SafeBoosC-III - central monitoring

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Contents

Introduction

The data report is generated automatically from data entered into the electronic case report forms (eCRF) related to the SafeBoosC-III trial. Missing data are attended to in another report. The data report is used every third month to monitor quality deficiencies, and noteworthy data deviations. Furthermore, an exploratory Mahalanobis distance will be used to detect potentiel outlier-centres. The data will be examinated by the trial manager and coordinating investigator of SafeBoosC-III and collaborators from Copenhagen Trial Unit (CTU). Any identified quality deficiencies, noteworthy data deviations and outlying centres will be noted in the central monitoring log and discussed with the local investigator. Results from the monitoring will be logged in the central monitoring log.

The protocol for the central monitoring plan and this report is be uploaded to the SafeBoosC-III website (www.safeboosc.eu).

Methods and material

The data report is generated automatically after extraction of data from the eCRF every three months *(data extracted 18th of May 2021)*. Data from centres with less than five included participants will be excluded since systematic errors and flaws will not be identifiable for small sample sizes.

Participants included in SafeBoosC-III are depicted in boxplots for continous data and stacked barcharts for categorical data. Missing data are removed from the output, since these are handled in a separate monthly report. Boxplots are presented with median line and with the interquartile range as hinges. Mean is presented as a diamond.

The data report is generated using R version 4.0.0 (R Core Team, Vienna, Austria) together with Rmarkdown [Allaire et al., 2020]. The code might change during the course of the study, but any changes of data presented and analyses will be approved by the monitoring committee. These changes to the code will be recorded in the central monitoring log.

Quality measures

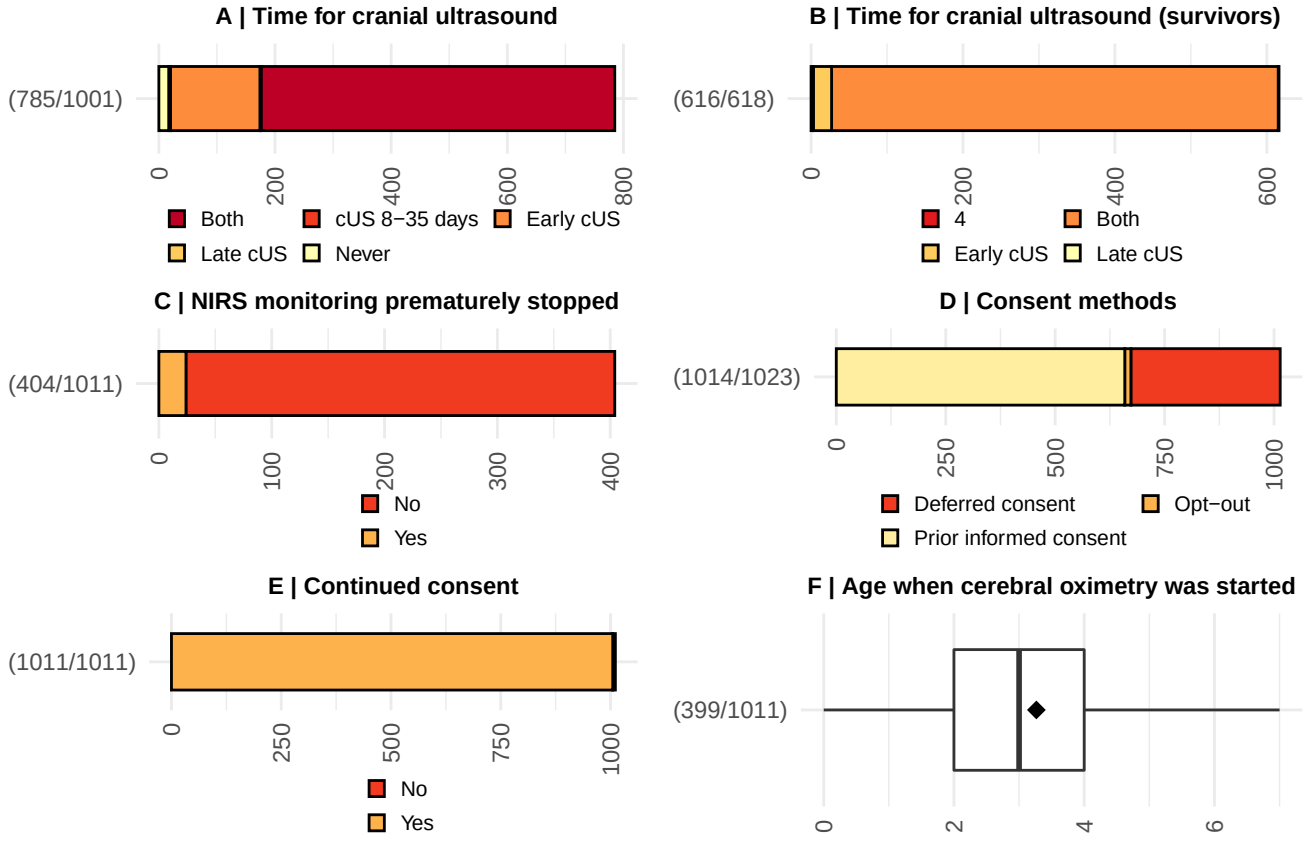

Figure 1 | Stacked barcharts shown for all participants. **(A)** Time for cranial ultrasound for all and **(B)** for survivors (extracted from *F07_cus*); **(C)** proportion of participants with prematurely stopped NIRS monitoring (*E07_prematurenirsstop*); **(D)** types of consent used to enroll participants (*R04_consentform*); **(E)** with continued consent (*E12_parentswithdrawconsent*); and **(F)** a boxplot showing age in full hours when cerebral oximetry was started (*E06_ageinhoursnirs*). Vertical line depicts median, whereas a diamond represents mean.

Randomisation

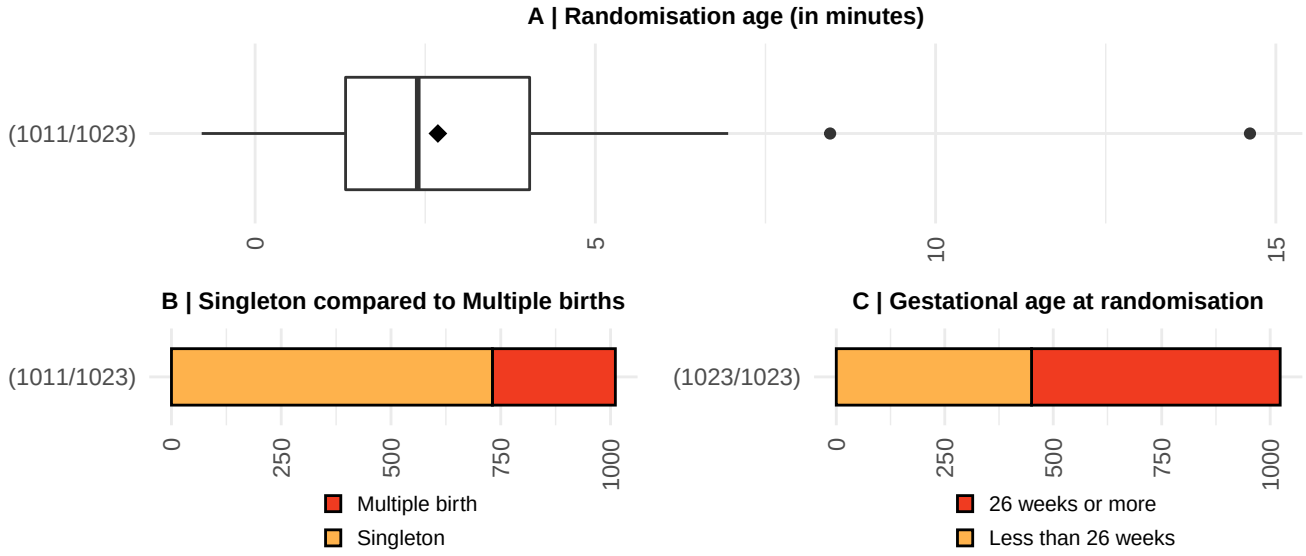

Figure 2 | (A) Age of participants at the time of randomisation in minutes presented using a boxplot. Vertical line depicts median, whereas a diamond represents mean. Stacked barcharts from the 'randomisation' module. **(B)** Proportion of singleton compared to multiple births (extracted from *R02a_singlemulti*); and **(C)** gestational age of participants at randomisation (*R07_galessthan26wks*).

End of monitoring

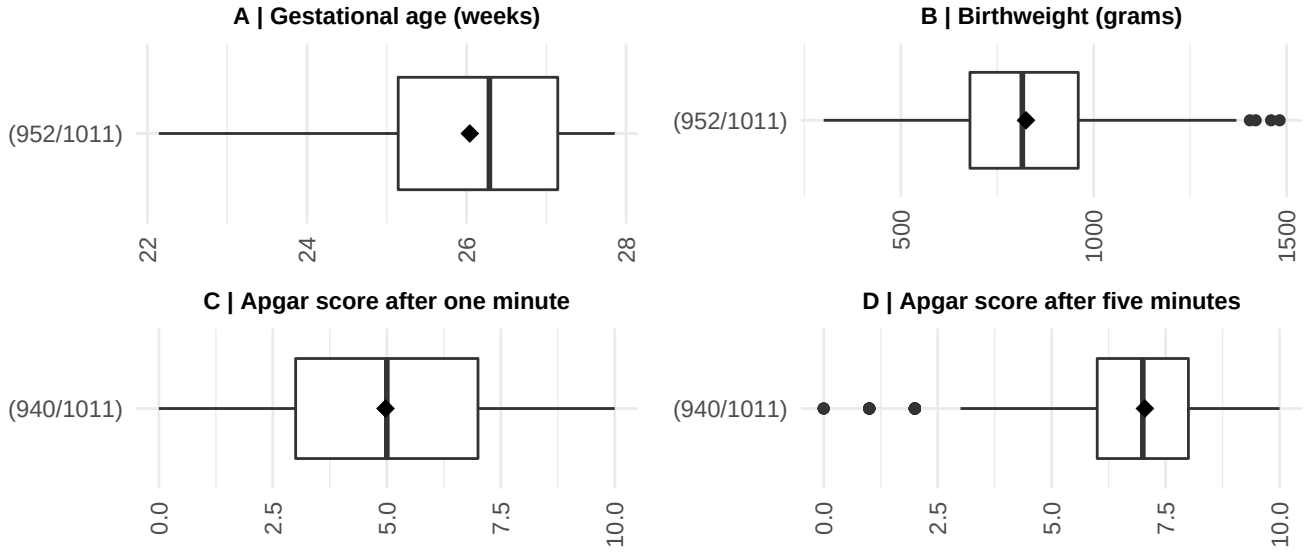

Figure 3 | Boxplots from the 'end of monitoring' module, shown for all participants. **(A)** Gestational age of participants in gestational weeks (extracted from *E01_gestationalage*); **(B)** birthweight in grams of participants (*E02_birthweight*); **(C)** Apgar score for participants one minute after birth (*E03_apgar1min*); and **(D)** Apgar score for participants five minutes after birth (*E04_apgar5min*).

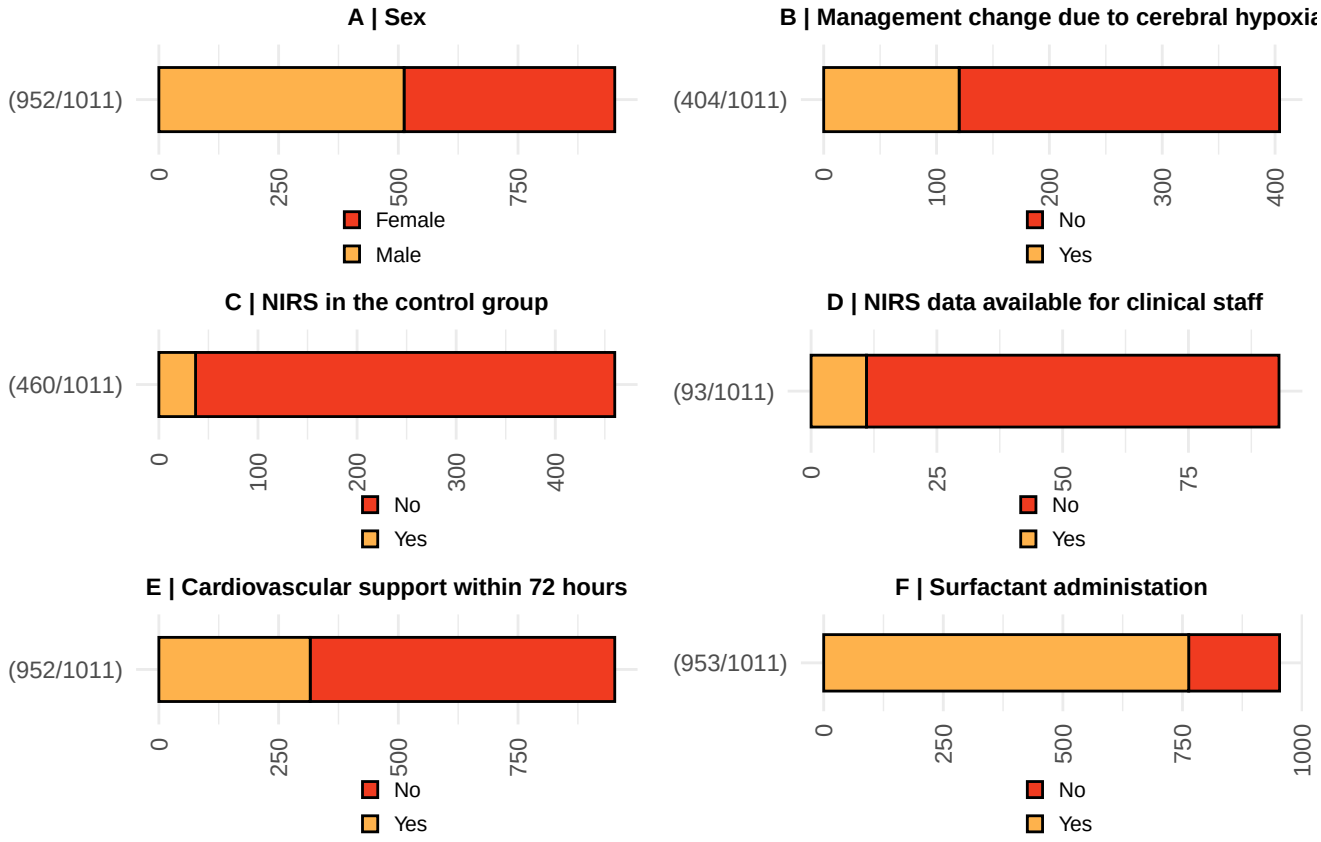

Figure 4 | Stacked barcharts from the 'end of monitoring' module, shown for all participants. **(A)** Sex of participants (extracted from *E05_sex*); **(B)** Proportion of participants with changed treatment due to cerebral hypoxia (*E08_changeoftreatmenthypoxia*); **(C)** with NIRS despite being in the control group (*E11_nirsincontrol*); **(D)** where NIRS was available for the clinical staff (*E11a_nirsdata*); **(E)** who recieved cardiovascular support during the first 72 hours after birth (*E09_cardiovascsupp*); and **(F)** who recieved surfactant administration (*E13_surfterap*).

Follow-up (36 weeks postmenstrual age or discharge to home)

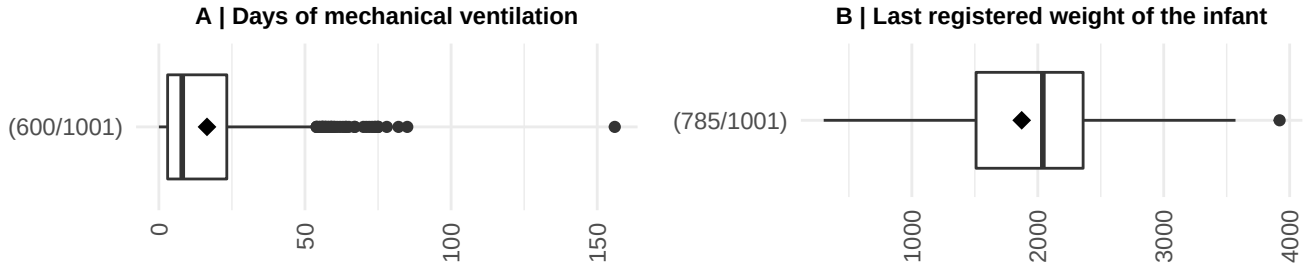

Figure 5 | Boxplots from the 'follow-up' module, shown for all participants. **(A)** Days of mechnical ventilation (extracted from *F03a_daysofvent*); and **(B)** weight at follow-up (*F05_weightatfollowup*).

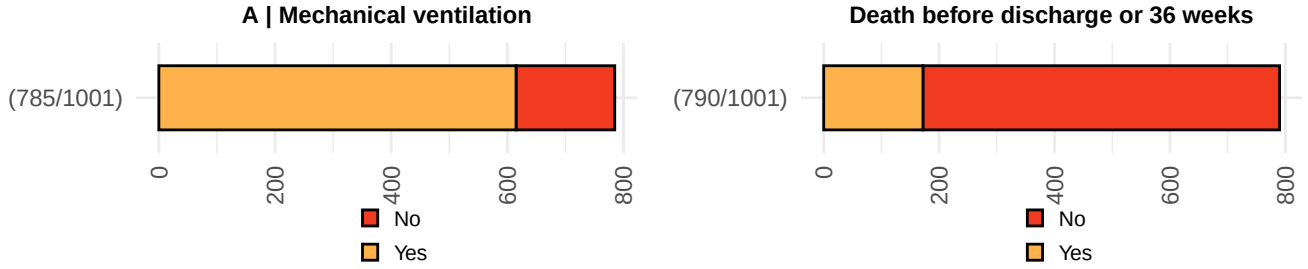

Figure 6 | Stacked barcharts from the 'follow-up' mobule, shown for all participants. **(A)** Proportion of participants on mechanical ventilation during admission (extracted from *F03_mechanicvent*); and **(B)** who died before discharge or before 36 weeks (*F12_death*).

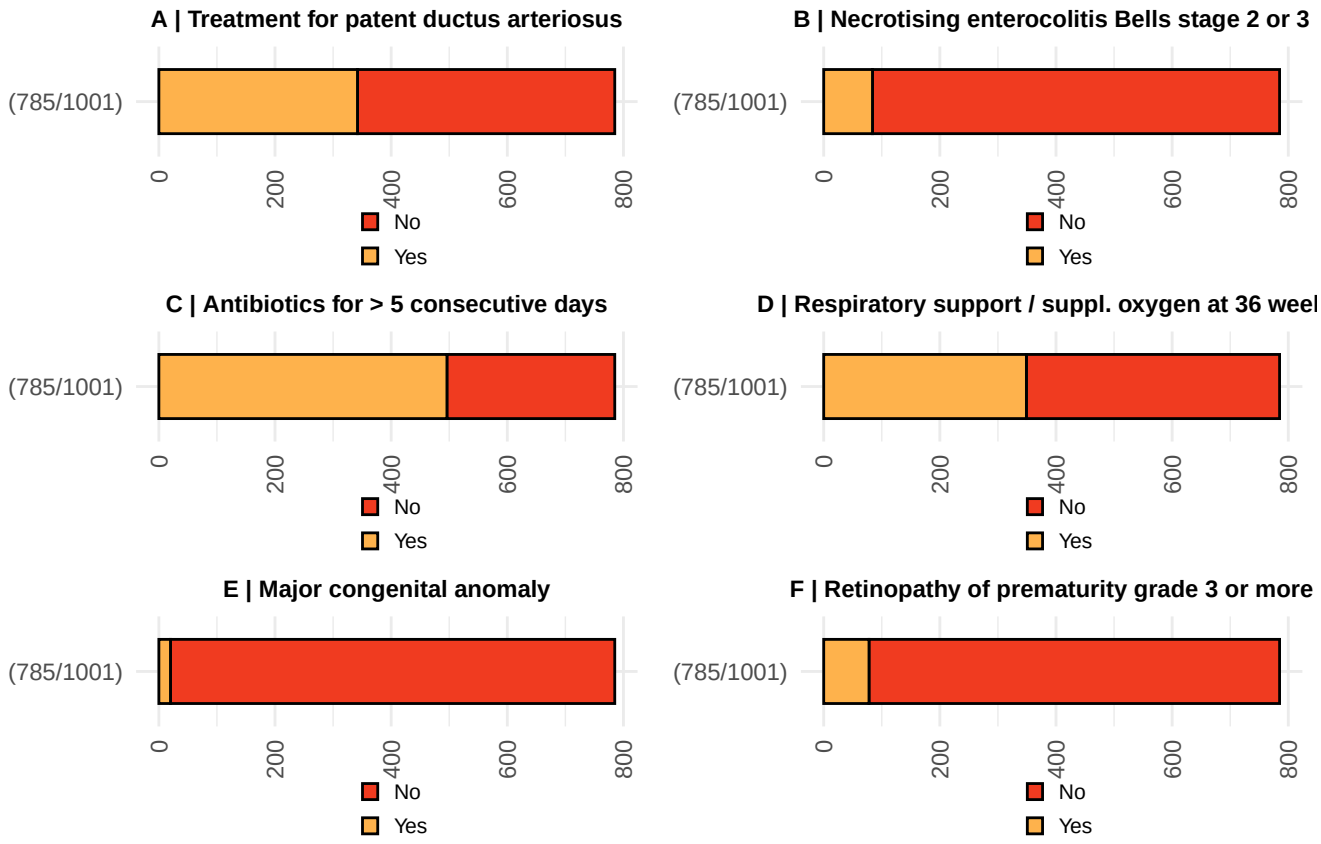

Figure 7 | Stacked barcharts from the 'follow-up' module, shown for all participants. **(A)** Proportion of participants who recieved treatment for patent ductus arteriosus (extracted from *F04_PDA*); **(B)** with necrotising enterocolitis Bells stage 2 or 3 (*F09_nec*); **(C)** who recieved antibiotics for more than five consecutive days (*F11_sepsis*); **(D)** proportion of participants who recieved respiratory support or suplemental oxygen at 36 weeks (*F08_respsupp36wk*); **(E)** with major congenital anomaly (*F02_major_congenitalanomaly*); and **(F)** with retinopathy of prematurity grade 3 or more (*F10_rop*).

Blinded follow-up (36 weeks post menstrual age or discharge to home)

Figure 8 | Stacked barcharts from the 'blinded follow-up' module. **(A)** Proportion of participants who were never scanned (extracted from *BF6_neverscanned*); **(B)** with intraventricular haemorrhage grade 3 or 4; **(C)** with cystic periventricular leukomalacia (*BF02_cpvl*); **(D)** with post-haemorrhagic ventricular dilatation (*BF03_PHVD*); **(E)** with cerebellar haemorrhage (*BF04_cerebhaem*); and **(F)** with cerebral atrophy (*BF05_cerebatroph*).

Central monitoring log

2nd of March 2021 - blinded version

Quality deficiencies

Quality deficiency	Blinded site ID	Comment on the issue	Will any course of action be taken?	Summary of course of action
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	Wq	Only an early cUS was conducted on one participant - 018	Yes	The investigator has been contacted, no response before 30th of June
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	cd	Only a late cUS was conducted on participant - 005	Yes	The investigator has previously reported that 005 received both an early and late cUS. The investigator reports that the data entry has now been changed.
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	1a	Only an early cUS was conducted on one participant	Yes	The investigator reports that the participant was scanned once a week and therefore, the data entry is incorrect. The investigator will correct the data entry accordingly.
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	D9	One participant was never scanned	Yes	The participant did not survive until follow up and received no ultrasound scans. The investigator will correct data entries accordingly.
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	1a	Only an early cUS was conducted on two participants	Yes	The investigator reports that one participant had early and late cUS and that the data entry now have been corrected. The second participant only received an early cUS. No changes are needed.

Quality deficiency	Blinded site ID	Comment on the issue	Will any course of action be taken?	Summary of course of action
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	07	Only an early cUS was conducted on one participant	Yes	The investigator reports that data entries are correct. The participant was discharged by the parents against the physician's advice and therefore, no late cranial ultrasound. No changes needed.
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	K7	Only an early cUS was conducted on one participant Only a late cUS was conducted on two participants Only a cUS between 8 and 35 days of life was conducted on one participant	Yes	The investigator reports that data entries are correct. Two participants also received an ultrasound scans between day 8 and 35, but this cannot be registered as only one answer possibility may be chosen in OpenClinica.
Late initiation of cerebral oximetry monitoring (0-6 hours)	u6	One participant had initiation after six hours of age	Yes	The investigator reports that he was not aware of the late mean time for initiation of NIRS monitoring. The investigator reports to keep an eye on this for future enrolment of participants. Data entries are correct. A mean time of 5 hours for initiation of NIRS monitoring.
Late initiation of cerebral oximetry monitoring (0-6 hours)	Wq	The centre had a mean initiation time of x hours	Yes	A mean time of 5 hours for initiation of NIRS monitoring. The investigator has reported to investigate this. However, no response received before 30th of June.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	cd	One participant has been registered: -032A	No	The baby died after one day of life. The investigator reports that the data entry has been corrected.

Quality deficiency	Blinded site ID	Comment on the issue	Will any course of action be taken?	Summary of course of action
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	Vi	One participant has been registered	Yes	The investigator reports that the data entry is correct. The monitoring was shortly discontinued due to a semi-acute intubation, and due to miscommunication in-between shifts, it was not started again.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	o3	One participant has been registered	Yes	Premature NIRS stop due to seizures. The investigator reports that data entry is correct, no changes needed.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	MR	One participant has been registered	Yes	The investigator has previously reported that this was a data entry error, since the participant died within the first 72 hrs of life, and that the data entry had been corrected. The PI now reports to have corrected the data entry.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	Vr	One participant has been registered	Yes	The investigator reports that the data entry is correct. Due to device failure of the oximeter, no monitoring was conducted. No changes needed.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	U6	One participant has been registered	Yes	The investigator reports that this is a data entry error, and that data has been corrected.
Proportion of participants where consent was withdrawn or declined by the parents	tW	One participant has been registered	Yes	The investigator reports that this is a data entry error. Consent was not withdrawn, and the data entry has been corrected.

Quality deficiency	Blinded site ID	Comment on the issue	Will any course of action be taken?	Summary of course of action
Proportion of participants where consent was withdrawn or declined by the parents	l9	Three participants have been registered	Yes	The investigator reports that data entries are correct. No changes needed.
Proportion of participants with post-haemorrhagic ventricular dilatation or cerebral atrophy but no late cranial ultrasound scan	2j	One participant has been registered	Yes	The investigator reports that data entries are correct. No changes needed.
Proportion of participants with post-haemorrhagic ventricular dilatation or cerebral atrophy but no late cranial ultrasound scan	MR	Two participants have been registered	Yes	The investigator reports that data entries are correct. No changes needed.
Proportion of participants with post-haemorrhagic ventricular dilatation or cerebral atrophy but no late cranial ultrasound scan	W9	One participant has been registered: -003B	Yes	The investigator has been contacted; no response received.
Proportion of participants in the control group that underwent unblinded cerebral oximetry monitoring	MM	Two participants have been registered	Yes	The investigator reports that data entries are correct. The physicians in the centre decided that the participants would benefit from NIRS due to clinical deterioration, despite being in the control group. Equipoise was discussed with the investigator he reported that it was only a few of the physicians that were in doubt. After an internal discussion in the physician group, all agreed that they could maintain equipoise and continue recruiting to the trial.

Quality deficiency	Blinded site ID	Comment on the issue	Will any course of action be taken?	Summary of course of action
Proportion of participants in the control group that underwent unblinded cerebral oximetry monitoring	l9	Two participants have been registered	Yes	The investigator reports that data entries are correct. A discussion on equipoise has been initiated with the investigator. Awaiting reply.
Proportion of participants in the control group that underwent unblinded cerebral oximetry monitoring	W9	Two participants have been registered	Yes	The investigator reports that the attending neonatologists was not aware of the fact, that participants in the control group should not receive NIRS monitoring (the attending thought all participants should be monitoring with NIRS, but only receive interventions according to the treatment guideline in the experimental group). The investigator reports that this has been clarified in the physician group and that no further misunderstandings are expected. Data entries are correct, no changes needed.
Proportion of participants in the control group that underwent unblinded cerebral oximetry monitoring	iQ	One participant has been registered	Yes	The investigator reports that the data entry is correct. The participant was monitored despite being in the control, due to severe clinical condition. A discussion has been initiated with the investigator in regards of potential loss of equipoise in the centre. Awaiting reply.

Quality deficiency	Blinded site ID	Comment on the issue	Will any course of action be taken?	Summary of course of action
Proportion of participants in the control group that underwent unblinded cerebral oximetry monitoring	Vr	Three participants have been registered - 010 - 011 - 015A	Yes	The investigator reports that all participants were NIRS monitored due to participation in another study. It is unsure whether the monitoring was done blinded, awaiting reply from investigator.

* data entries that have been flagged, but registered as correct during previous monitoring visits, will not be included in the present log

Noteworthy data deviations

Variable	Blinded site ID	Which suspicion has been raised?	Will any course of action be taken?	Result of the course of action
Randomisation after 6 hrs of age	KF	Suspected misunderstanding, one participant	Yes	The investigator reports that the participant was randomised 8hrs and 30 minutes after birth, due to technical difficulties with connecting to OpenClinica. Data entry is correct, no changes needed.
Randomisation after 6 hrs of age	cd	Suspected misunderstanding - 002 - 003	Yes	The investigator reports that this were data entry errors and that they have now been corrected.
Randomisation after 6 hrs of age	MM	Suspected misunderstanding, one participant	Yes	The investigator reports that time of birth in the eCRF is wrong and that the participant was randomised after four hours of birth. This has now been corrected by the trial manager.
Initiation of NIRS monitoring later than six hours of life	jq	Suspected misunderstanding, one participant	Yes	The investigator reports that the data entry is correct. The participant was born in a different hospital and was admitted four hours after birth. When the NIRS monitoring was initiated, the oximeter was dysfunction and therefore, a new oximeter had to be used, which delayed initiation of NIRS monitoring until 7 hrs after birth.

Variable	Blinded site ID	Which suspicion has been raised?	Will any course of action be taken?	Result of the course of action
Mean gestational age is higher than additional centres	tW	Suspected misunderstanding	Yes	Mean gestational age around 27,5 weeks, very narrow distribution. The investigator reports that data entries are correct. Three participants below 26 weeks GA has been eligible in the centre, since trial initiation. However, the parents declined participation in SafeBoosC-III, since they were not willing to pay for the expensive medical treatment, for children with such a poor prognosis.
Mean gestational age is higher than additional centres	0z	Suspected misunderstanding	Yes	The investigator reports that data entries are correct. Mean gestational age is 27w1,5d.
High birthweight (above 1450 gram)	7r	Suspected outlier, one participant	No	Gestational age almost 28 weeks. Therefore, no action is taken.
High birthweight (above 1450 gram)	QQ	Suspected outlier, one participant	No	Gestational age almost 28 weeks. Therefore, no action is taken.
High birthweight (above 1450 gram)	MM	Suspected outlier, one participant	No	Gestational age almost 28 weeks. Therefore, no action is taken.
High birthweight (above 1450 gram)	xS	Suspected outlier, one participant	No	Gestational age almost 28 weeks. Therefore, no action is taken.
High proportion of retinopathy of prematurity	Wq	Make sure that data after 36 weeks PMA is not used	Yes	The investigator has been contacted, no response before 30th of June

Variable	Blinded site ID	Which suspicion has been raised?	Will any course of action be taken?	Result of the course of action
High proportion of retinopathy of prematurity	vl	Make sure that data after 36 weeks PMA is not used	Yes	The investigator reports that only data up until 36 weeks follow-up is used for all outcomes. Furthermore, no errors in data entries. No further action necessary.

Central monitoring log for statistical outlier identification by Mahalanobis distance

Blinded site ID	Mahalanobis distance	Identified outliers	Already mentioned in the central monitoring log?	Will any course of action be taken?
E8	17.5	A high mortality rate, most in mechanical ventilation but only for a few days, most had cardiovascular support, most treated for persistent duct, few had a brain injury and few underwent cerebral ultrasound	No	The central monitoring group suspected that this centre was flagged due to the high number of severely ill participants and aggressive treatment therapy (high mortality rate, early death, all in mechanical ventilation but only a few days, high use of cardiovascular support and treatment for persistent duct). Since multiple participants died early, they also have very little ultrasound scans and thus, almost no registered brain injuries. After unblinding of the site ID, it was noted that this site was also flagged in the last monitoring report. The investigator confirmed our suspicion and stated that the participants included so far, had been very small and severely ill from the beginning. As only data for two additional participants have been entered for this site, since the last monitoring meeting, no additional action will be taken.

Blinded site ID	Mahalanobis distance	Identified outliers	Already mentioned in the central monitoring log?	Will any course of action be taken?
nu	19.4	Few participants in the dataset, limited ultrasound data, only singletons, high mean gestational age, good APGAR scores, few die, limited use of cardiovascular support, all received antibiotics for more than five days consecutively, few brain injuries, long time in mechanical ventilation	No	The monitor group could not identify a pattern and thereby, a clear reason as to why this centre was flagged in Mahalanobis analysis. The number of participants included in the dataset is also limited. Thus, no action will be taken. However, if the centre is flagged again in future reports, the investigator will be contacted.

Changes to the central monitoring report

- The data manager will try to *flag* previously identified outliers in the next report, where investigator has reported that the data entry is correct.
- Data in figure 6B *Last registered weight of the infant (survivors)* will be converted to standard deviation scores (weight for gestational age) in the next report

NOTA

- **NIRS monitoring initiated before randomisation time _**

After registration of a late randomisation time (after 6 hrs of age) in centre KF, we decided to cross check with time of NIRS monitoring initiation. It was noted that in centre KF, NIRS monitoring seemed to be initiated within the six-hour limit, which does not match with randomisation times later than six hours. This made us realise, that any participants who have been registered with initiation of NIRS monitoring before time of randomisation must be an error in the data entry, a misunderstanding or fabricated data.

Therefore, we decided to identify all such participants. Eleven participants were registered.

The relevant investigators have been contacted, see replies below.

- One centre, one participant: the investigator reports that the data entry is correct, the NIRS monitoring was initiated before randomisation due to clinical deterioration. A discussion on loss of equipoise has been initiated with the investigator.
- One centre, one participant: the investigator reports that the data entry on time for initiation of NIRS monitoring is incorrect, and that it has now been corrected.
- One centre, one participant: the investigator reports that the participant was randomised in a different study before the SafeBoosC-III randomisation and, thus started NIRS monitoring before SafeBoosC-III randomisation. As the participant was allocated to the experimental group, it is not a problem. However, for future similar situations, NIRS monitoring should be blinded, until the participant has been randomised to SafeBoosC-III. The investigator has been informed about this.
- One centre, three participants: the investigator reports that it is probably due to the time difference between Turkey and Denmark (2 hrs prior Denmark), but will check again. The data manager has been contacted to check if this is the actual problem.
- One centre, two participants: investigator reports that data entries are correct. It is due to that the centre has limited number of NIRS equipment, so they start monitoring before randomisation, to ensure that equipment is available. The investigator has been asked if the NIRS monitoring is then removed from participants if they are randomised to the control group.
- One centre, one participant: the investigator reports that the data entry on time for initiation of NIRS monitoring is incorrect, and that it has now been corrected.
- One centre, one participant: the investigator reports that the data entry on time for initiation of NIRS monitoring is incorrect, and that it has now been corrected.
- One centre, two participants: no response from the investigator

A validation has been added to OpenClinica, so that it is not possible to enter time of NIRS start later than time of randomisation.

- **Days of mechanical ventilation longer than possible due to the 36 weeks follow-up limit _**

Based on the identification of a participant with 156 days of mechanical ventilation – which were also identified in the last monitoring report as a misunderstanding, but have not been corrected by the investigator yet – we decided to crosscheck and identify all participants with days of mechanical ventilation extending after the 36 weeks follow-up data.

Five participants were registered.

The relevant investigators have been contacted, see replies below

- One centre, two participants: the investigator reports that this was a random error, and that data entries will be corrected.
- One centre, two participants: the investigator reports that this was a random error, and that data entries will be corrected.
- One centre, one participant: no response from the investigator.

- **YES to "NIRS data available for clinical staff" when registered as NO to "NIRS in the control group" _**

As one participant was registered with the above mentioned answer combination, and since we still have not heard from the investigator, the combination was once more crosschecked.

One participant was registered

The investigator reports that this is a data entry error, which has now been corrected.