SafeBoosC-III - central monitoring

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30 marts, 2022

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 2nd of February 2022)*. 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

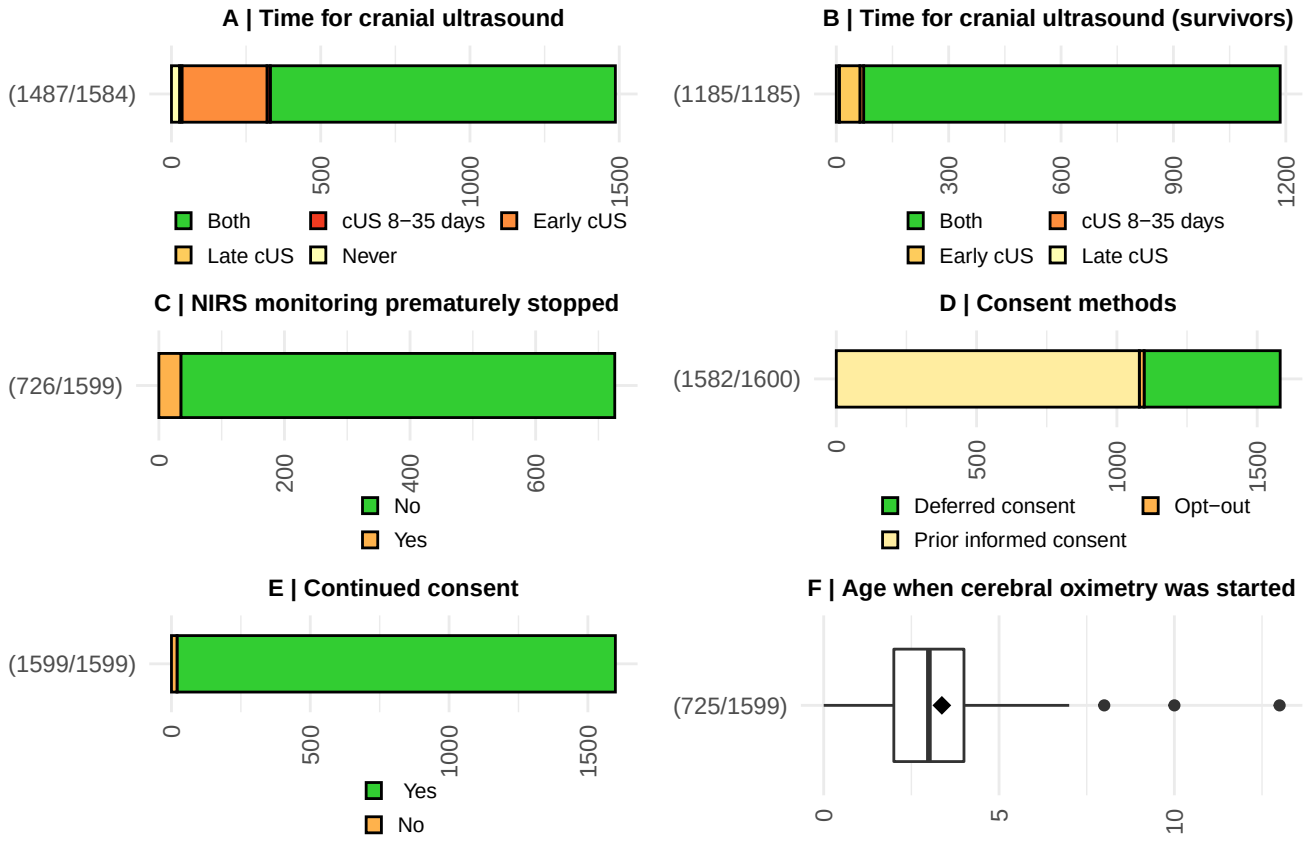

Figure 1 | Stacked barcharts shown for all participants. **(A)** Time for cranial ultrasound for all and **(B)** for survivors (extracted from *F07_cus*); **(C)** proportion of participants with prematurely stopped NIRS monitoring (*E07_prematurenirsstop*); **(D)** types of consent used to enroll participants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

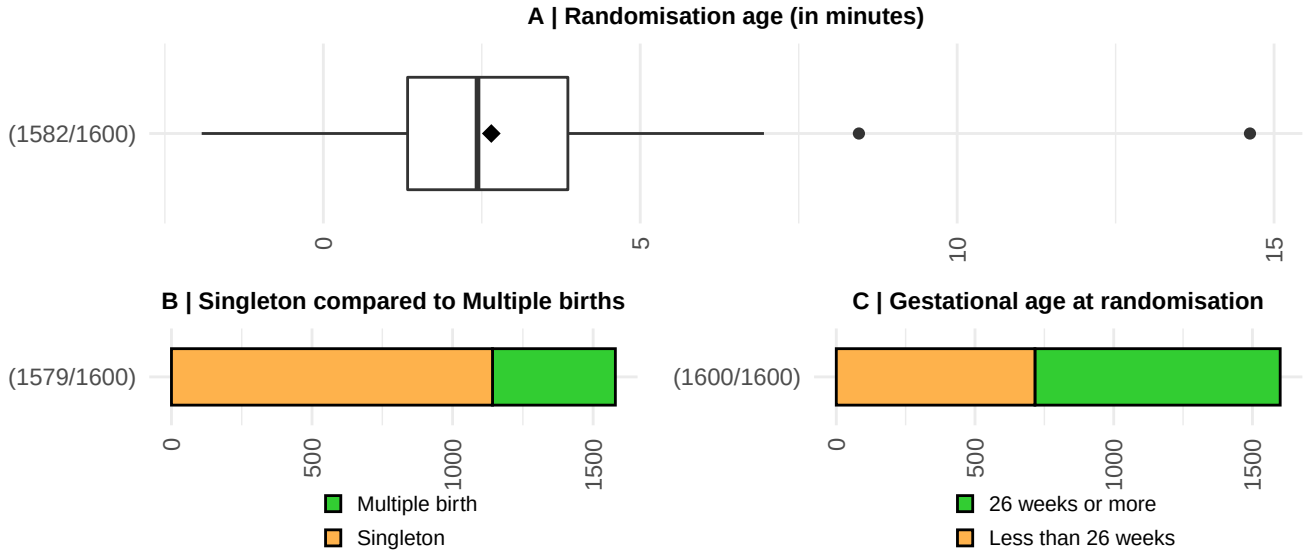

Figure 2 | (A) Age of participants at the time of randomisation in minutes presented using a boxplot. Vertical line depicts median, whereas a diamond represents mean. Stacked barcharts from the 'randomisation' module. **(B)** Proportion of singleton compared to multiple births (extracted from *R02a_singlemulti*);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

End of monitoring

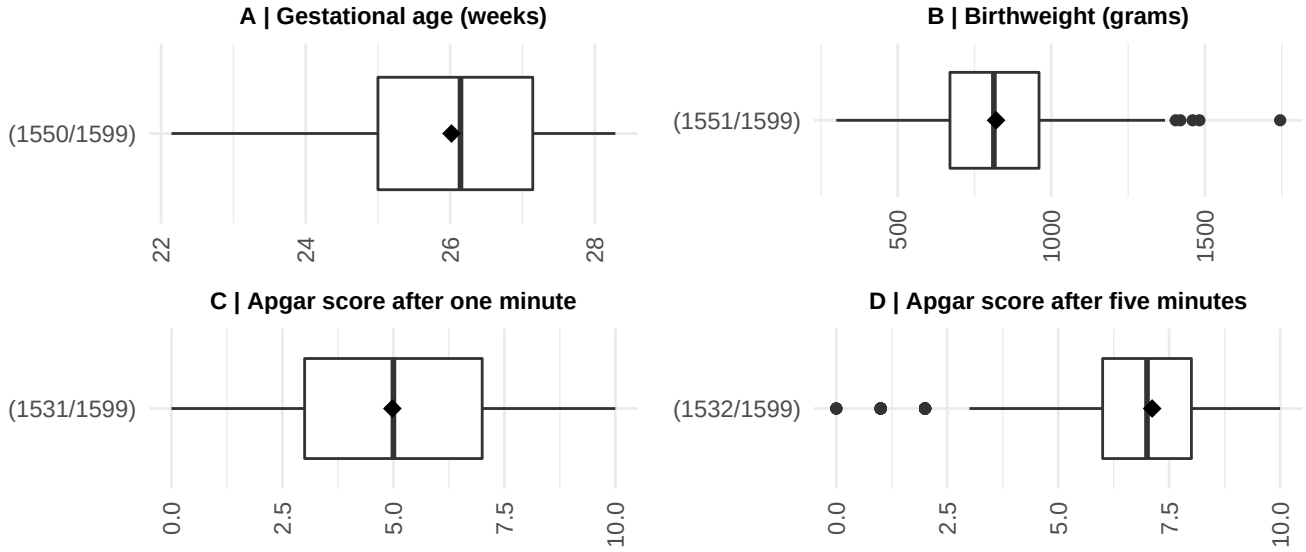

Figure 3 | Boxplots from the 'end of monitoring' module, shown for all participants. **(A)** Gestational age of participants in gestational weeks (extracted from *E01_gestationalage*); **(B)** birthweight in grams of participants (*E02_birthweight*); **(C)** Apgar score for participants one minute after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

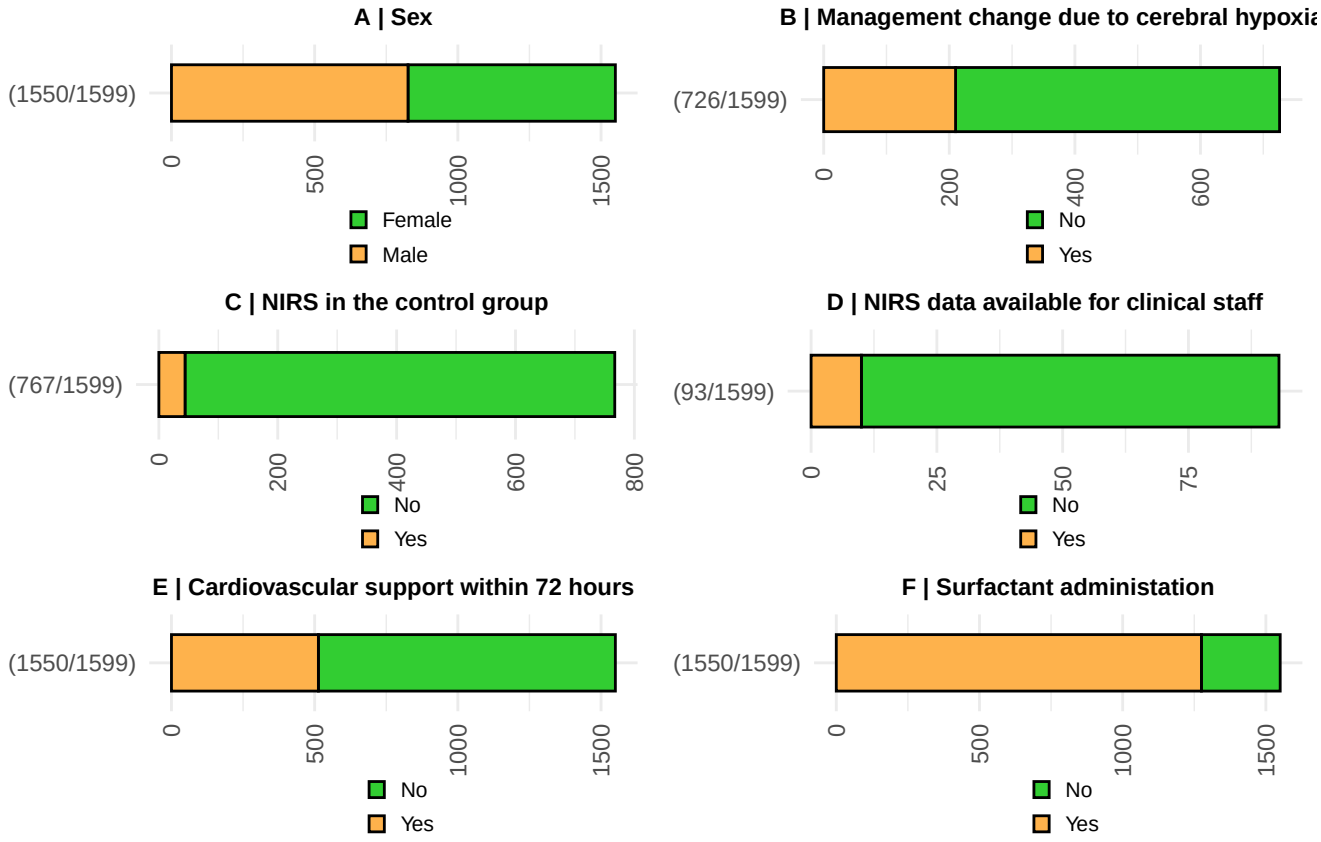

Figure 4 | Stacked barcharts from the 'end of monitoring' module, shown for all participants. **(A)** Sex of participants (extracted from *E05_sex*); **(B)** Proportion of participants with changed treatment due to cerebral hypoxia (*E08_changeoftreatmenthypoxia*); **(C)** with NIRS despite being in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

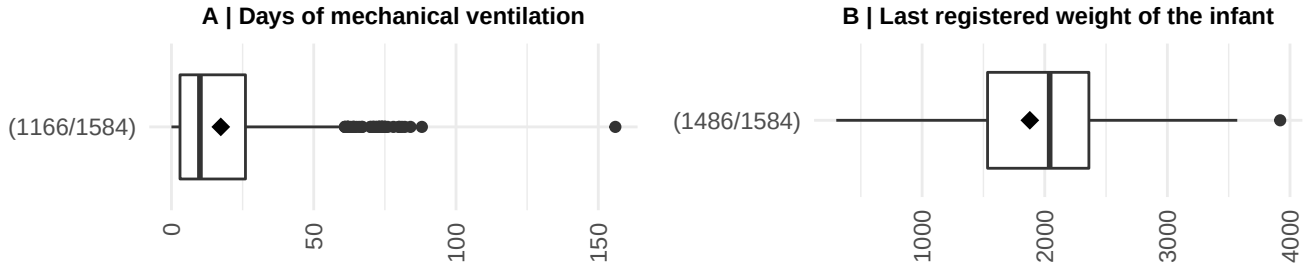

Figure 5 | Boxplots from the 'follow-up' module, shown for all participants. **(A)** Days of mechnical ventilation (extracted from *F03a_daysofvent*); and **(B)** weight at follow-up (*F05_weightatfollowup*).

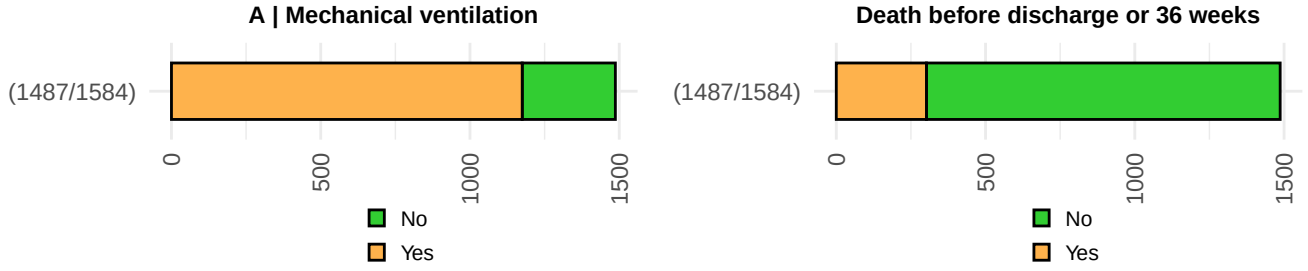

Figure 6 | Stacked barcharts from the 'follow-up' mobule, shown for all participants. **(A)** Proportion of participants on mechanical ventilation during admission (extracted from *F03_mechanicvent*); and **(B)** who died before discharge or before 36 weeks (*F12_death*).

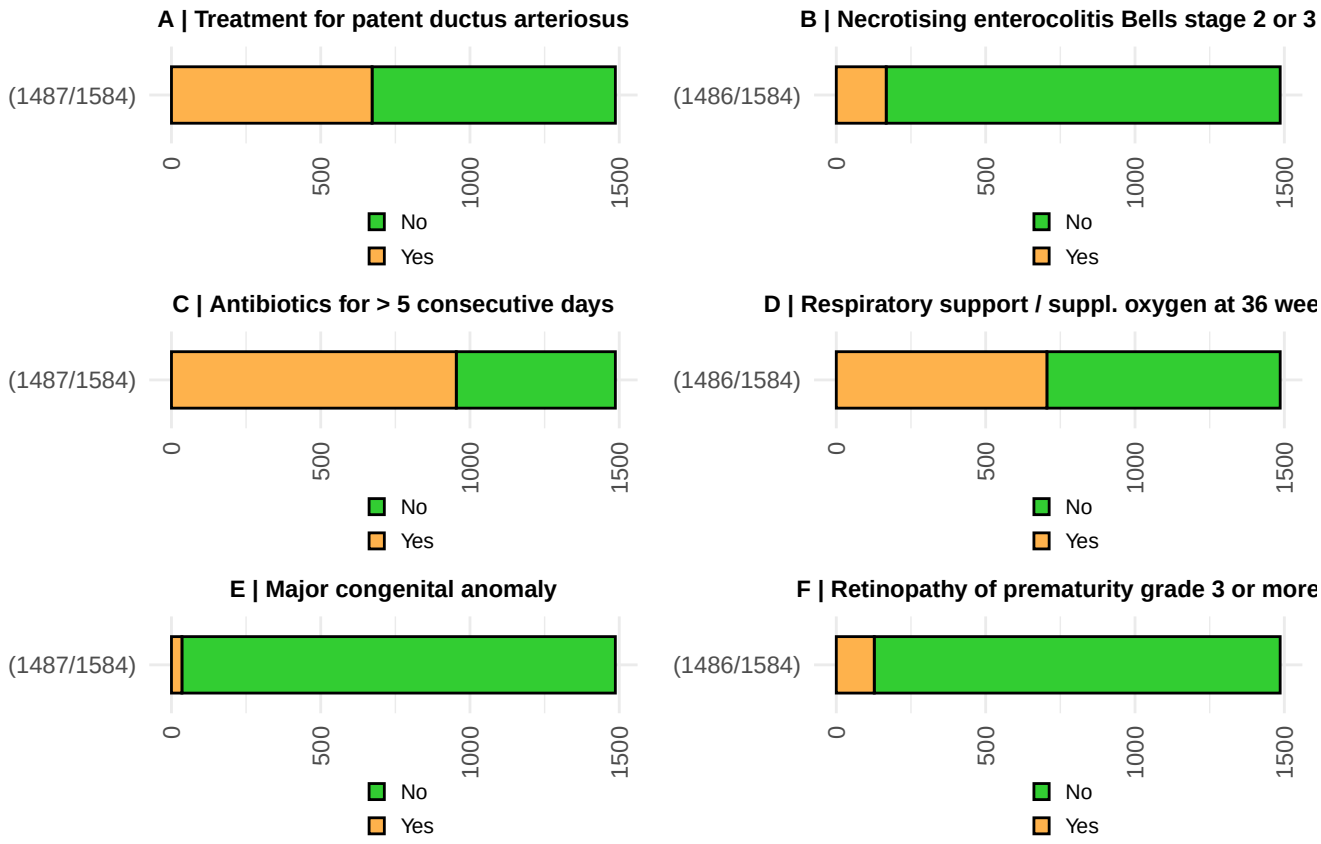

Figure 7 | Stacked barcharts from the 'follow-up' module, shown for all participants. **(A)** Proportion of participants who recieved treatment for patent ductus arteriosus (extracted from *F04_PDA*); **(B)** with necrotising enterocolitis Bells stage 2 or 3 (*F09_nec*); **(C)** who recieved antibiotics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

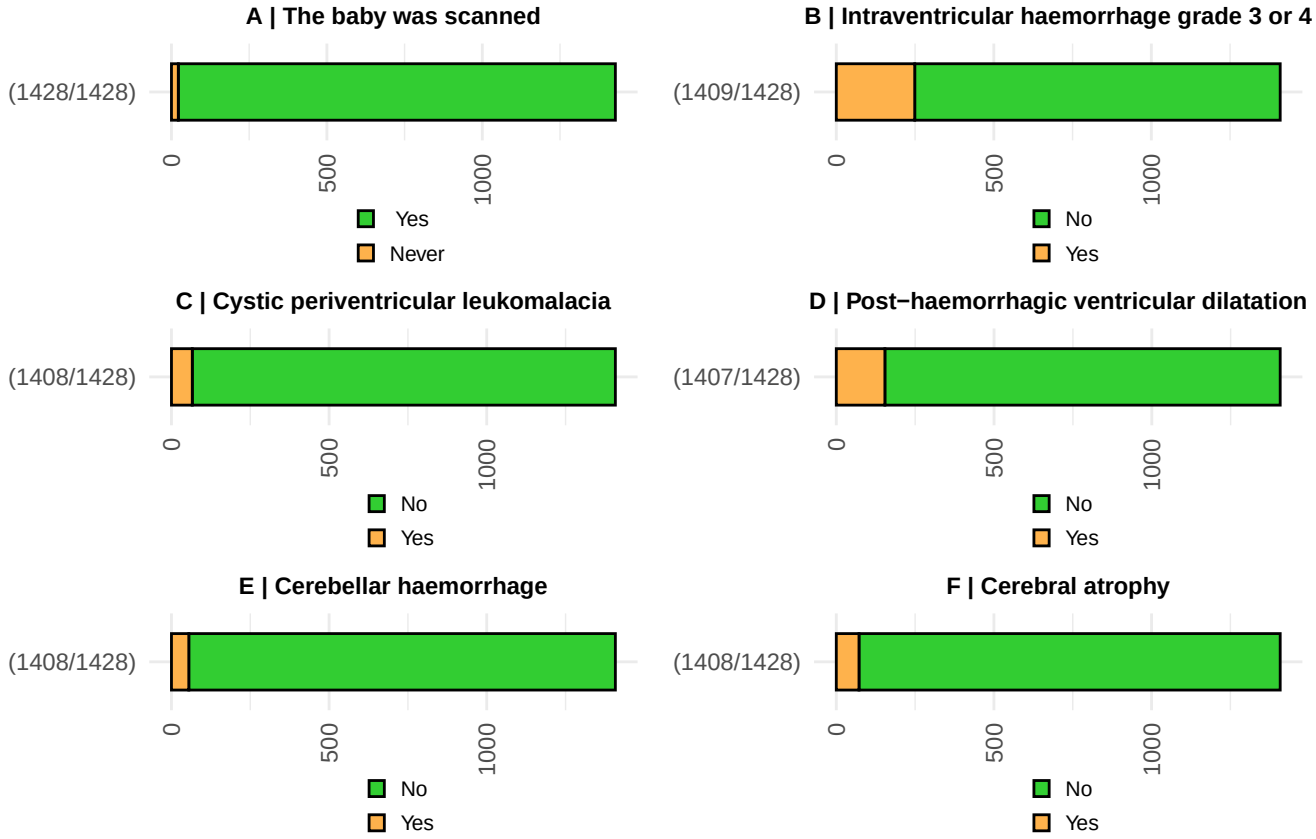

Figure 8 | Stacked barcharts from the 'blinded follow-up' module. **(A)** Proportion of participants who were never scanned (extracted from *BF6_neverscanned*); **(B)** with intraventricular haemorrhage grade 3 or 4; **(C)** with cystic periventricular leukomalacia (*BF02_cpvl*); **(D)** with post-haemorrhagic 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)	Sb	Only an early cUS was conducted on one participant.	Yes	The investigator reports that both an early and a late cUS were conducted, and therefore, the investigator has been asked to correct this.
—	—	—	—	—
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	3O	Only an early cUS was conducted on one participant.	Yes	The investigator reports that the data entry is correct. No change needed.
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	Lk	Only an early cUS was conducted on four participants. Only a late cUS was conducted on two participants.	Yes	The investigator that data entries for the four participants only registered with an early scan are correct. For the two participants only registered with a late scan, one was correct, and one received both and early and a late scan. The single data entry error will be corrected by the investigator. The investigator also reports that two additional participants neither received both a late and an early scan.

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)	jG	Only an early cUS was conducted on two participants. Only a cUS between 8 and 35 days was conducted on two participants.	Yes	The investigator reports that it is correct two participants had early and not late cSU. No changes needed for these two. The two participants registered with cUS only between 8 and 35 days of life, was scanned on day 7 and 30 days. Therefore, they should be registered as having undergone early cUS. The investigator reports that data has been corrected.
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	Lj	Only an early cUS was conducted on one participant.	Yes	The investigator reports that the data entry is correct. No change needed.
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	3m	Only an early cUS was conducted on nine participants.	Yes	The investigator reports that the data entries are correct. No change needed.
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	Om	Only an early cUS was conducted on one participant.	Yes	The investigator reports that the data entry is correct. No change needed.
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	Fj	Only an early cUS was conducted on three participants.Only a cUS between 8 and 35 days was conducted on two participants.	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)	tp	Only an early cUS was conducted on one participant.	Yes	The investigator reports that the data entry is correct. No change 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)	7d	Only an early cUS was conducted on three participants.Only a cUS between 8 and 35 days was conducted on two participants.	Yes	The investigator reports that data entries for the two participants only registered with an early cUS are correct. No changes needed.For the participant registered with a scan between 8 and 35 days, the participant was also scanned between day 3 and 8. The investigator has been asked to change the answer possibility to "early cUS".
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	h2	Only a late cUS was conducted on one participant.	Yes	The investigator reports that the data entry is correct. No change needed.
Late initiation of cerebral oximetry monitoring (0-6 hours)	UD	One participant has been registered (10 hrs from birth to initiation).	Yes	The national GCP monitor person reports that this is correct. No changes needed.
Late initiation of cerebral oximetry monitoring (0-6 hours)	Lk	One participant has been registered (13 hrs from birth to initiation).	Yes	The investigator reports that the data entry is correct. No change needed.
Late initiation of cerebral oximetry monitoring (0-6 hours)	uC	One participant has been registered (7 hrs from birth to initiation).	Yes	The investigator reports that the data entry is correct. The reason was technical problems with the oximeter and therefore, they had to connect and start up monitoring with a new oximeter.
Late initiation of cerebral oximetry monitoring (0-6 hours)	9r	One participant has been registered (8 hrs from birth to initiation).	Yes	The investigator reports that the data entry is correct. The monitoring was not initiated until eight hrs after birth despite randomisation early. This was due to a mistake by the bedside nurse. 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)	Lk	One participant has been registered.	Yes	The investigator reports that the data entry is correct. No change needed.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	h2	Four participants have been registered.	Yes	The investigator reports that the data entries are correct. The main reason was discomfort and destabilisation of the infants.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	jG	One participant has been registered.	Yes	The investigator reports that the data entry is correct. The parents withdraw the participant from the trial and wanted the monitoring with NIRS to stop. No change needed.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	jo	One participant has been registered.	Yes	The investigator reports that the data entry is correct. The monitoring was stopped due to a skin injury. No change needed.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	JR	One participant has been registered.	Yes	The investigator reports that the data entry is correct. The monitoring was stopped due to technical issues with the monitoring device.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	pY	One participant has been registered.	Yes	The investigator reports that the data entry is correct. The monitoring was stopped one day early by a mistake. No change needed.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	7d	One participant has been registered.	Yes	The investigator reports that monitoring was missing for only 8 hours. As the definition of "significant amount of missing monitoring" is 14 hours, the investigator has been asked to change the answer to a "No".

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	7d	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	9r	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	aJ	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	am	One participant has been registered.	Yes	The investigator reports that no ventricular dilatation was present and therefore, the data entry has been changed accordingly.
Proportion of participants with post-haemorrhagic ventricular dilatation or cerebral atrophy but no late cranial ultrasound scan	F5	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	ha	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	kE	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	Lj	One participant has been registered.	Yes	The investigator reports that the data entry is correct. No change 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 with post-haemorrhagic ventricular dilatation or cerebral atrophy but no late cranial ultrasound scan	mY	One participant has been registered.	Yes	The investigator reports that the data entry is correct. No change needed.
Proportion of participants with post-haemorrhagic ventricular dilatation or cerebral atrophy but no late cranial ultrasound scan	Om	One participant has been registered.	Yes	The investigator reports that the data entry is correct. No change needed.
Proportion of participants with post-haemorrhagic ventricular dilatation or cerebral atrophy but no late cranial ultrasound scan	tp	One participant has been registered.	Yes	The investigator reports that the data entry is correct, no change needed.
Proportion of participants with post-haemorrhagic ventricular dilatation or cerebral atrophy but no late cranial ultrasound scan	Y3	Three participants have been registered.	Yes	The investigator reports that the data entries are correct, no change needed.
Proportion of participants in the control group that underwent unblinded cerebral oximetry monitoring	Sb	Two participants have been registered.	Yes	The investigator reports that this is correct, one was monitored for six hours as decided by clinical staff due to birth asphyxia and one was monitored for two hours for unknown reason.
Proportion of participants in the control group that underwent unblinded cerebral oximetry monitoring	CU	One participant has been registered.	Yes	The investigator reports that the data entry is correct, no change needed.
Proportion of participants in the control group that underwent unblinded cerebral oximetry monitoring	Ml	One participant has been registered.	Yes	The investigator reports that the clinical staff decided to monitor the participant with NIRS during abdominal surgery and early after. Therefore, 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 minutes	UD	Suspected outlier due to 8.5 hours of age when randomised.	Yes	The national GCP monitor person reports that this is correct. No changes needed.
—	—	—	—	—
Change in management due to cerebral hypoxia	wT	Suspected misunderstanding since no participants in the experimental group have been registered with treatment due to cerebral hypoxia.	Yes	The investigator reports that it is correct, no changes needed.
Change in management due to cerebral hypoxia	h2	Suspected misunderstanding since no participants in the experimental group have been registered with treatment due to cerebral hypoxia.	Yes	The investigator reports that it is correct, no changes needed.
Change in management due to cerebral hypoxia	jG	Suspected misunderstanding since no participants in the experimental group have been registered with treatment due to cerebral hypoxia.	Yes	The investigator reports that it is correct, no changes needed.
Change in management due to cerebral hypoxia	c6	Suspected misunderstanding since no participants in the experimental group have been registered with treatment due to cerebral hypoxia.	Yes	The investigator reports that it is correct, no changes needed.
Change in management due to cerebral hypoxia	kU	Suspected misunderstanding since no participants in the experimental group have been registered with treatment due to cerebral hypoxia.	Yes	The investigator reports that it is 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
Change in management due to cerebral hypoxia	Lw	Suspected misunderstanding since no participants in the experimental group have been registered with treatment due to cerebral hypoxia.	Yes	The investigator reports that it is correct, no changes needed.
Change in management due to cerebral hypoxia	pj	Suspected misunderstanding since no participants in the experimental group have been registered with treatment due to cerebral hypoxia.	Yes	The investigator reports that it is correct, no changes needed.
Change in management due to cerebral hypoxia	08	Suspected misunderstanding since no participants in the experimental group have been registered with treatment due to cerebral hypoxia.	Yes	The investigator reports that it is correct, no changes needed.
Change in management due to cerebral hypoxia	UD	Suspected outlier due to a last registered weight standard-deviation score of 2.23.	Yes	The investigator reports that the entered weight was incorrect, and that the participants last weight at 36 weeks of PMA was 1000 g lower. This has now 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
jL	16.99	High gestational age, all singletons, almost all males, little use of cardiovascular support, almost all in mechanical ventilation and for a long time, no deaths, few receives treatment for ductus, no necrotising enterocolitis, all but one receives antibiotics, high incidence of cerebral atrophy.	Yes	No	No further action, similar data pattern as seen in previous rounds. Investigator has reported that the observation and subsequent data entries are correct.
ha	15.29	High mortality, most in mechanical ventilation, low gestational age and birthweight, high incidence of necrotizing enterocolitis and use of antibiotics.	Yes	No	No further action, similar data pattern as seen in previous rounds. Investigator has reported that the observation and subsequent data entries are correct.

NOTA

_ Days of mechanical ventilation longer than possible due to the 36 weeks follow-up limit - One participant was registered, the investigator has corrected the data entry.

Mahalanobis distance

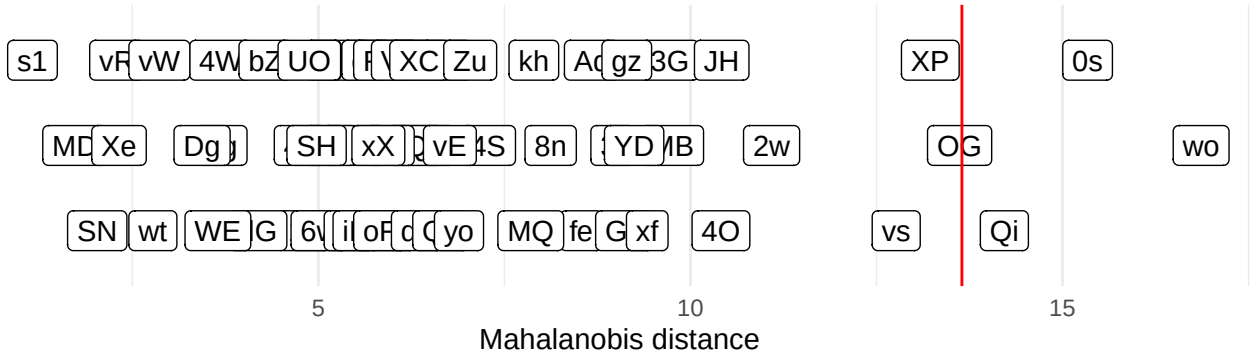

Figure A1 | Mean Mahalanobis distance using clinical parameters with 10.000 resamplings (with 10^4 successful). Gestational age (extracted from *E01_gestationalage*), birthweight (*E02_birthweight*), days of mechanical ventilation (where non-ventilated are set to 0, *F03a_daysofvent*), treatment for 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.