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 15th of February 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

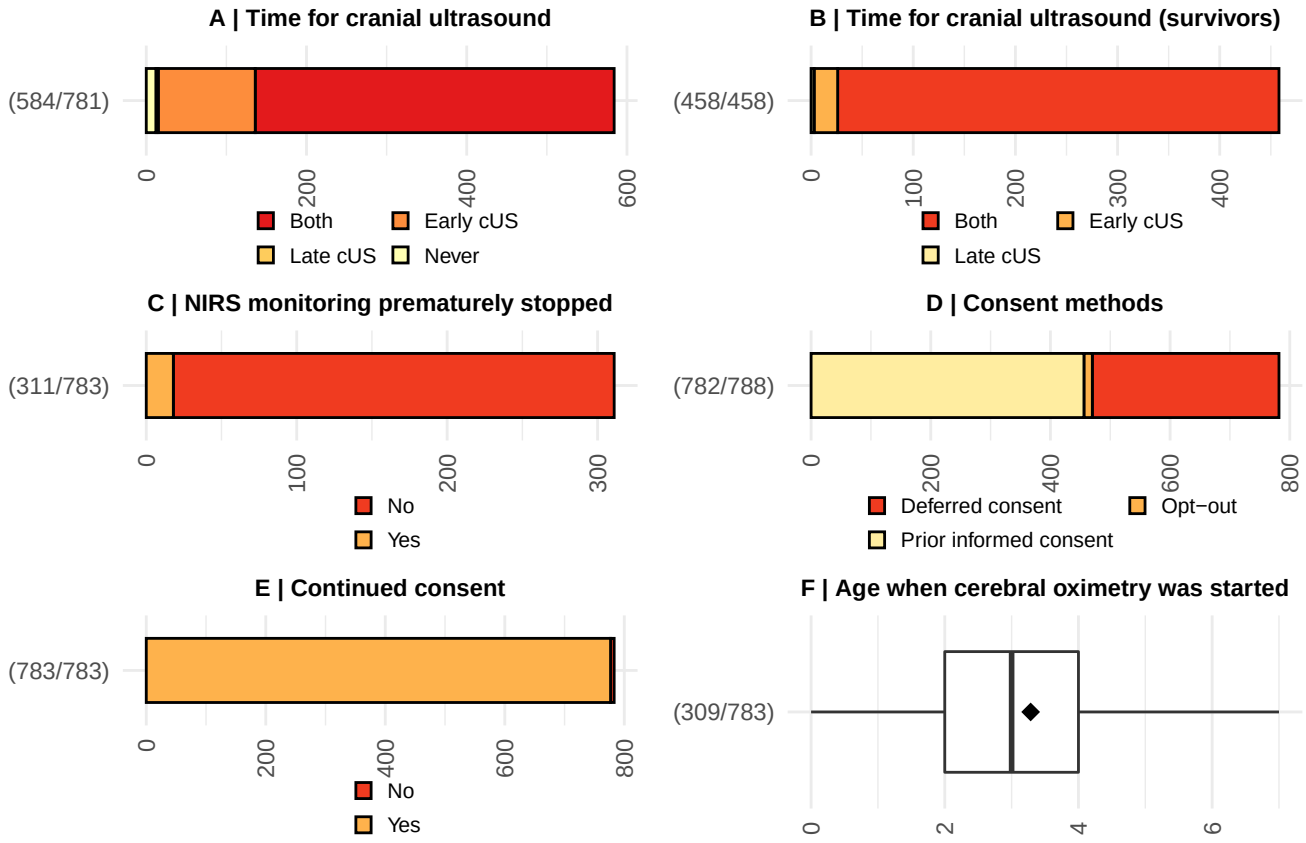

Figure 1 | Stacked barcharts shown for all participants. **(A)** Time for cranial ultrasound for all and **(B)** for survivors (extracted from *F07_cus*); **(C)** proportion of participants with prematurely stopped NIRS monitoring (*E07_prematurenirsstop*); **(D)** types of consent used to enroll participants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

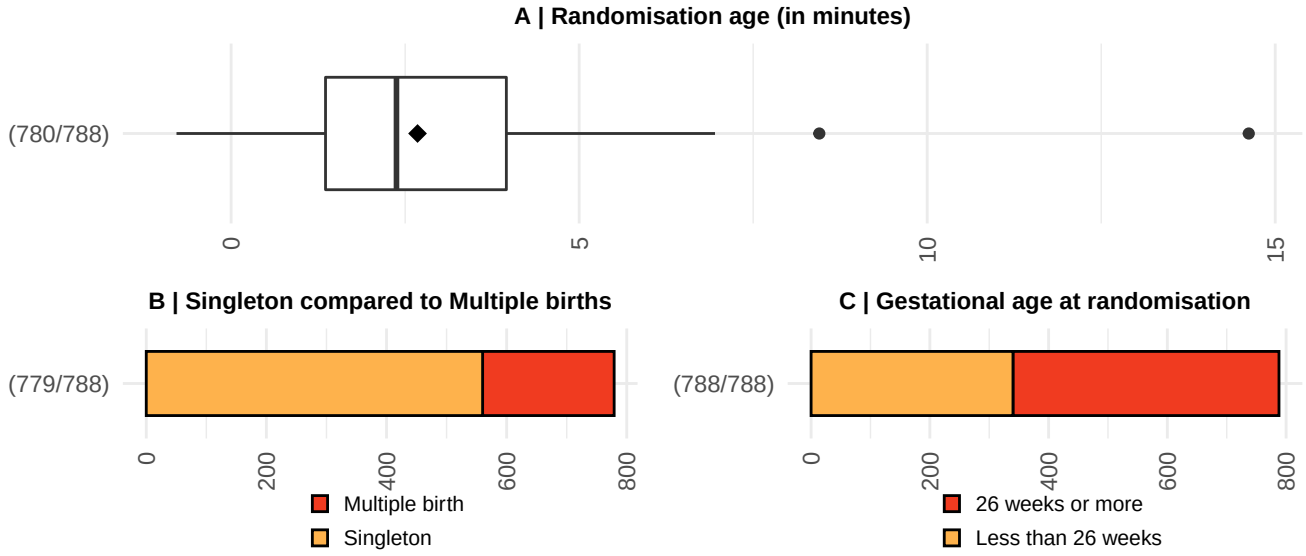

Figure 2 | (A) Age of participants at the time of randomisation in minutes presented using a boxplot. Vertical line depicts median, whereas a diamond represents mean. Stacked barcharts from the 'randomisation' module. **(B)** Proportion of singleton compared to multiple births (extracted from *R02a_singlemulti*);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

End of monitoring

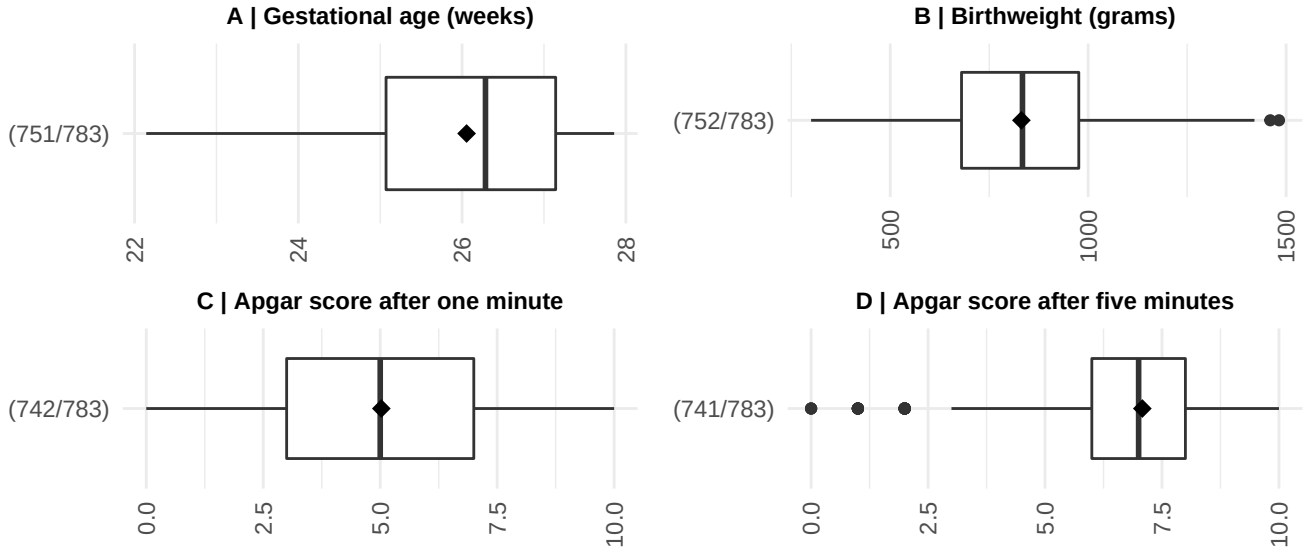

Figure 3 | Boxplots from the 'end of monitoring' module, shown for all participants. **(A)** Gestational age of participants in gestational weeks (extracted from *E01_gestationalage*); **(B)** birthweight in grams of participants (*E02_birthweight*); **(C)** Apgar score for participants one minute after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

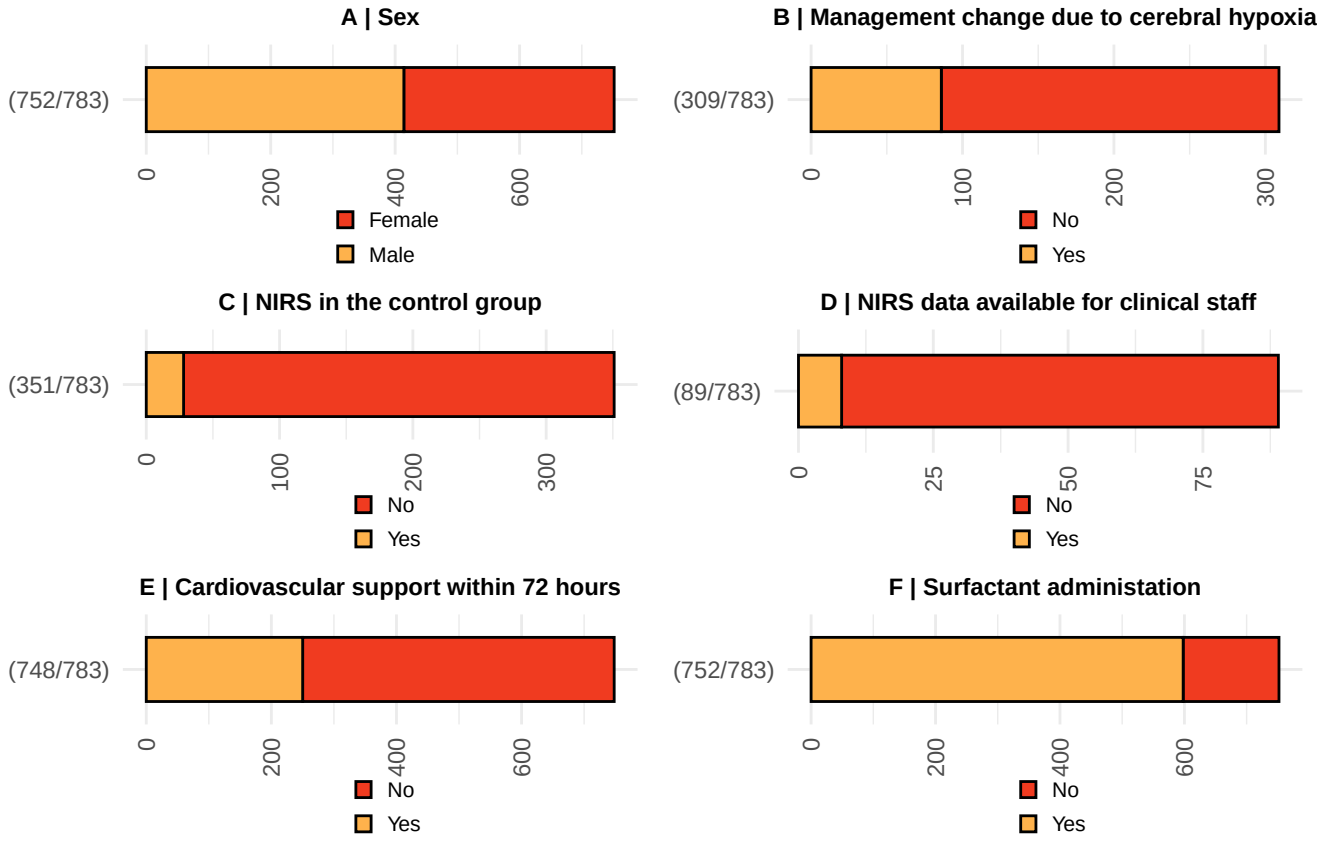

Figure 4 | Stacked barcharts from the 'end of monitoring' module, shown for all participants. **(A)** Sex of participants (extracted from *E05_sex*); **(B)** Proportion of participants with changed treatment due to cerebral hypoxia (*E08_changeoftreatmenthypoxia*); **(C)** with NIRS despite being in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

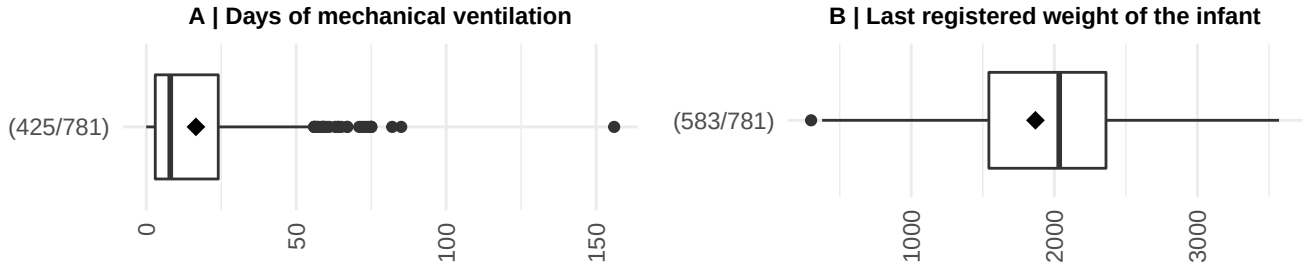

Figure 5 | Boxplots from the 'follow-up' module, shown for all participants. **(A)** Days of mechnical ventilation (extracted from *F03a_daysofvent*); and **(B)** weight at follow-up (*F05_weightatfollowup*).

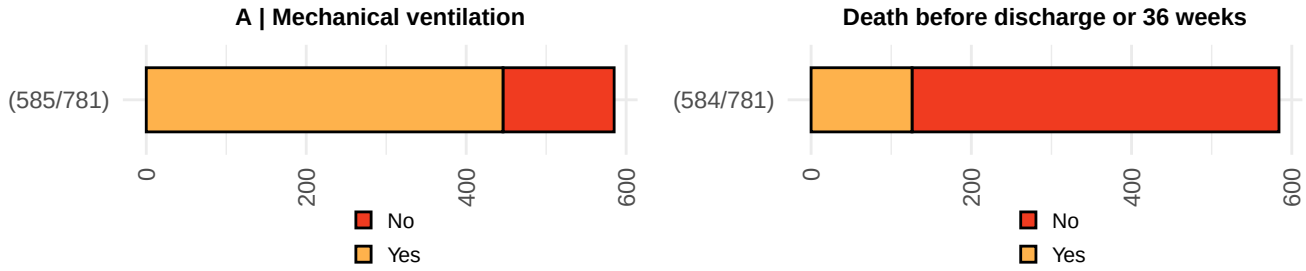

Figure 6 | Stacked barcharts from the 'follow-up' mobule, shown for all participants. **(A)** Proportion of participants on mechanical ventilation during admission (extracted from *F03_mechanicvent*); and **(B)** who died before discharge or before 36 weeks (*F12_death*).

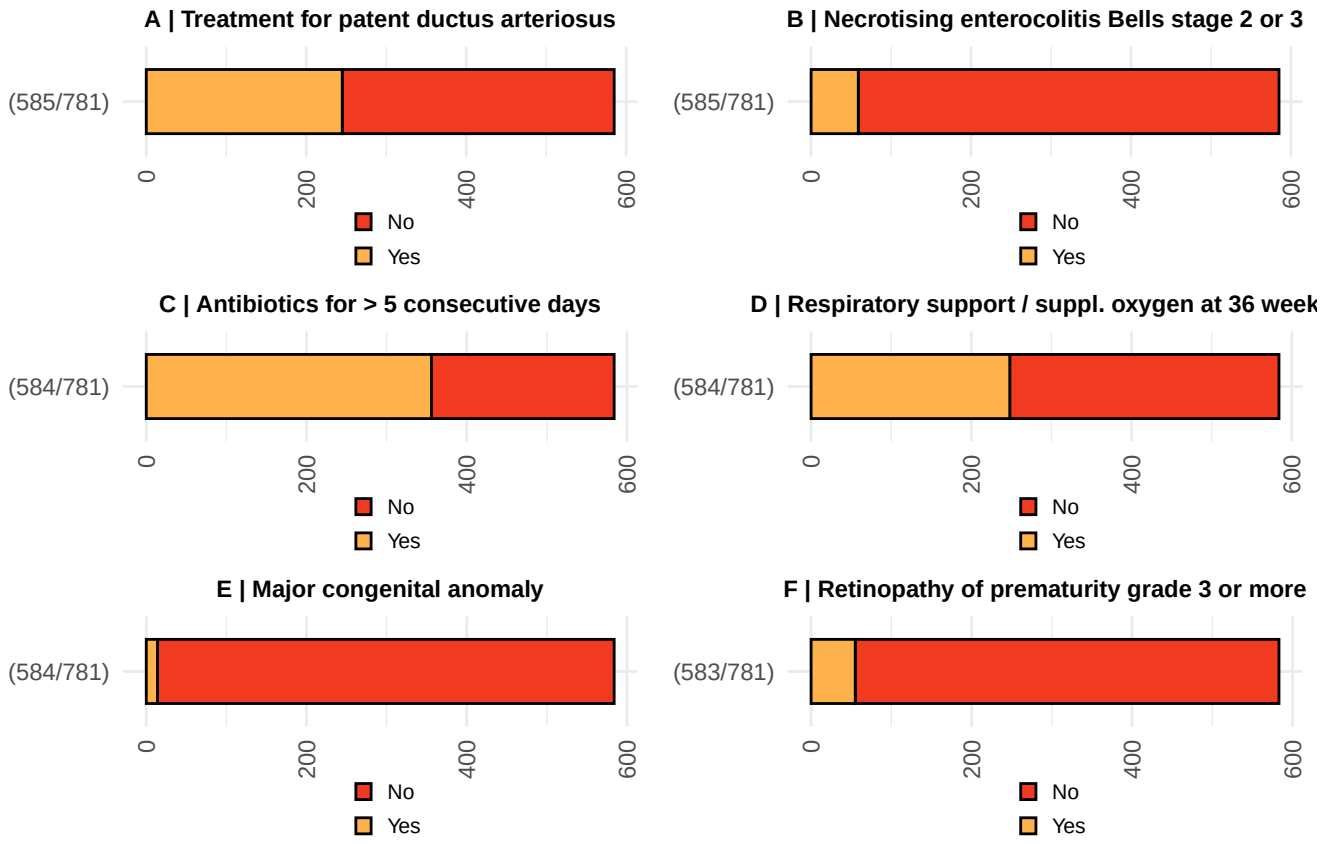

Figure 7 | Stacked barcharts from the 'follow-up' module, shown for all participants. **(A)** Proportion of participants who recieved treatment for patent ductus arteriosus (extracted from *F04_PDA*); **(B)** with necrotising enterocolitis Bells stage 2 or 3 (*F09_nec*); **(C)** who recieved antibiotics 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)	NU	Three babies were registered as having only an early cranial ultrasound	Yes	The investigator reports that data entries are correct, no changes needed.
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	0W	Five babies were registered as having only an early cranial ultrasound One baby was registered as having only a late cranial ultrasound	Yes	The investigator reports that data entries are correct, no changes needed.
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	ed	Nine babies were registered as having only an early cranial ultrasound	Yes	002, 008A, 008B, 010, 013, 014, 015 and 017 only had an early cUS. Therefore, no correction. 016 had both and early and a late cUS scan. Therefore, the data entry has been corrected.
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	KN	One baby weas registered as having only an early cranial ultrasound	Yes	This was a reporting error. The baby underwent both a late and early cUS. The data entry has been corrected.
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	D9	One baby was registered as having only a late cranial ultrasound	Yes	The principal investigator has reported that 004 had both an early and a late cUS. Therefore, data entry has been corrected.
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	zU	One baby was registered as having only an early cranial ultrasound	Yes	The investigator reports that data entries are correct, no changes 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 where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	vG	Two babies were registered with premature stop of NIRS	Yes	The investigator reports that data entries are correct, no changes needed. The clinician decided that the baby was too unstable to manipulate the head and thus, monitoring was not possible.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	uQ	One baby was registered with premature stop of NIRS	Yes	The baby had stoppage due to death. The investigator has now corrected the data entry, so that the answer is “No”.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	W6	One baby was registered with premature stop of NIRS	Yes	The investigator reports that data entries are correct, no changes needed. The monitoring was never initiated due to NIRS device failure.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	qj	One baby was registered with premature stop of NIRS	Yes	The investigator reports that data entries are correct, no changes needed. The monitoring was stopped multiple times and only spot measurements were made, since the consultant did not find the monitoring compatible with the respiratory support.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	kK	Two babies were registered with premature stop of NIRS	Yes	The investigator reports that data entries are correct, no changes needed.007 had NIRS stopped due to NEC surgery and NIRS was never initiated again. For 008B the NIRS monitor was broken, thus monitoring was never initiated. In both cases, monitoring was missing for more than 14 hrs.

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)	Zq	One baby was registered with premature stop of NIRS	Yes	020 had stoppage due to death. Data entry is now corrected.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	mr	One baby was registered with premature stop of NIRS	Yes	The investigator reports that this was a data entry error and that the baby did not have premature NIRS stop. Data entry is now corrected.
Proportion of participants with post-haemorrhagic ventricular dilatation or cerebral atrophy but no late cranial ultrasound scan	uQ	The following babies have been registered - 001 - 009	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	NU	The following babies have been registered - 004 - 006A - 010B - 014	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	zU	One baby was 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	FN	One baby was registered	Yes	The investigator reports that data entry is correct. No changes needed.
Proportion of participants with post-haemorrhagic ventricular dilatation or cerebral atrophy but no late cranial ultrasound scan	Tc	One baby was registered	Yes	The principal investigator has been asked whether this is correct, 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 with post-haemorrhagic ventricular dilatation or cerebral atrophy but no late cranial ultrasound scan	ed	Two babies were registered	Yes	The investigator reports that data entry is correct. No changes needed.
Proportion of participants with post-haemorrhagic ventricular dilatation or cerebral atrophy but no late cranial ultrasound scan	Zq	One baby was registered	Yes	The investigator reports that data entry is correct. No changes needed.
Proportion of participants with post-haemorrhagic ventricular dilatation or cerebral atrophy but no late cranial ultrasound scan	KN	One baby was registered	Yes	The investigator reports that data entry is correct. No changes needed.
Proportion of participants with post-haemorrhagic ventricular dilatation or cerebral atrophy but no late cranial ultrasound scan	mr	Four babies were registered	Yes	The investigator reports that data entry is correct. No changes needed.
Proportion of participants in the control group that underwent unblinded cerebral oximetry monitoring	uQ	One baby was registered	Yes	Investigator reports that this was an error in the data entry, which has now been corrected.
Proportion of participants in the control group that underwent unblinded cerebral oximetry monitoring	RZ	One baby was registered	Yes	Investigator reports that data entry is correct. A doctor on-call thought that the baby would benefit from NIRS and thus broke the study protocol. No changes needed.
Proportion of participants in the control group that underwent unblinded cerebral oximetry monitoring	4Q	One baby was registered	Yes	The principal investigator has been asked whether this is correct, awaiting reply.
Proportion of participants in the control group that underwent unblinded cerebral oximetry monitoring	y3	Three babies were registered	Yes	The principal investigator has been asked whether this is correct, awaiting reply.

* 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
Days of mechanical ventilation	Y3	One suspected outlier due to 156 days of mechanical ventilation, i.e. beyond 36 weeks PMA	Yes	This participant underwent 156 of mechanical ventilation before proceeding to palliative care. However, as this includes days preceding 36 weeks PMA, the investigator will correct the number of days in mechanical ventilation so that it only constitute number of days up until 36+0 weeks of postmenstrual age.
Birthweight	Ie	One suspected outlier due to a birthweight of 1500 grams	Yes	The principal investigator states that data are correct. The baby was large-for-date. No changes needed.
Last registered weight of the infant (survivors)	RZ	One suspected outlier due to a last registered weight of 1030 grams	Yes	Data entries are correct, no changes needed. The infant suffered from severe malnutrition and multiple abdominal surgeries.
Last registered weight of the infant (survivors)	YH	One suspected outlier due to a last registered weight of 1100 grams	Yes	The principal investigator states that data are correct. No changes needed.

Variable	Blinded site ID	Which suspicion has been raised?	Will any course of action be taken?	Result of the course of action
Management change due to cerebral hypoxia	nq	Suspected misunderstanding due to that only one out of more than ten participants, have had change of management due to cerebral hypoxia	No	This was discussed in December with the principal investigator who explained that only in one case, had medical management been changed due to NIRS values. Very few participants experienced NIRS values below the threshold and if they did, it was decline in other monitoring parameters that facilitated the treatment change. Thus, at this time point, no contact is made to the PI again.
Management change due to cerebral hypoxia	KN	Suspected misunderstanding due to that no participants, out of 10, have had change of management due to cerebral hypoxia	Yes	The principal investigator has been asked whether this is correct, awaiting reply.
Death before 36 weeks PMA or discharge	vG	Suspected misunderstanding due that no participants have died out of more than ten	Yes	The investigator reports that data entry is correct. No changes needed.

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
1w	17.45	A high mortality rate, one baby with a birthweight of 400 grams, all of them in mechanical ventilation but only for a few days, only one baby that underwent cranial ultrasound scans, no brain injury diagnosis and very little late-onset sepsis	No	Yes	The central monitoring group suspected that this centre was flagged in the analysis, due to the high number of severely ill babies (high mortality rate, early death, all in mechanical ventilation but only a few days) included. Since multiple babies died early, only a small proportion have undergone cerebral ultrasound scans. The local investigator confirms this suspicion and states, that the babies included so far, have been very small and severely ill from the beginning. Based on the communication, no changes in data nor practice is necessary.

Changes to the central monitoring report

- Changed layout of all figures, for easier interpretation

NOTA

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

The data monitoring also revealed that the trial participant y3005 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.

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 relevant investigator has been contacted for an elaboration, still awaiting reply. During the next monitor meeting, we will test whether this error have been corrected.

- **Registered follow-up date later than 36 weeks of postmenstrual age**

Following the central data monitoring meeting on the 2nd of March, it was discovered that for 103 babies, the follow-up date was registered to be after 36+0 weeks of postmenstrual age.

In the majority of the 103 registered cases, the registered follow-up date is only a little later than 36+0 weeks PMA and primarily due to one of the following issues: 1) date of last weighing is used as follow-up date or 2) the investigator has used the date where he/she sat on the computer and entered data from the clinical files, i.e. not when the baby reached 36 weeks PMA. In both situations, it has been reported that only data up until 36+0 weeks PMA have been used, when entering data on primary and exploratory outcomes.

From a trial quality perspective, it would be most optimal if the follow-up dates, and any relevant data, were corrected. However, this would require a significant amount of work for investigators. Especially since this 'misunderstanding' on follow-up date entries, is a potential problem for all babies that have reached 36 weeks PMA. If some investigators have reported the follow-up date to 36 weeks PMA (because they misunderstood that this date is not the day where you are actually entering data, but instead should be the date where data is used up until), but in reality, the baby was discharged earlier, this would give a falsely high rate of babies with follow-up at 36 weeks PMA.

Possible solutions to this issue was discussed in the executive committee and the following was decided in writing:

"As the majority of cases have a follow-up date that is only a few days after 36+0 weeks PMA and the potential effect of an outcome assessment bias is small since very few babies die around 36+0 weeks PMA, we decide not to do any further. However, OpenClinica will be revised so that it is no longer possible to enter a follow-up date later than 36+0 weeks PMA"

The steering committee has been informed on 22nd of March and additional investigators on 23rd of March.