to the SafeBoosC-III trial, without which there would have been no need for central monitoring, nor the chance to develop the semi-automatic system that we present in the article. Your names will appear in the section on 'contributions' which is a part of the manuscript. Medline searches this section for names under the heading 'non-author investigators', to make the Medline system - and Pubmed - associate your name with the article.

So, the article will appear if you search Pubmed by you name and [ir] in square brackets. 'Investigator' indicates an academic, formal and permanent attachment to the project behind the article and 'non-author' reflects the fact that you did not take part in the preparations or submission of the manuscript. We think this is a fair description of the reality and hope that you can agree. For more information see the MedLine page here: https://www.nlm.nih.gov/bsd/policy/authorship.html

As for now, the full central monitoring plan can be found here:

https://www.rigshospitalet.dk/english/departments/juliane-marie-centre/department-of-neonatology/research/SafeboosC-III/Documents/for-professionals/central-monitoring-plan-safeboosc-iii-260820.pdf

Data quality monitoring report
The third round of data quality monitoring was conducted on 2nd of March 2021. In the link below you will find the report.

https://www.rigshospitalet.dk/english/departments/juliane-marie-centre/department-of-neonatology/research/SafeboosC-III/Documents/for-professionals/data-quality-report-march.pdf

The monitoring reports evaluating data quality will be written every third month and the relevant investigators will be contacted with inquiries.

Data completion monitoring report
In the link below you will find the central monitoring report on data completion from April 2021.

https://www.rigshospitalet.dk/english/departments/juliane-marie-centre/department-of-neonatology/research/SafeboosC-III/Documents/for-professionals/data-completion-report-15-apr-2021.pdf

For the end of monitoring and follow-up form, completion of data entries is still good with 97% completion for both forms. Completion of the blinded follow-up form has increased from 91% last month to 92% this month. Completion of the SAR form is 92%, which is the same as last month. Thus, completion rates are still fairly good, despite the number of recruited babies increases. However, as we aim for less than five percent missing data, there is still room for improvement.

Once again, we would like to state that timely reporting is an important part of the quality of the trial and thus we hope you will prioritize these data entries despite your busy daily schedule.

Investigators with missing data entries have been contacted and urged to complete data entries.

The two-year follow-up study
The SafeBoosC-III progresses well, the rate of inclusion is good and quality of the data we receive in OpenClinica is good. Therefore, the Trial Steering Group has decided to engage in a follow-up at two years of corrected age. We call this study SafeBoosC-IIIfu, – fu for follow-up. The first child will reach that point in September this year, and the last child is expected to reach it during the spring 2024.

Last year we asked about the routine follow-up of extremely preterm infants in the hospitals taking part in SafeBoosC-III. A great majority (90%+) routinely follow this group of infants until two years or longer, and a majority (70%+) utilise a formal method to assess mental/cognitive development, such as the Bayley scales of infant development.

So, the plan is to collect information from the clinical records. To increase the reliability as regards the effect of the SafeBoosC-III intervention, the steering group has decided that the principal investigators should liase with a colleague who is blinded to the group allocation of the child (experimental or control) to do the data extraction and enter it into OpenClinica. The steering group also decided to offer non-author investigatorship to these colleagues. This will appear in the contribution section that is part of the manuscript(s) that will report the findings of the SafeBoosC-fu.

Furthermore, we will provide a multi-language web-platform, where the parents can report their assessment of the child' development (we will use the PARCA-R non-verbal cognitive scale) as well as give information on other health issues as well as other concerns of theirs.

The goal is the get the maximum possible follow-up rate. Loss to follow-up is the threat to all studies. Partly due the loss of statistical power, but more due the risk of bias. Loss to follow-up cannot be assumed to be at random, and hence the estimate of the effect of the intervention may be biased. More biased the greater the loss to follow-up.

So, as a principal investigator, you can prepare this work by

1. Identifying the clinical records of your hospital which can be relevant, identify the colleague who can be blinded and do the data extraction, and prepare the workflow, and
2. Maintain your patient list with identifiers and parent contact information. Since parents will get a patient-specific link from us to the web-platform to ensure correct data entry, you will need an email or a mobile phone number to send the link/QR code.

In SafeBoosC-IIIfu, we are planning to draw on all sources of data to reduce the loss to follow-up as much as possible, and hope that you all will do as much as possible to achieve that.

Best wishes
Gorm, Marie and Mathias