SafeBoosC-III - central monitoring

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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 October 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

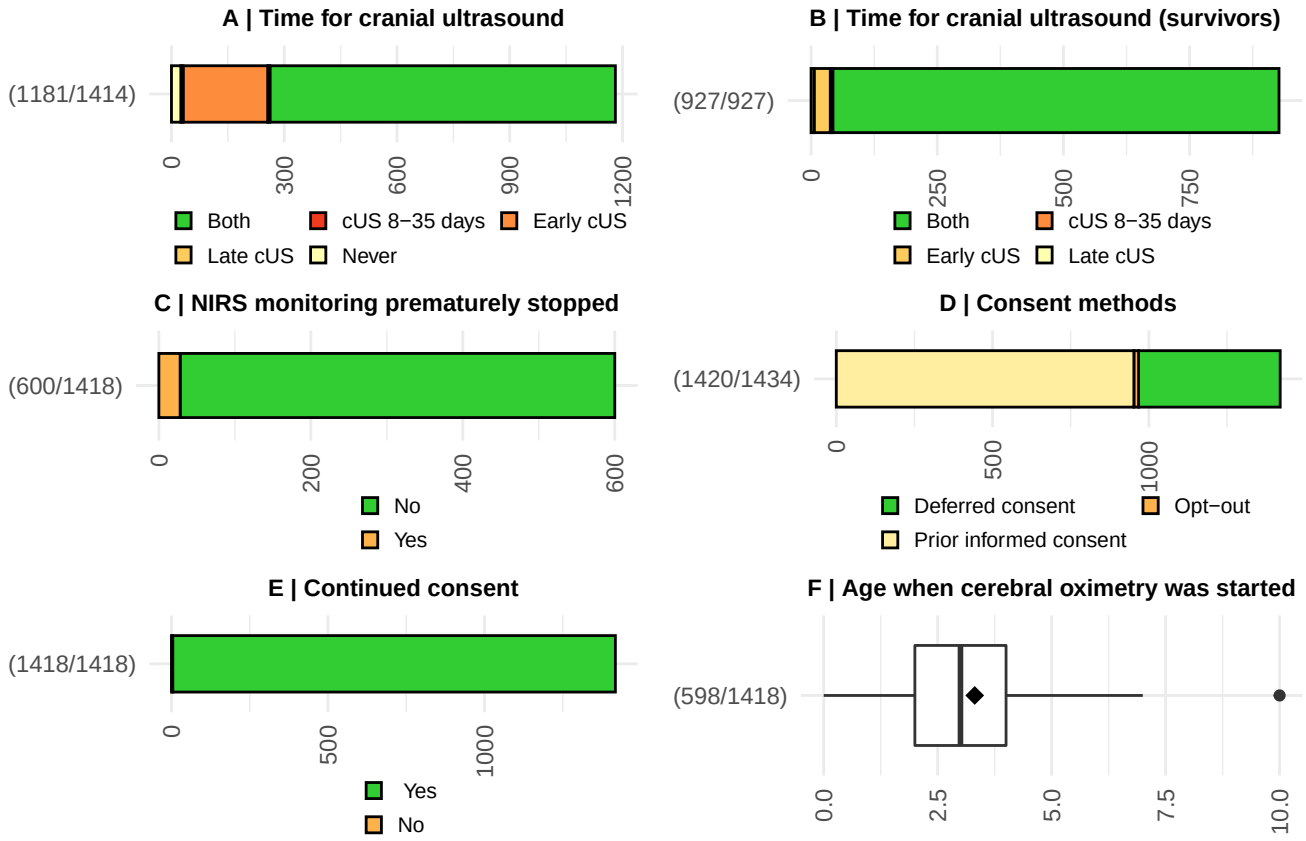

Figure 1 | Stacked barcharts shown for all participants. **(A)** Time for cranial ultrasound for all and **(B)** for survivors (extracted from *F07_cus*); **(C)** proportion of participants with prematurely stopped NIRS monitoring (*E07_prematurenirsstop*); **(D)** types of consent used to enroll participants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

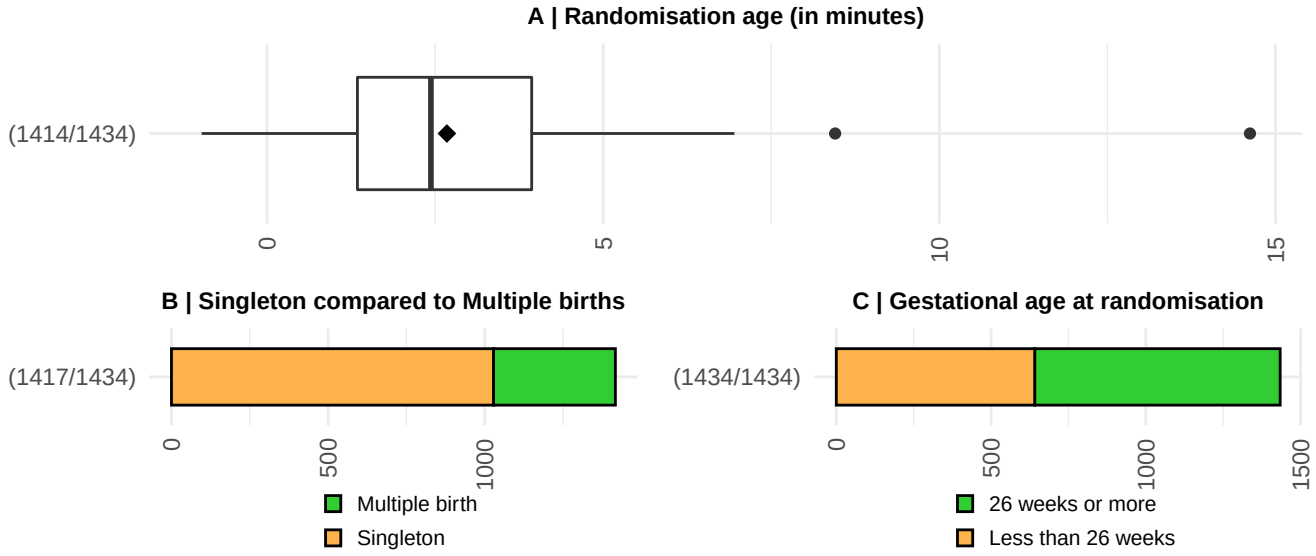

Figure 2 | (A) Age of participants at the time of randomisation in minutes presented using a boxplot. Vertical line depicts median, whereas a diamond represents mean. Stacked barcharts from the 'randomisation' module. **(B)** Proportion of singleton compared to multiple births (extracted from *R02a_singlemulti*);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

End of monitoring

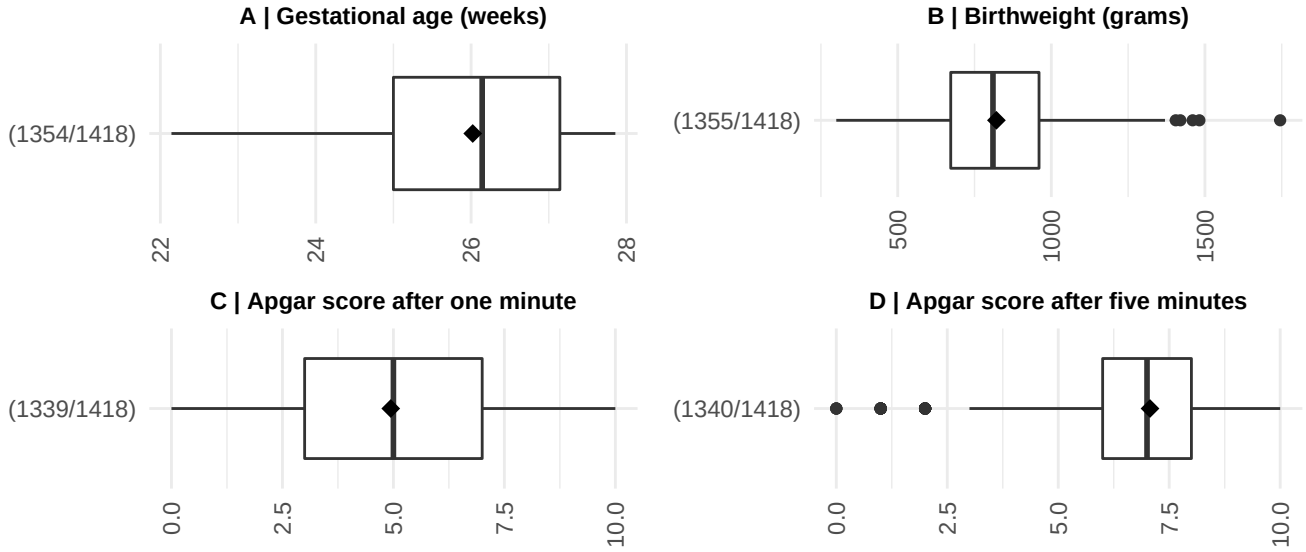

Figure 3 | Boxplots from the 'end of monitoring' module, shown for all participants. **(A)** Gestational age of participants in gestational weeks (extracted from *E01_gestationalage*); **(B)** birthweight in grams of participants (*E02_birthweight*); **(C)** Apgar score for participants one minute after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

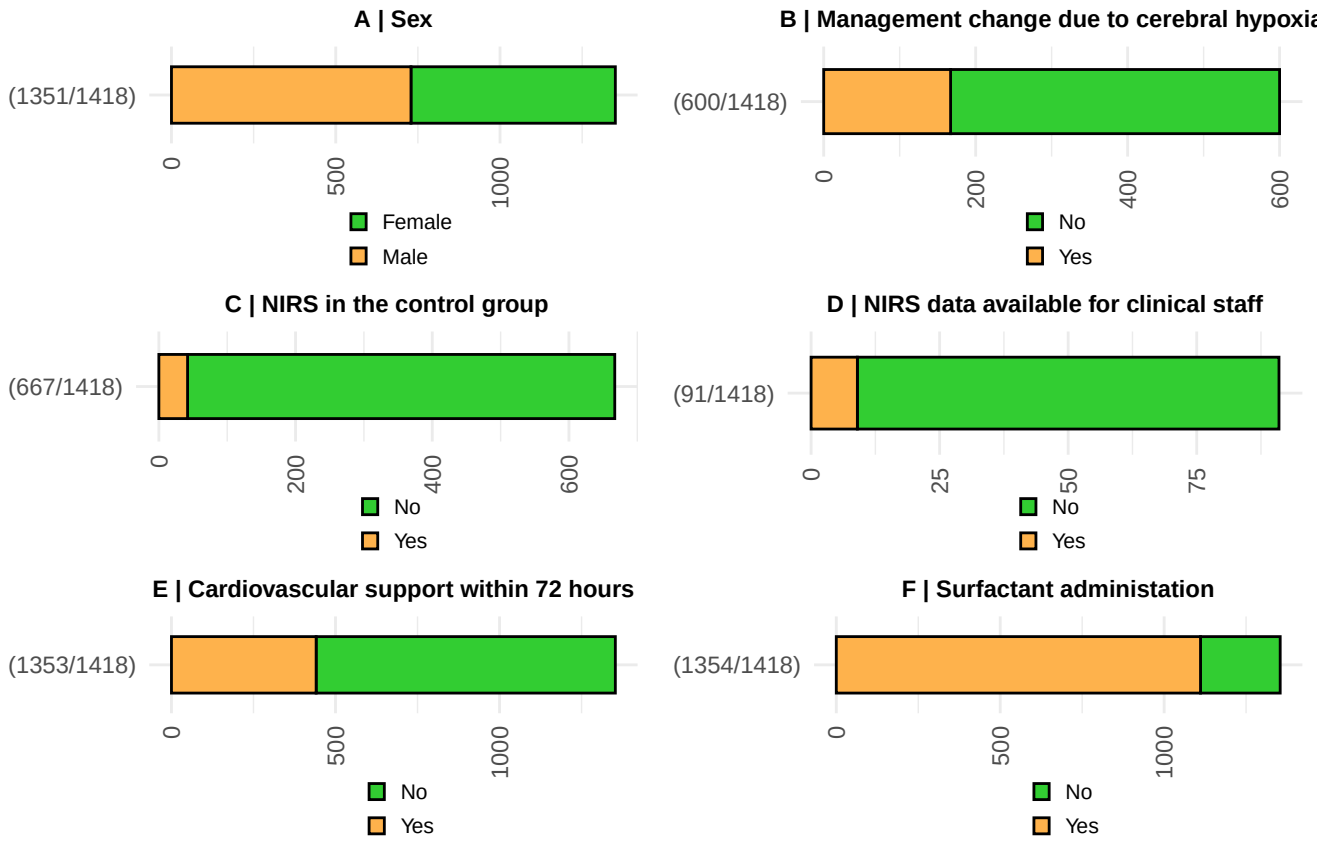

Figure 4 | Stacked barcharts from the 'end of monitoring' module, shown for all participants. **(A)** Sex of participants (extracted from *E05_sex*); **(B)** Proportion of participants with changed treatment due to cerebral hypoxia (*E08_changeoftreatmenthypoxia*); **(C)** with NIRS despite being in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

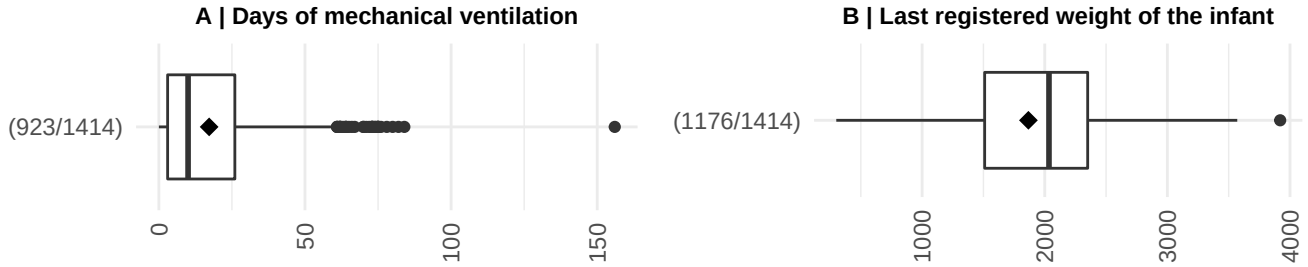

Figure 5 | Boxplots from the 'follow-up' module, shown for all participants. **(A)** Days of mechnical ventilation (extracted from *F03a_daysofvent*); and **(B)** weight at follow-up (*F05_weightatfollowup*).

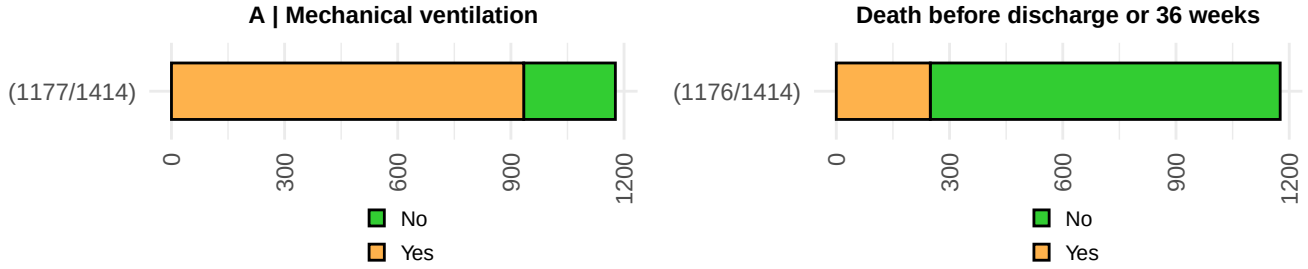

Figure 6 | Stacked barcharts from the 'follow-up' mobule, shown for all participants. **(A)** Proportion of participants on mechanical ventilation during admission (extracted from *F03_mechanicvent*); and **(B)** who died before discharge or before 36 weeks (*F12_death*).

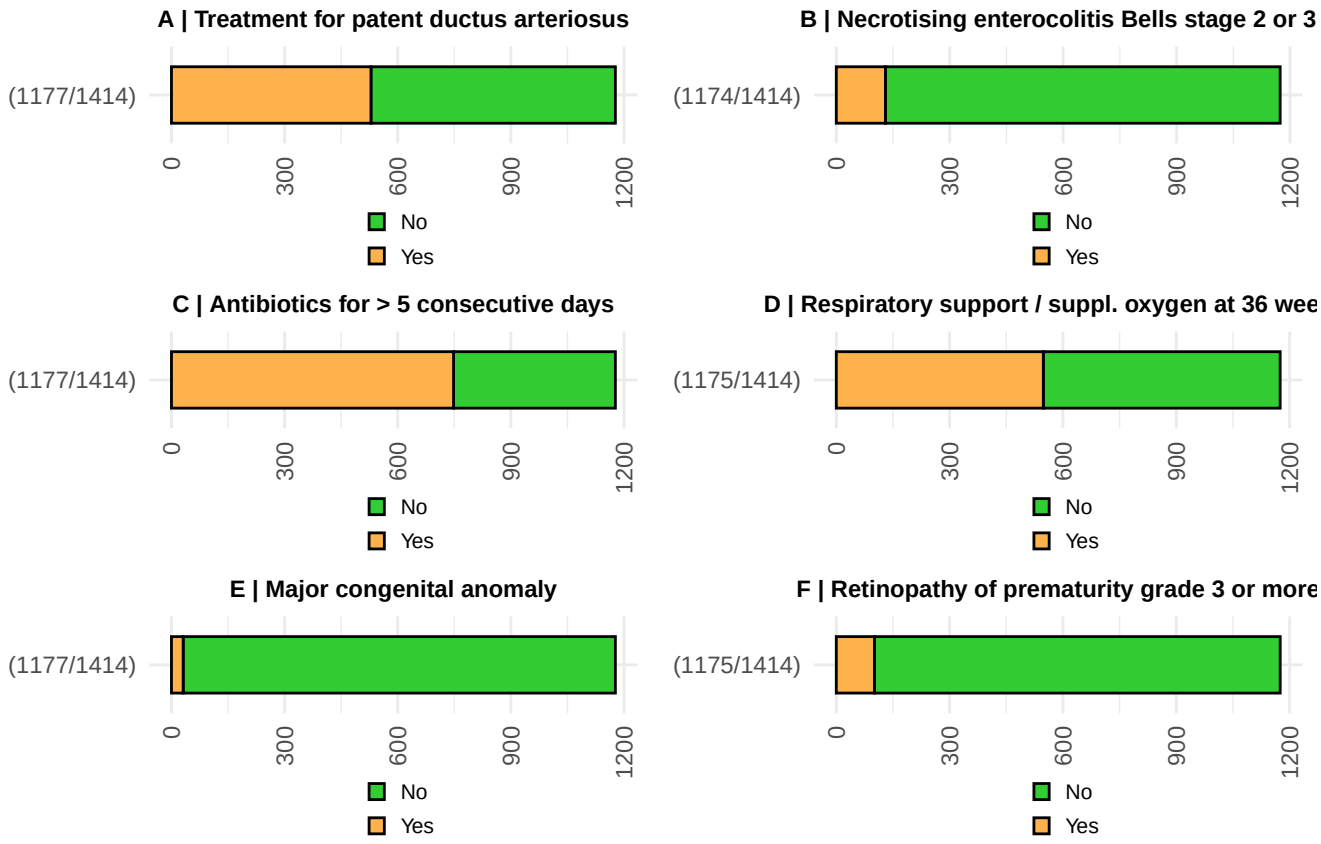

Figure 7 | Stacked barcharts from the 'follow-up' module, shown for all participants. **(A)** Proportion of participants who recieved treatment for patent ductus arteriosus (extracted from *F04_PDA*); **(B)** with necrotising enterocolitis Bells stage 2 or 3 (*F09_nec*); **(C)** who recieved antibiotics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

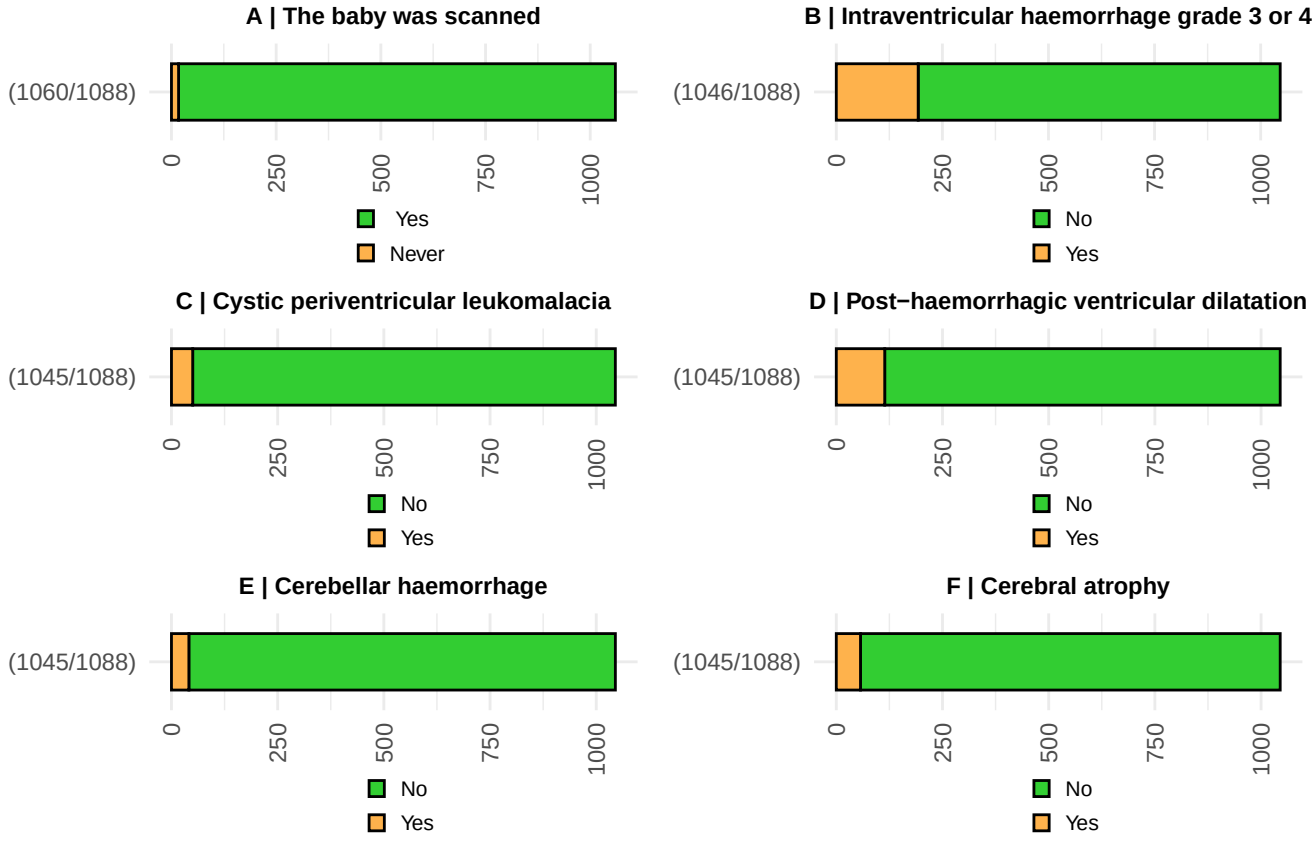

Figure 8 | Stacked barcharts from the 'blinded follow-up' module. **(A)** Proportion of participants who were never scanned (extracted from *BF6_neverscanned*); **(B)** with intraventricular haemorrhage grade 3 or 4; **(C)** with cystic periventricular leukomalacia (*BF02_cpvl*); **(D)** with post-haemorrhagic 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)	H9	Only an early cUS was conducted on one participant	Yes	The investigator has been contacted, no response received
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	W2	Only a late cUS was conducted on four participants	Yes	The investigator has been contacted, no response received
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	xQ	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)	Mm	Only an early cUS was conducted on three 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)	n8	Only an early cUS 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)	Uv	Only an early cUS was conducted on one participant. Only a late cUS was conducted on four participants	Yes	The investigator reports that data entries are correct, no changes needed.
Late initiation of cerebral oximetry monitoring (0-6 hours)	Bi	One participant has been registered	Yes	The investigator has been contacted, no response received

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)	D7	One participant has been registered	Yes	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)	xQ	One participant has been registered	Yes	The investigator reports that the data entry is correct, the parents withdrew consent due to the size of the NIRS sensor and thus, monitoring was stopped prematurely. No changes needed.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	Q6	One participant has been registered	Yes	The investigator has been contacted, no response received
Proportion of participants with post-haemorrhagic ventricular dilatation or cerebral atrophy but no late cranial ultrasound scan	aH	One participant has been registered	Yes	The investigator has been contacted, no response received
Proportion of participants with post-haemorrhagic ventricular dilatation or cerebral atrophy but no late cranial ultrasound scan	Dr	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	eE	One participant has been registered	Yes	The investigator has been contacted, no response received
Proportion of participants in the control group that underwent unblinded cerebral oximetry monitoring	Y3	One participant has been registered	Yes	The investigator reports that this was a data entry error and that it has been corrected.
Proportion of participants in the control group that underwent unblinded cerebral oximetry monitoring	H9	One participant has been registered	Yes	The investigator has been contacted, no response received

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	gO	One participant has been registered	Yes	The investigator has been contacted, no response received
Proportion of participants where parents withdrew consent	xQ	One participant has been registered	Yes	The investigator reports that the data entry is correct, the parents withdrew consent due to the size of the NIRS sensor. No changes needed. The process of requesting use of future data is ongoing.

* 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 more than 6 hours from birth	Bi	One participant randomised 8.45 hrs from birth, suspected outlier	Yes	The investigator has been contacted, no response received
Management change due to cerebral hypoxia	KW	No changes in management due to cerebral hypoxia in the first 11 participants randomised to the experimental group, suspected misunderstandings	No	The investigator reported in the previous round of central data monitoring that this was correct after the first nine randomised participants in the experimental group. Therefore, no further action is required for now.
Days of mechanical ventilation	aH	One participant registered as being mechanically ventilated for 156 which is longer than 36 weeks of postmenstrual age, suspected misunderstanding	Yes	The investigator has been contacted, no response received
SDS >1, based on last registered weight of the infant	Bi	One participant had an SDS of 2.2 for the last registered weight, suspected outlier	Yes	The investigator has been contacted, no response 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
aR	16.84	11 participants randomised; randomised early; majority female; all in mechanical ventilation but for a short time, almost all deceases	No	No	The randomised participants are average compared to the rest of the sample but have a very high mortality rate. However, due to low numbers, we cannot exclude that the high mortality rate is 'by chance'. Thus, no action will be taken. If the centre is identified by Mahalanobis distance during the next round of central monitoring, the investigator will be contacted.
NI	22.12	10 participants randomised; majority males; all with a gestational age above 26 weeks (median 27.2); high APGAR; no use of cardiovascular support; all but one in mechanical ventilation and in mechanical ventilation up until follow-up; no one deceased and only one suffered from severe brain injuries.	Yes	Yes	The investigator reports that the data is correct. The trial participants have so far had a high gestational age, and all been in mechanical ventilation (invasive and non-invasive) from birth and until 36 weeks PMA). Thus, it reflects well the centres general clinical practice. No further actions are needed.

Mahalanobis distance

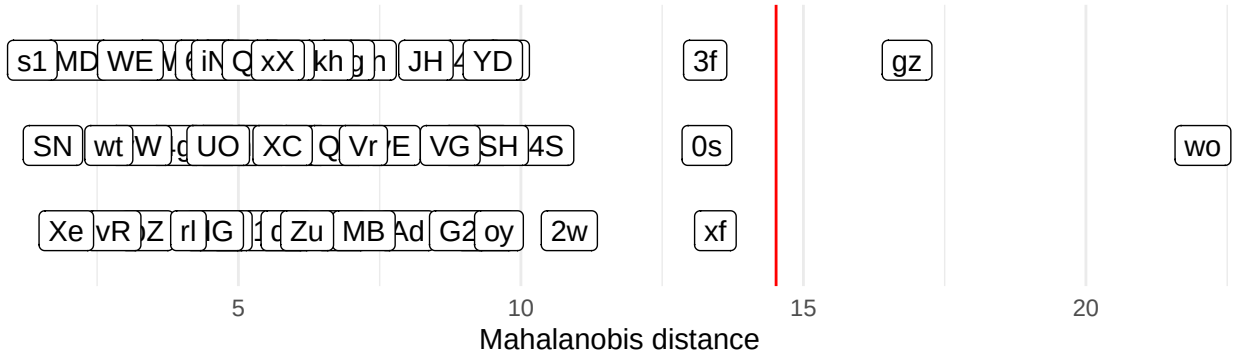

Figure A1 | Mean Mahalanobis distance using clinical parameters with 10.000 resamplings (with 10^4 successful). Gestational age (extracted from *E01_gestationalage*), birthweight (*E02_birthweight*), days of mechanical ventilation (where non-ventilated are set to 0, *F03a_daysofvent*), treatment for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