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 19th of November 2020)*. 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

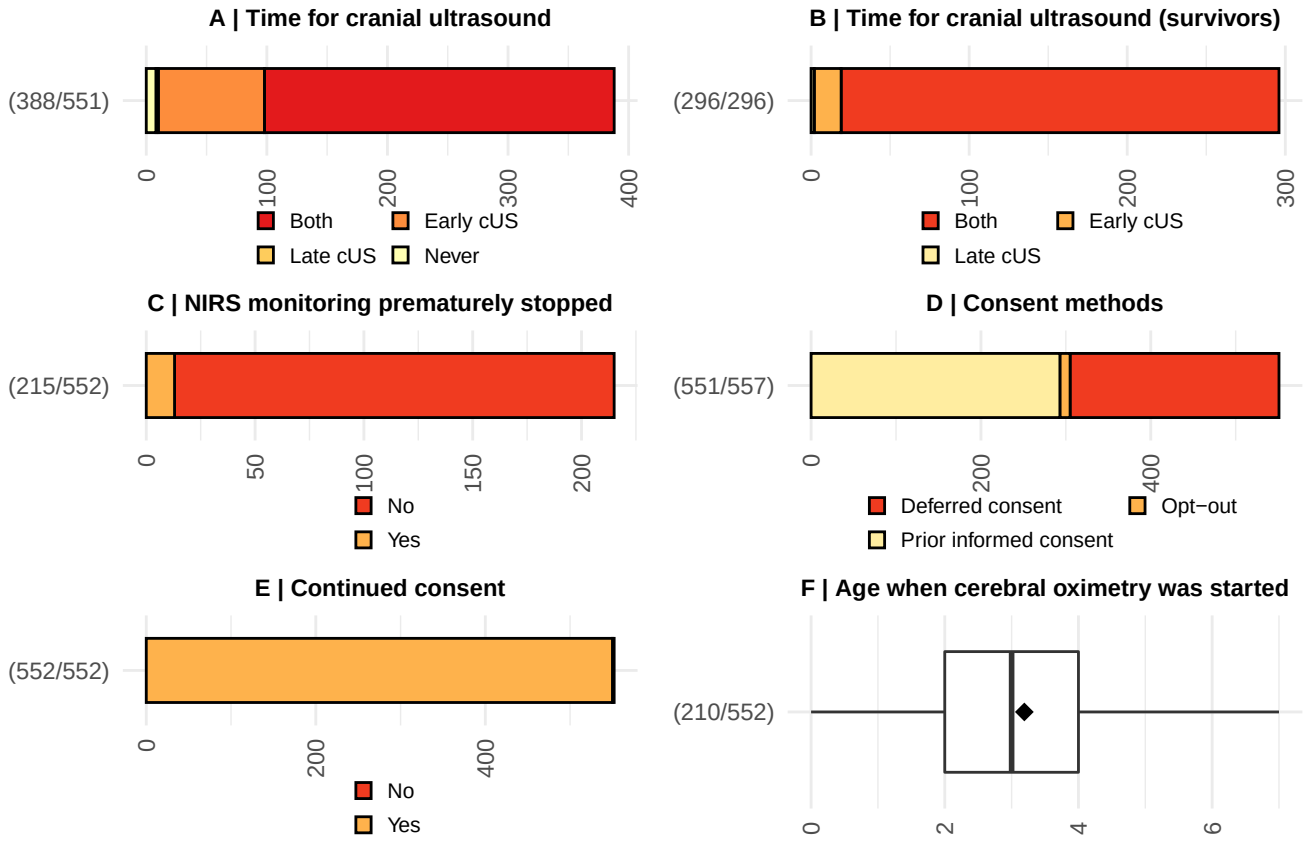

Figure 1 | Stacked barcharts shown for all participants. **(A)** Time for cranial ultrasound for all and **(B)** for survivors (extracted from *F07_cus*); **(C)** proportion of participants with prematurely stopped NIRS monitoring (*E07_prematurenirsstop*); **(D)** types of consent used to enroll participants (*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

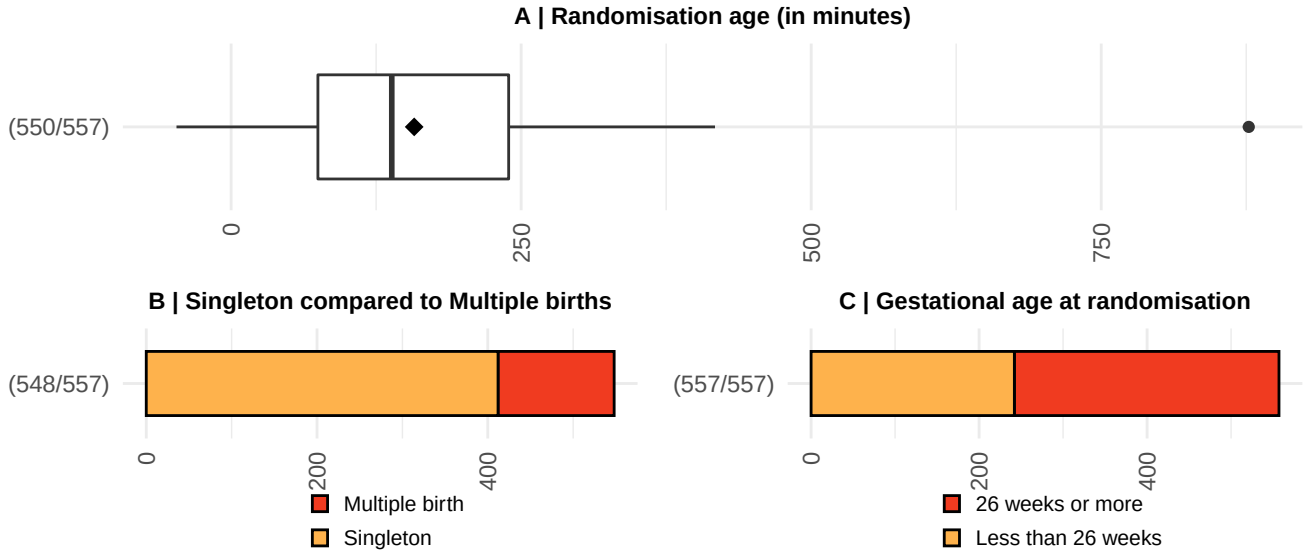

Figure 2 | (A) Age of participants at the time of randomisation in minutes presented using a boxplot. Vertical line depicts median, whereas a diamond represents mean. Stacked barcharts from the 'randomisation' module. **(B)** Proportion of singleton compared to multiple births (extracted from *R02a_singlemulti*);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

End of monitoring

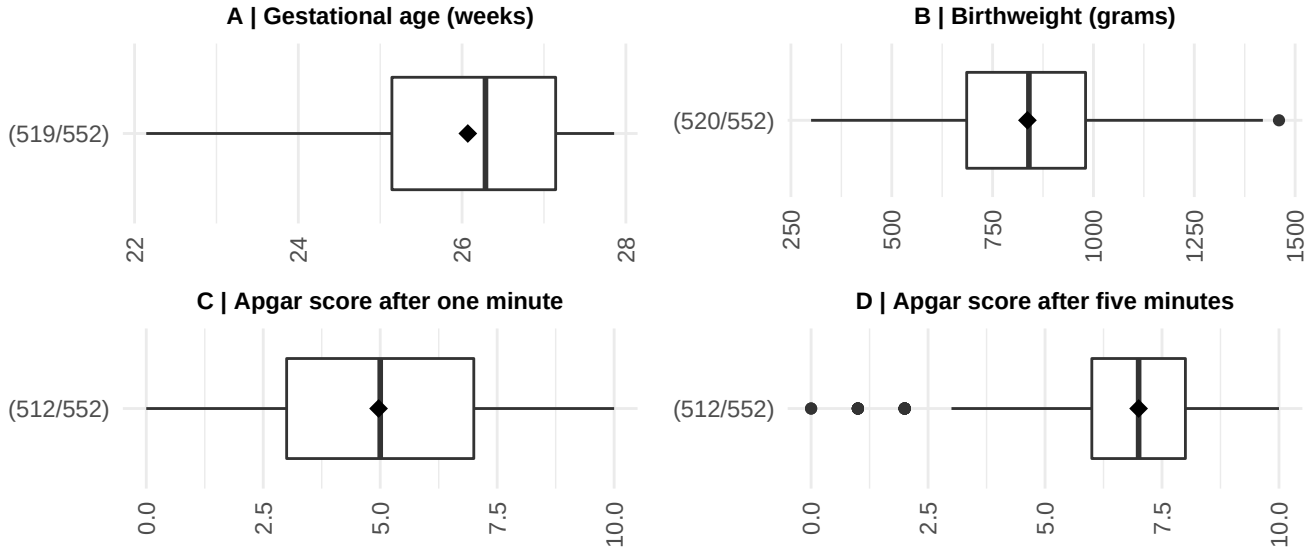

Figure 3 | Boxplots from the 'end of monitoring' module, shown for all participants. **(A)** Gestational age of participants in gestational weeks (extracted from *E01_gestationalage*); **(B)** birthweight in grams of participants (*E02_birthweight*); **(C)** Apgar score for participants one minute after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

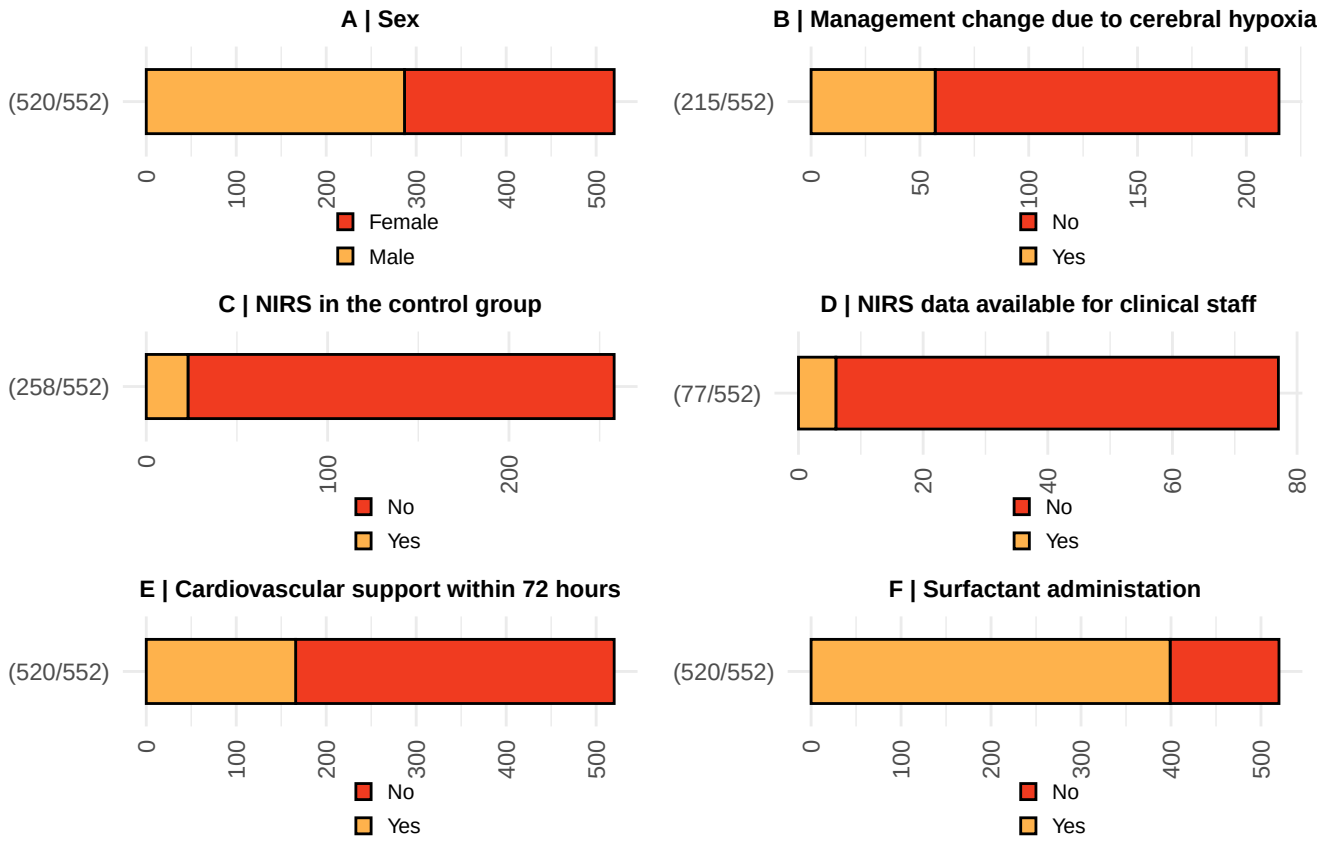

Figure 4 | Stacked barcharts from the 'end of monitoring' module, shown for all participants. **(A)** Sex of participants (extracted from *E05_sex*); **(B)** Proportion of participants with changed treatment due to cerebral hypoxia (*E08_changeoftreatmenthypoxia*); **(C)** with NIRS despite being in 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)

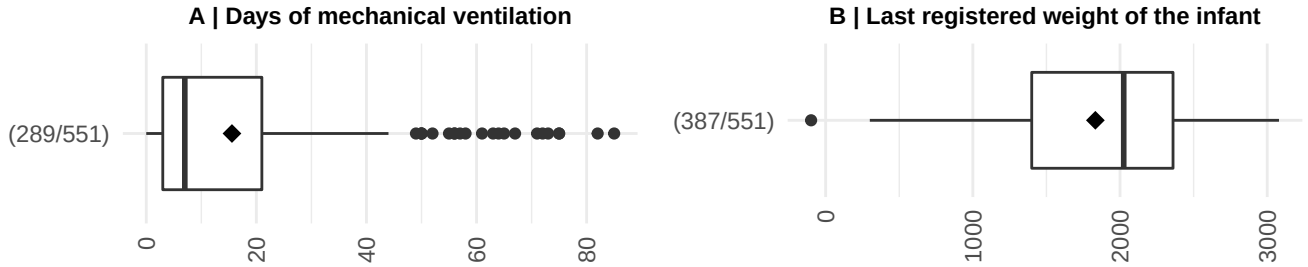

Figure 5 | Boxplots from the 'follow-up' module, shown for all participants. **(A)** Days of mechnical ventilation (extracted from *F03a_daysofvent*); and **(B)** weight at follow-up (*F05_weightatfollowup*).

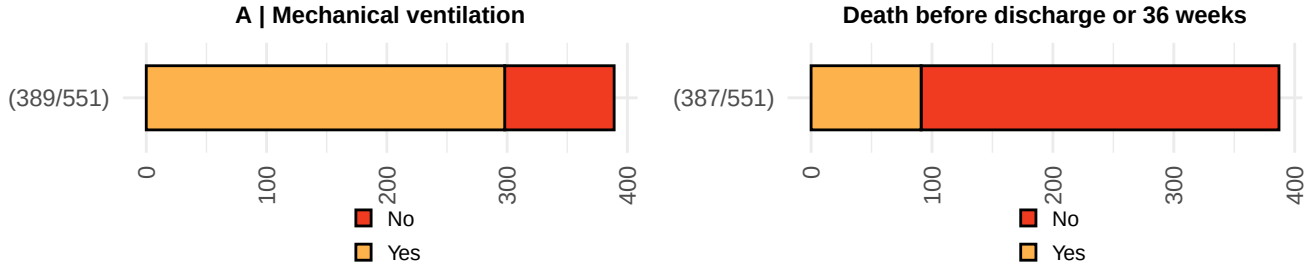

Figure 6 | Stacked barcharts from the 'follow-up' mobule, shown for all participants. **(A)** Proportion of participants on mechanical ventilation during admission (extracted from *F03_mechanicvent*); and **(B)** who died before discharge or before 36 weeks (*F12_death*).

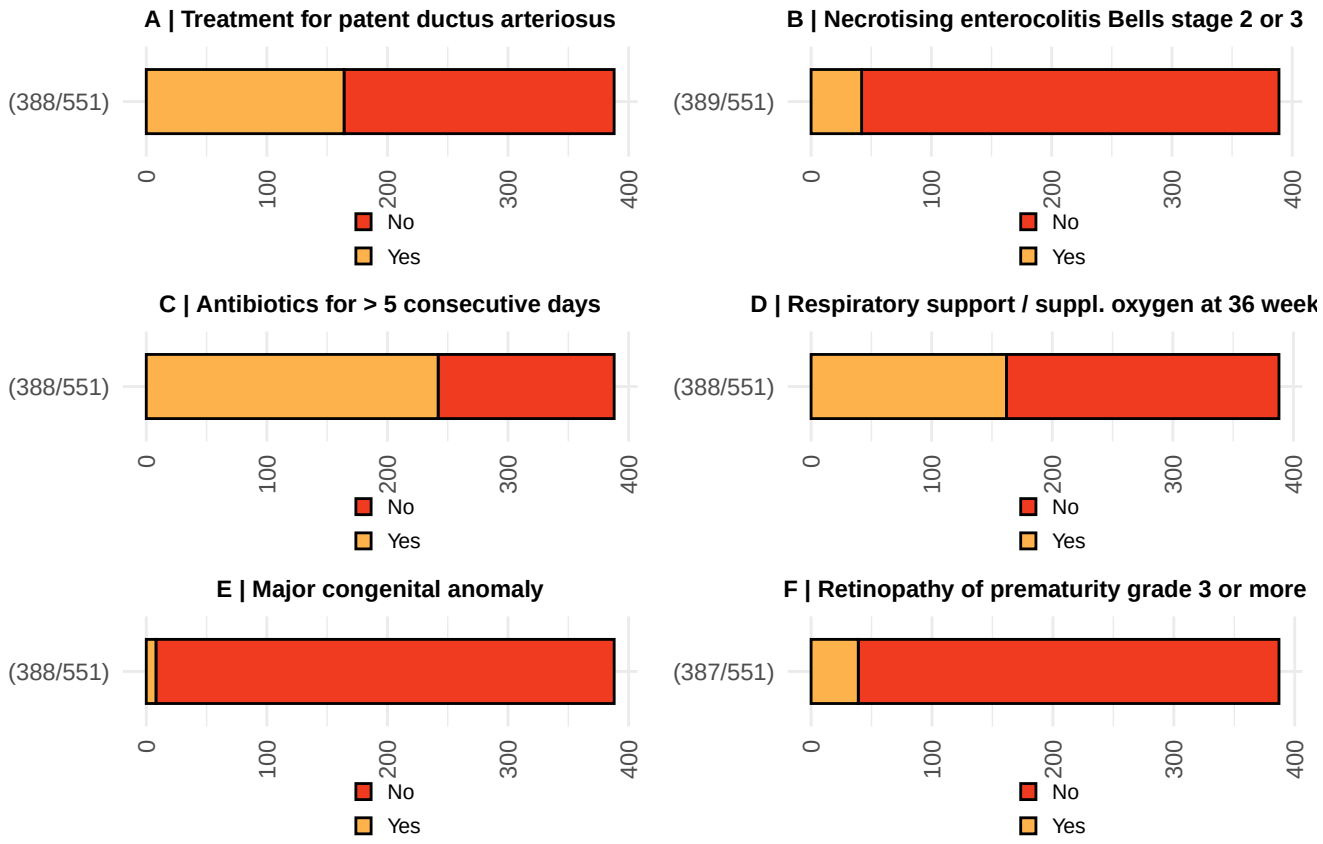

Figure 7 | Stacked barcharts from the 'follow-up' module, shown for all participants. **(A)** Proportion of participants who recieved treatment for patent ductus arteriosus (extracted from *F04_PDA*); **(B)** with necrotising enterocolitis Bells stage 2 or 3 (*F09_nec*); **(C)** who recieved antibiotics 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

30th of November 2020 - 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)	PI	Eight babies were registered as having only an early cranial ultrasound	Yes	For three of the eight babies, data entries were supposed to be changed to both early and late cUS by the local investigator, following the 1st central monitoring meeting. However, this was not been done. The local investigator has now corrected this. Remaining data entries were correct.
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	74	Six babies were registered as having only an early cranial ultrasound One baby was registered as having had only a late cranial ultrasound	Yes	The local investigator reported that the baby registered with only a late scan, have had both an early and a late scan. The local investigator has now corrected this. Remaining data entries are correct.
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	Ee	One baby was registered as having only an early cranial ultrasound	No	No course of action since the issue was isolated to one baby. If the numbers have increased at the next meeting, contact will be made to the investigator.
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	uo	One baby was registered as having only an early cranial ultrasound	No	No course of action since the issue was isolated to one baby. If the numbers have increased at the next meeting, contact will be made to the investigator.
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	oT	One baby was registered as having only an early cranial ultrasound	No	No course of action since the issue was isolated to one baby. If the numbers have increased at the next meeting, contact will be made to the investigator.

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)	dn	One baby was registered as having only a late cranial ultrasound	No	No course of action since the issue was isolated to one baby. If the numbers have increased at the next meeting, contact will be made to the investigator.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	Pv	Four babies were registered with premature stop of NIRS	Yes	All four babies had stoppage of NIRS monitoring for more than 14 hours. one due to transfer to another hospital, two of them due to visible skin marks, and one due to withdrawal of parental consent. Therefore, data entries are correct.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	74	One baby was registered with premature stop of NIRS	Yes	Parents decided to stop NIRS monitoring of this baby due to unstable vital signs within one day of life. Therefore, data entries are correct.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	Ni	Two babies were registered with premature stop of NIRS	Yes	NIRS monitoring were stopped for both babies due the physician reporting that monitoring was not compatible with sNIPPV and that the NIRS monitoring made the babies unstable. Therefore, data entries are correct.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	Fh	One baby was registered with premature stop of NIRS	No	As per the 1st central monitoring report, data entry on this baby is correct.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	Pl	One baby was registered with premature stop of NIRS	Yes	NIRS monitoring was discontinued for more than 14 hrs due to skin damage. Therefore, data entry is correct. Investigator reports that data entries are correct, therefore no changes.

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)	DX	One baby was registered with premature stop of NIRS	No	As per the 1st central monitoring report, data entry on this baby is correct.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	E9	One baby was registered with premature stop of NIRS	Yes	NIRS monitoring was discontinued for more than 14 hrs due to transfer to another hospital, in order to receive surgery for NEC. Therefore, data entry is correct.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	uo	Two babies were registered with premature stop of NIRS	No	As per the 1st central monitoring report, data entries on these babies are correct.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	vp	One baby was registered with premature stop of NIRS	No	As per the 1st central monitoring report, data entry on this baby is correct.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	yR	One baby was registered with premature stop of NIRS	Yes	NIRS monitoring was stopped due to death within the 72 hrs intervention period. Therefore, the baby should not be registered as having had premature NIRS stoppage. Data entry has been corrected.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	Dh	Two babies were registered with premature stop of NIRS	Yes	NIRS monitoring was stopped due to death after 32 hrs of life, i.e. within the 72 hrs intervention period. Therefore, the babies should not be registered as having had premature NIRS stoppage. Data entries have 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)	Ky	Two babies were registered with premature stop of NIRS	Yes	The local investigator has entered that one baby had premature NIRS stoppage due to death. As informed in OpenClinica, babies that have premature NIRS stoppage due to death shall not be registered with a "Yes". The local investigator has been asked to change this. The local investigator has also been asked whether NIRS monitoring was discontinued for more than 14 hrs for the second baby (device failure). Still awaiting answer.
Proportion of participants in the control group that underwent unblinded cerebral oximetry monitoring	74	One baby was registered as such.	No	As per the 1st central monitoring report, data entry on this baby is correct.
Proportion of participants in the control group that underwent unblinded cerebral oximetry monitoring	Ee	Two babies were registered as such	No	As per the 1st central monitoring report, data entries on these babies are correct.
Proportion of participants in the control group that underwent unblinded cerebral oximetry monitoring	dn	Two babies were registered as such	No	As per the 1st central monitoring report, data entries on these babies are correct.
Proportion of participants in the control group that underwent unblinded cerebral oximetry monitoring	Ky	Two babies were registered as such	Yes	The local investigator has been asked whether these babies underwent unblinded cerebral NIRS monitoring despite being in the control group. Still awaiting answer.

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
Last registered weight of the infant (survivors)	vp	Suspected outlier due to a negative last registered weight (-99 grams) - 002	Yes	The local investigator reports that this was a data entry error, and that it now has been corrected.

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?	Result of the course of action
Dh	15.05	Too few participants to identify significant outliers	No	No	No contact will be made to the investigator due to the low number of participants. However, it will be checked whether the site is still outlying during the next round of central monitoring. If so, and number of participants has increased, contact will be made.

Changes to the central monitoring report setup for February meeting

- None

NOTA

- **Management changes due to cerebral hypoxia**

During the central monitoring meeting, it was noted that the frequency of "Yes" responses regarding 'Management changes due to cerebral hypoxia' was low, and in some centres, no changes had been registered among the first seven or eight babies randomised to the experimental group. As the effect of cerebral NIRS monitoring relies on actions taken during events of cerebral hypoxia, it is important that staff members respond to the hypoxia alarms – and that they register in the clinical records when treatment has been changed to avoid cerebral hypoxia.

Therefore, an e-mail has been sent out to all principal investigators, reminding them of the importance of this.

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

The data monitoring also revealed that one trial participant from site Ky was registered with a NO to "NIRS in the control group, but also registered with a YES to"NIRS data available for clinical staff" – which is not practically possible.

We suspect that this is due to a previous flaw in the eCRF which was corrected in May 2020, which allowed investigators to click NO to "NIRS in the control group, but still click YES to"NIRS data visible for clinical staff".

The local investigator has been contacted for an elaboration. However, we are still awaiting a reply. During the next monitor meeting, we will test whether these errors have been corrected.