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 August 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

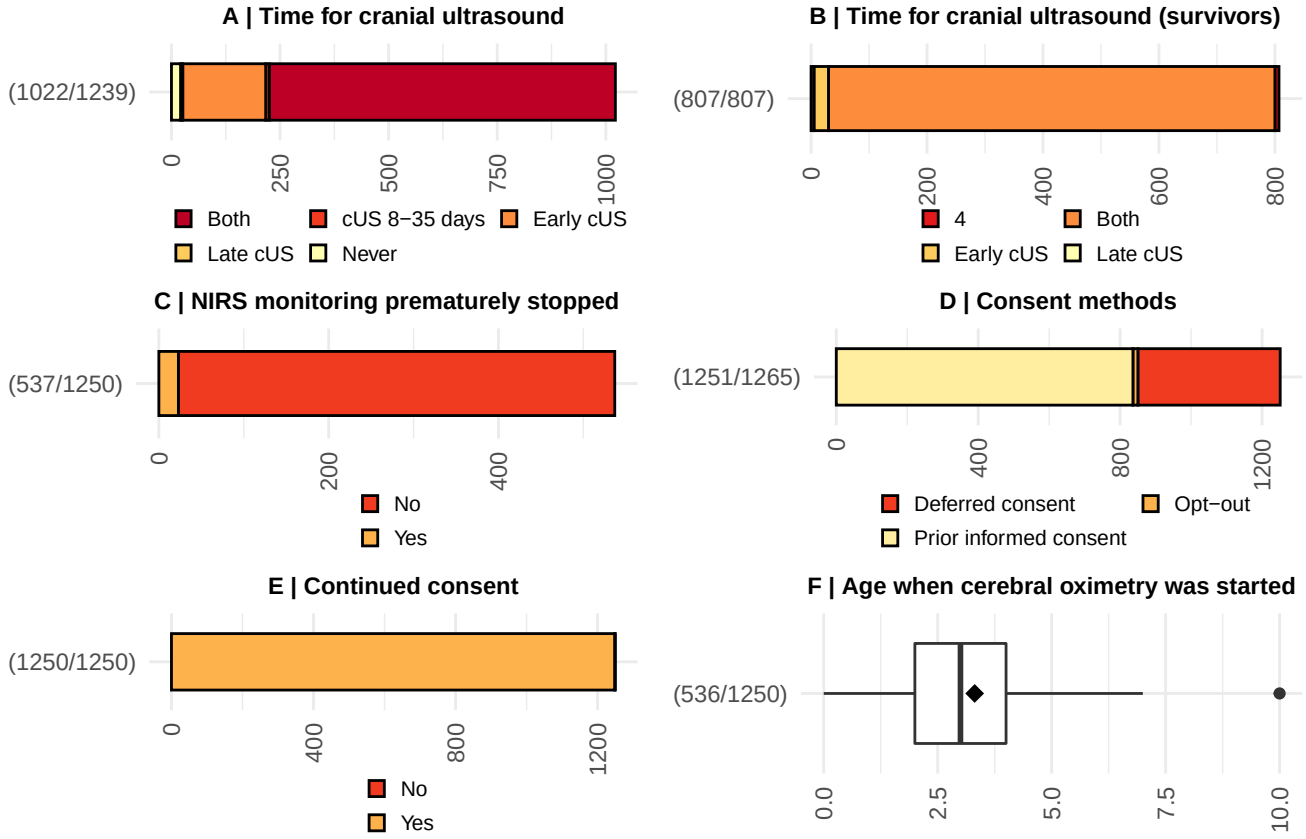

Figure 1 | Stacked barcharts shown for all participants. **(A)** Time for cranial ultrasound for all and **(B)** for survivors (extracted from *F07_cus*); **(C)** proportion of participants with prematurely stopped NIRS monitoring (*E07_prematurenirsstop*); **(D)** types of consent used to enroll participants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

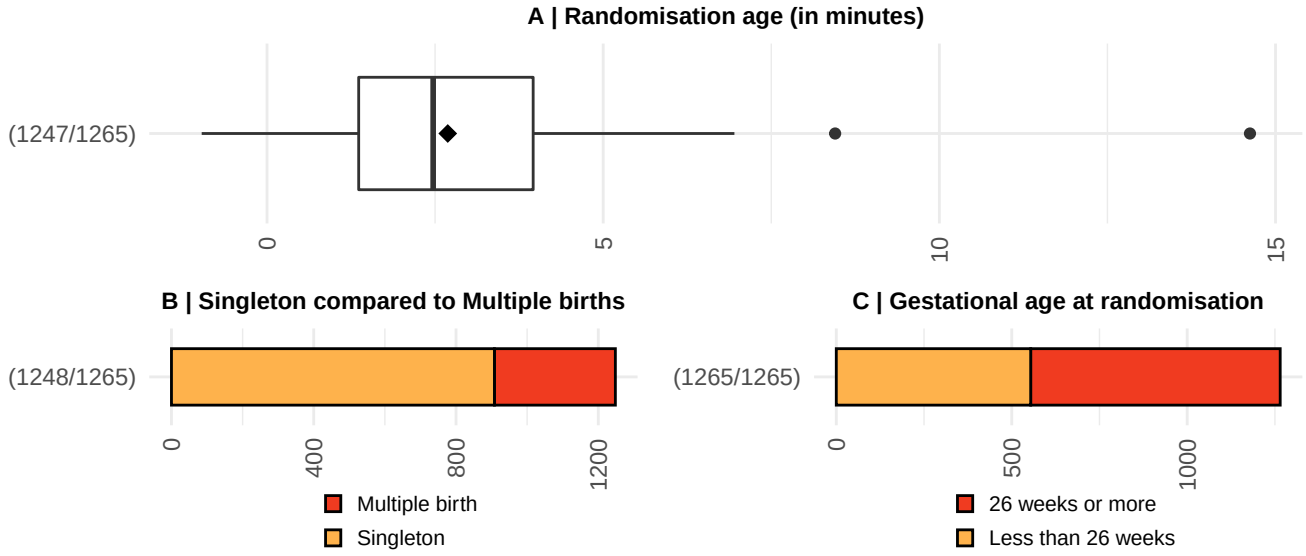

Figure 2 | (A) Age of participants at the time of randomisation in minutes presented using a boxplot. Vertical line depicts median, whereas a diamond represents mean. Stacked barcharts from the 'randomisation' module. **(B)** Proportion of singleton compared to multiple births (extracted from *R02a_singlemulti*);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

End of monitoring

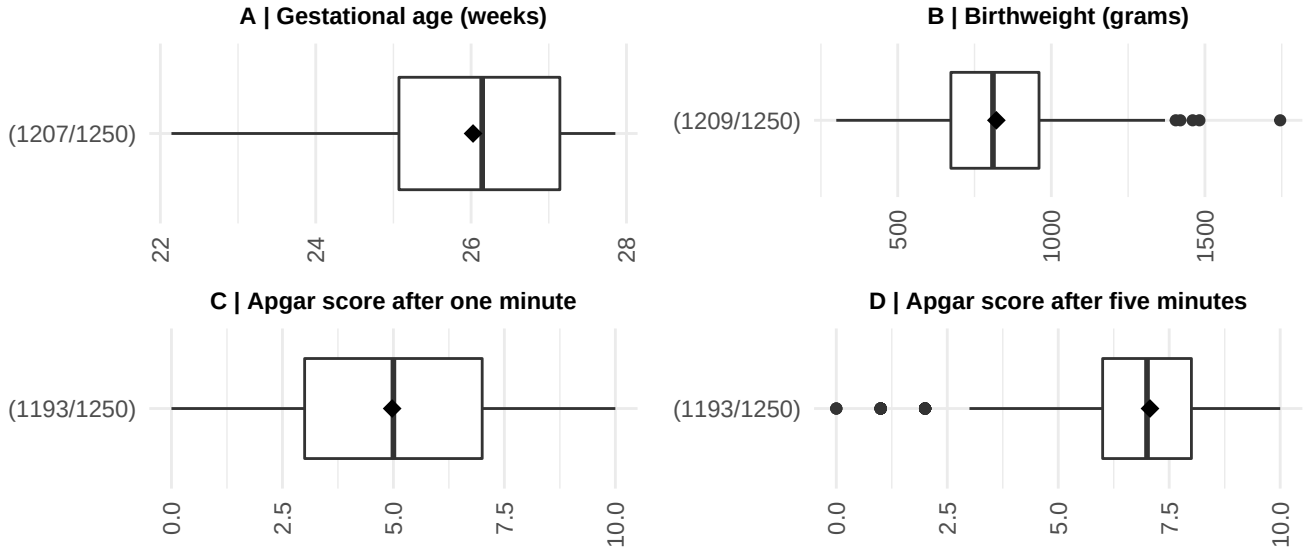

Figure 3 | Boxplots from the 'end of monitoring' module, shown for all participants. **(A)** Gestational age of participants in gestational weeks (extracted from *E01_gestationalage*); **(B)** birthweight in grams of participants (*E02_birthweight*); **(C)** Apgar score for participants one minute after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

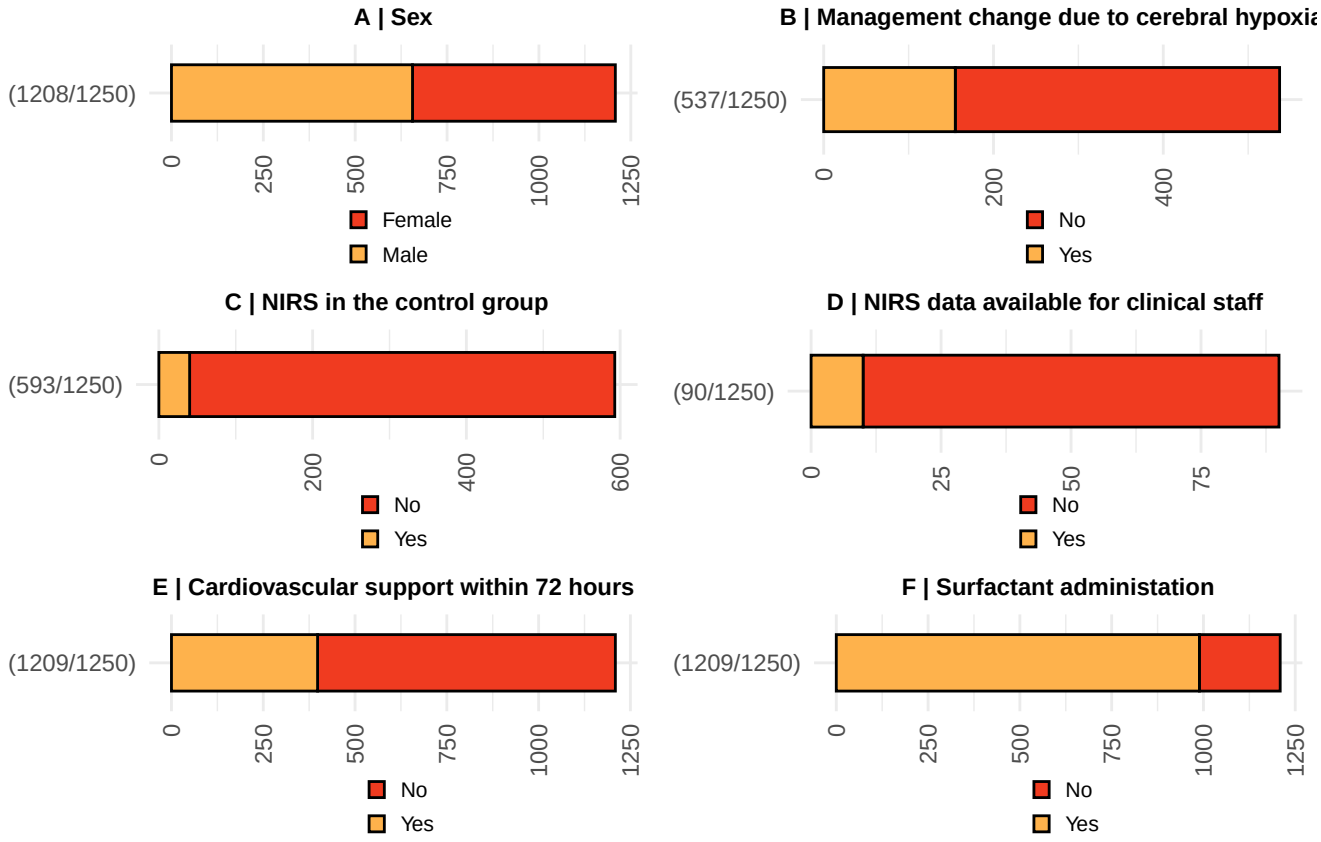

Figure 4 | Stacked barcharts from the 'end of monitoring' module, shown for all participants. **(A)** Sex of participants (extracted from *E05_sex*); **(B)** Proportion of participants with changed treatment due to cerebral hypoxia (*E08_changeoftreatmenthypoxia*); **(C)** with NIRS despite being in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

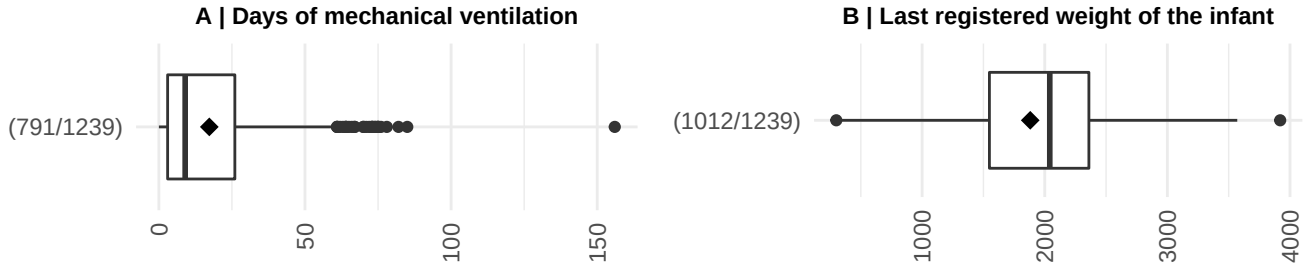

Figure 5 | Boxplots from the 'follow-up' module, shown for all participants. **(A)** Days of mechnical ventilation (extracted from *F03a_daysofvent*); and **(B)** weight at follow-up (*F05_weightatfollowup*).

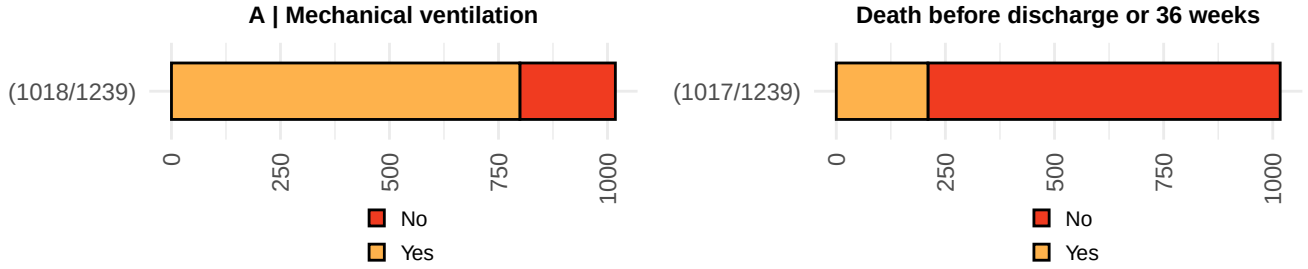

Figure 6 | Stacked barcharts from the 'follow-up' mobule, shown for all participants. **(A)** Proportion of participants on mechanical ventilation during admission (extracted from *F03_mechanicvent*); and **(B)** who died before discharge or before 36 weeks (*F12_death*).

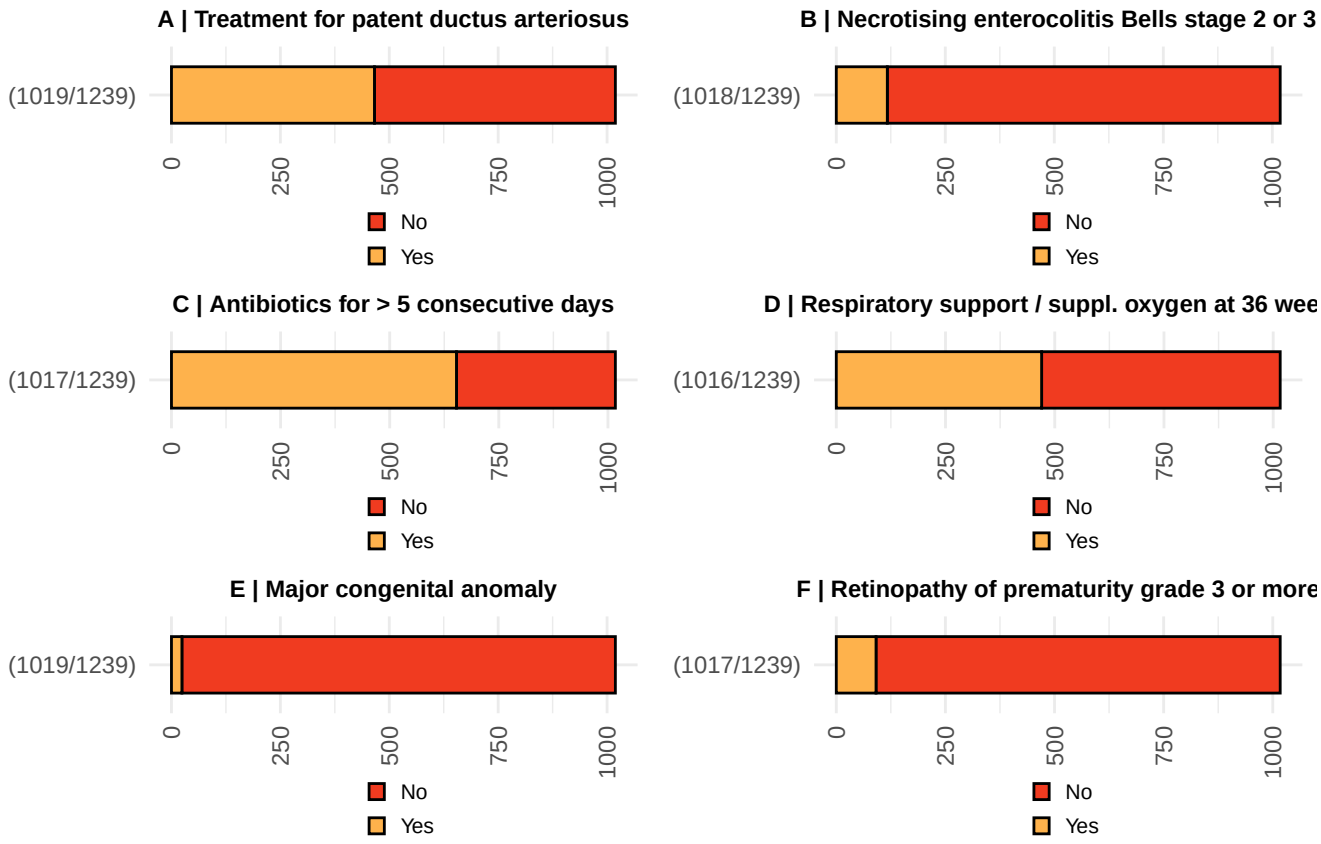

Figure 7 | Stacked barcharts from the 'follow-up' module, shown for all participants. **(A)** Proportion of participants who recieved treatment for patent ductus arteriosus (extracted from *F04_PDA*); **(B)** with necrotising enterocolitis Bells stage 2 or 3 (*F09_nec*); **(C)** who recieved antibiotics 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)	Fb	Only an early cUS was conducted on one participant	Yes	The investigator reports that the participant also had a late cUS, and that the data entry will be corrected.
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	so	Only a cUS between 8 and 35 days was conducted on one participant	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)	AG	Only a cUS between 8 and 35 days was conducted on two participants	Yes	The investigator reports that both participants had early and late cUS, and that data entries have now been corrected.
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	hc	Only an early cUS was conducted on two participants. Only a late cUS was conducted on four participants	Yes	One participant registered as having only had an early cUS, had had a late scan as well. The investigator reports that the date entry has been corrected. The additional 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)	hx	One participant was never scanned	Yes	The participant died after three days of life. Therefore, no scans were conducted after day three. Data entry is 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)	yc	Two participants were never scanned	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 without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life	nP	One participant was never scanned	Yes	The investigator reports that data entries are correct, the participant died within three days of life. No changes needed.
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	ie	Only a cUS between 8 and 35 days was conducted on two participants	Yes	The investigator reports that one participant also had a late cUS and that the data entry is corrected. The other participants data entry is correct.
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	Li	Only an early cUS was conducted on one participant	Yes	The investigator reports that the data entry is 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)	fE	Only an early cUS was conducted on one participant	Yes	The investigator reports that the data entry is correct, no changes needed.
Late initiation of cerebral oximetry monitoring (0-6 hours)	N4	One participant (008) had cerebral oximetry initiated after 10 hrs	Yes	The investigator has been contacted, but no reply received
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	Gl	One participant has been registered	Yes	Correct, the participant only received 'spot' monitoring due to extremely immature skin. No changes needed.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	ie	One participant has been registered	Yes	This is correct, since the participant was never monitored due to device failure. No changes needed.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	nP	One participant has been registered	Yes	The investigator reports that this was a data entry error, and that it has now been changed.

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	fE	One participant has been registered	Yes	The investigator reports that there is an error in the data entry and that it will be corrected accordingly.
Proportion of participants with post-haemorrhagic ventricular dilatation or cerebral atrophy but no late cranial ultrasound scan	g8	One participant has been registered	Yes	The investigator reports that the data entry is correct, no changes needed.
Proportion of participants with post-haemorrhagic ventricular dilatation or cerebral atrophy but no late cranial ultrasound scan	kz	One participant has been registered	Yes	The investigator has been contacted, but no reply received
Proportion of participants with post-haemorrhagic ventricular dilatation or cerebral atrophy but no late cranial ultrasound scan	Li	One participant has been registered	Yes	The investigator reports that the data entry is correct, no changes needed.
Proportion of participants with post-haemorrhagic ventricular dilatation or cerebral atrophy but no late cranial ultrasound scan	sA	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	xX	Two participants have been registered:	Yes	The investigator reports that data entries are correct, no changes needed.
Proportion of participants in the control group that underwent unblinded cerebral oximetry monitoring	hx	One participant has been registered:	Yes	The investigator reports that this was a data entry error, and that it has now been corrected.
Proportion of participants in the control group that underwent unblinded cerebral oximetry monitoring	s6	One participant has been registered:	Yes	The investigator reports that this was a data entry error, and that it has now 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 in the control group that underwent unblinded cerebral oximetry monitoring	yc	Three participants have been registered	Yes	The investigator reports that this is correct, since the participants were included in another study as well. The investigator has been informed that this is a clear protocol violation and that participants in the control group should not undergo visible NIRS monitoring in the future. No changes needed.

* 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 age in hrs	N4	Suspected outlier. One participant was randomised at 8,5 hours of life	Yes	The investigator has been contacted, but no reply received
High birthweight above 1400 gram versus gestational age	Hm	Suspected outlier. One participant	No	Gestational age almost 28 weeks and therefore, the high birthweight could be valid
Management change due to cerebral hypoxia	sA	Suspected misunderstand. 18 participants randomised to the experimental and group and none have been registered with management change due to cerebral hypoxia	Yes	The investigator reports that none of the participants in the experimental group experienced cerebral hypoxia and therefore, none have had treatment based on cerebral hypoxia. No changes needed.
Management change due to cerebral hypoxia	Um	Suspected misunderstand. 15 participants randomised to the experimental and group and only one has been registered with management change due to cerebral hypoxia	Yes	The investigator reports that for the first 15 participants, no cerebral hypoxia was observed that could not be corrected by changing sensor position. No changes needed.
Management change due to cerebral hypoxia	Yw	Suspected misunderstand. 9 participants randomised to the experimental and group and only one have been registered with management change due to cerebral hypoxia	Yes	The investigator reports that data entries are correct. No participant experienced cerebral hypoxia and thus, no interventions have been made based on this. No changes needed.
Standard deviation score for last registered weight of infant, above 1	N4	Suspected outlier. One participant	Yes	The investigator has been contacted, but no reply received

Variable	Blinded site ID	Which suspicion has been raised?	Will any course of action be taken?	Result of the course of action
Participants that is registered as deceased after 36+0 weeks of postmenstrual age	Fb	Suspected misunderstanding. One participant	Yes	The investigator reports that for one participant, mortality status at 36 weeks in OpenClinica was incorrect, since the participant died at 38 weeks. This has been corrected.
Participants that is registered as deceased after 36+0 weeks of postmenstrual age	nP	Suspected misunderstanding. Four participants	Yes	The investigator has corrected the follow-up date for all four participants, mortality status was correct.
Participants that is registered as deceased after 36+0 weeks of postmenstrual age	eJ	Suspected misunderstanding. One participant	Yes	The investigator has been contacted, but no reply received

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
9y	20.06 SD	10 participants randomised; all with a gestational age above 26 weeks (median 27.2); all but one in mechanical ventilation, almost all up until follow-up; no one deceased and only one suffered from severe brain injuries.	Yes	Yes	The investigator has been contacted, but no reply received

Changes to the central monitoring report

NOTA

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

Three participants have been registered. One investigator reports that the data entries has been corrected for two participants, one investigator has not replied.

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

One participants has been registered, no reply from the investigator

Mahalanobis distance

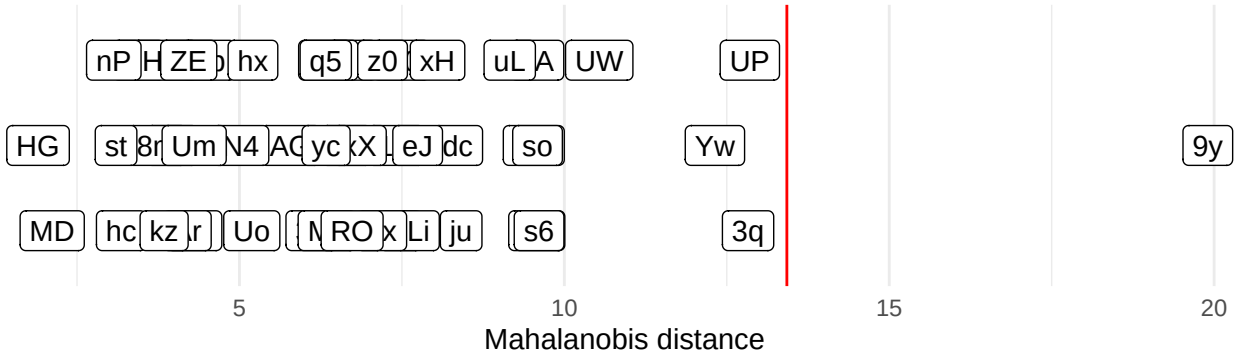

Figure A1 | Mean Mahalanobis distance using clinical parameters with 10.000 resamplings (with 10^4 successful). Gestational age (extracted from *E01_gestationalage*), birthweight (*E02_birthweight*), days of mechanical ventilation (where non-ventilated are set to 0, *F03a_daysofvent*), treatment for patent ductus arteriosus (*F04_PDA*), non-cerebral parameters ('yes' in either retinopathy of prematurity grade 3 or more (*F10_rop*), sepsis (*F11_sepsis*), or necrotising enterocolitis Bells stage 2 or 3 (*F09_nec*)), cerebral parameters ('yes' in either intraventricular haemorrhage grade 3 or 4 (*BF01_ivh*), cystic periventricular leukomalacia (*BF02_cpvl*), post-haemorrhagic ventricular dilatation (*BF03_PHVD*) or cerebellar haemorrhage (*BF04_cerebhaem*)), and death (*F12_death*). An outlier-center is defined by a Mahalanobis distance two standard deviations above the mean distance.