

SafeBoosC-III - central monitoring

Olsen MH, Hansen ML, Safi S, Jakobsen JC, Greisen G & Gluud C

25 September, 2020

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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 potential outlier-centres. The data will be examined 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 will be uploaded to the SafeBoosC-III website (www.safeboosc.eu).

Methods and material

The data report will be generated automatically after extraction of data from the eCRF every three months (*data extracted 17th of august 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 continuous data and stacked barcharts for categorical. 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

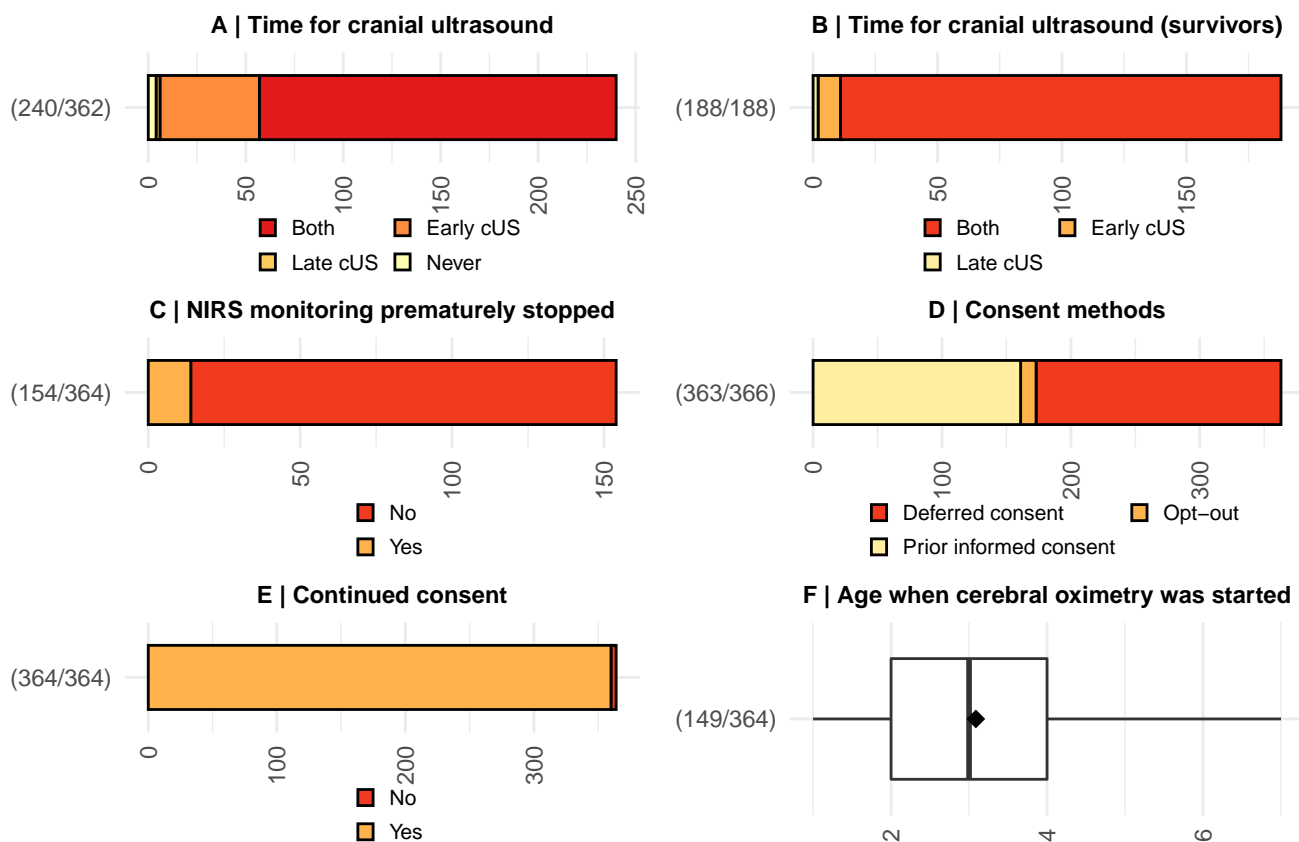


Figure 1 | Stacked barcharts shown for all participants. **(A)** Time for cranial ultrasound for all and **(B)** for survivors (extracted from *F07_cus*); **(C)** proportion of participants with prematurely stopped NIRS monitoring (*E07_prematurenirsstop*); **(D)** types of consent used to enroll participants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

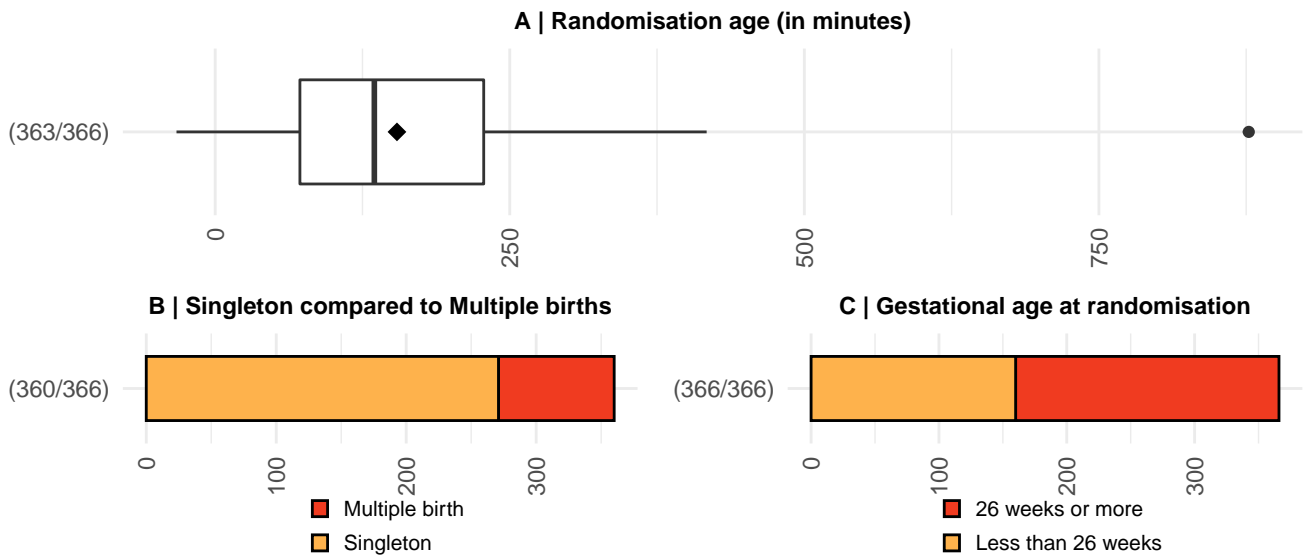


Figure 2 | (A) Age of participants at the time of randomisation in minutes presented using a boxplot. Vertical line depicts median, whereas a diamond represents mean. Stacked barcharts from the ‘randomisation’ module. (B) Proportion of singleton compared to multiple births (extracted from *R02a_singlemulti*);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

End of monitoring

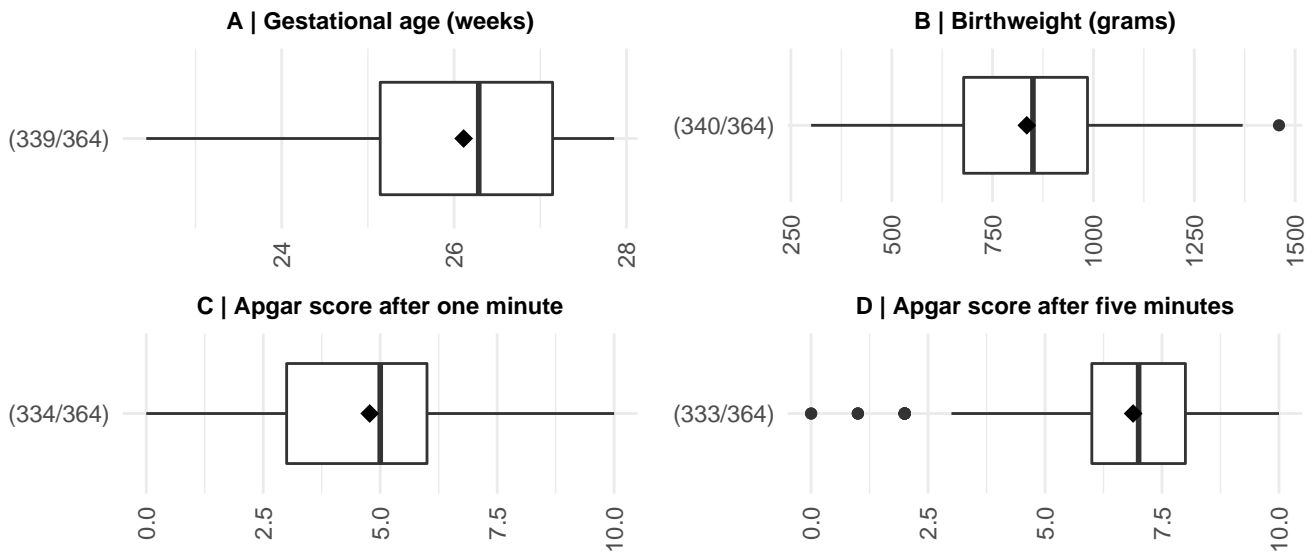


Figure 3 | Boxplots from the ‘end of monitoring’ module, shown for all participants. **(A)** Gestational age of participants in gestational weeks (extracted from *E01_gestationalage*); **(B)** birthweight in grams of participants (*E02_birthweight*); **(C)** Apgar score for participants one minute after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

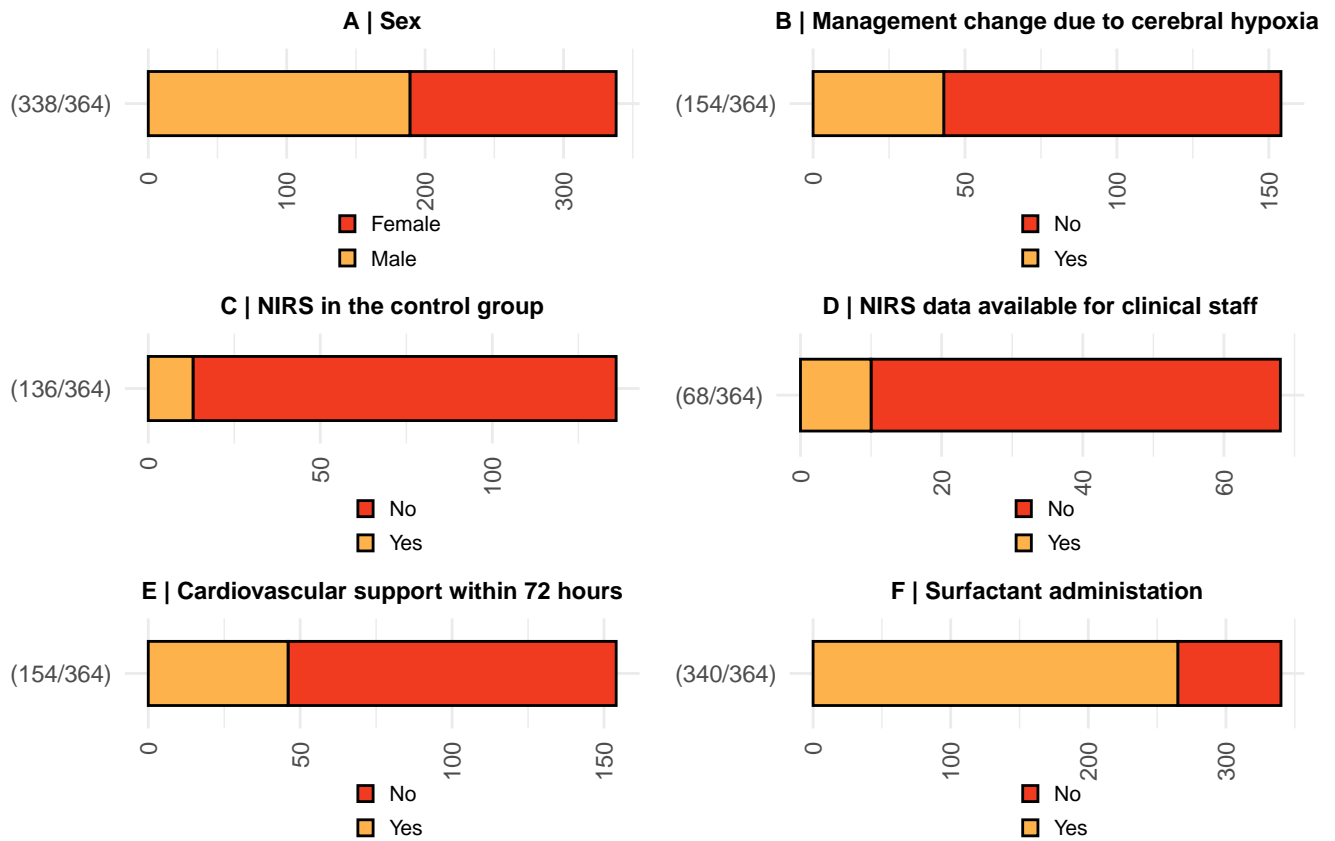


Figure 4 | Stacked barcharts from the ‘end of monitoring’ module, shown for all participants. **(A)** Sex of participants (extracted from *E05_sex*); **(B)** Proportion of participants with changed treatment due to cerebral hypoxia (*E08_changeoftreatmenthypoxia*); **(C)** with NIRS despite being in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

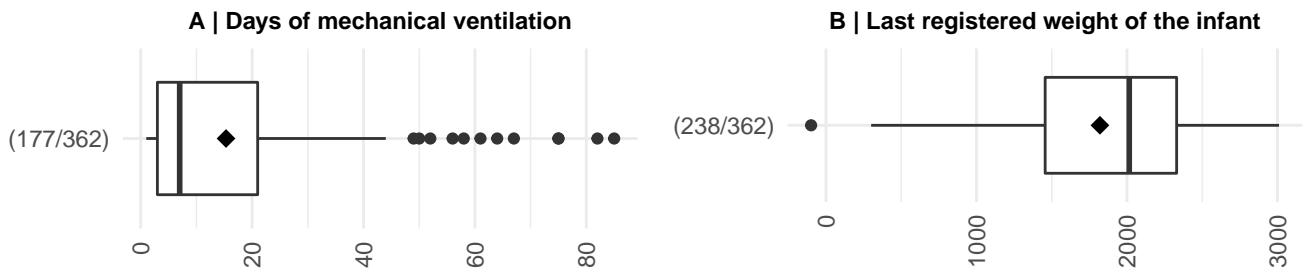


Figure 5 | Boxplots from the ‘follow-up’ module, shown for all participants. **(A)** Days of mechanical ventilation (extracted from *F03a_daysofvent*); and **(B)** weight at follow-up (*F05_weightatfollowup*).

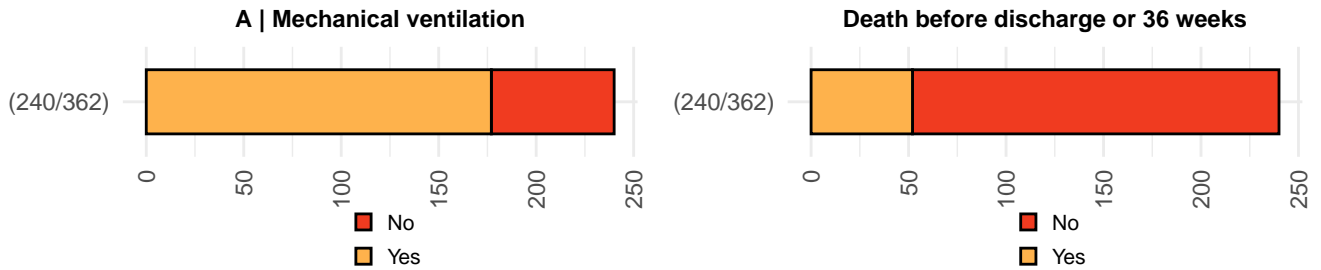


Figure 6 | Stacked barcharts from the ‘follow-up’ module, shown for all participants. **(A)** Proportion of participants on mechanical ventilation during admission (extracted from *F03_mechanicvent*); and **(B)** who died before discharge or before 36 weeks (*F12_death*).

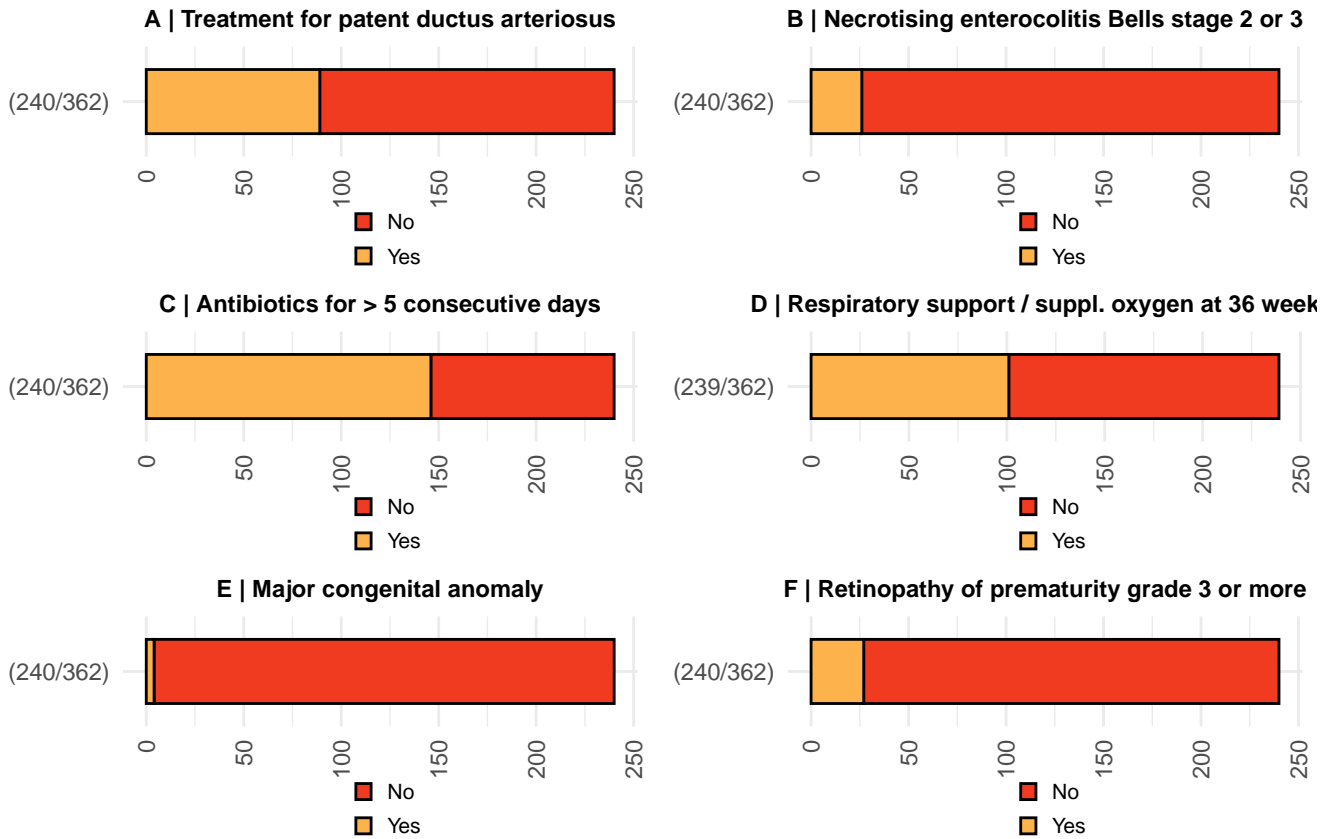


Figure 7 | Stacked barcharts from the ‘follow-up’ module, shown for all participants. **(A)** Proportion of participants who recieved treatment for patent ductus arteriosus (extracted from *F04_PDA*); **(B)** with necrotising enterocolitis Bells stage 2 or 3 (*F09_nec*); **(C)** who recieved antibiotics for more than five consecutive days (*F11_sepsis*); **(D)** proportion of participants who recieved respiratory support or supplemental 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

26th of August 2020 - blinded version

Quality deficiencies

Quality deficiency	Blinded site	Comment	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)	AD	One baby was registered as having had 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 local investigator.
Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)	If	Seven babies were registered as having only an early cranial ultrasound	Yes	The local investigator reported that three of the seven babies have had both early and late cUS and that data entry should be corrected accordingly. 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)	Ok	One baby was registered as having had 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)	OA	One baby was registered with premature stop of NIRS	No	In OpenClinica the cause of premature NIRS stop is described as due to "Exitus" meaning that the baby died. Investigator have been asked to confirm, that monitoring was stopped due to death within the 72 hrs. Still awaiting answer from investigator.

Quality deficiency	Blinded site	Comment	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)	RX	Two babies were registered with premature stop of NIRS	Yes	One baby died within 72 hrs of life and thus, monitoring was stopped. Since we do not intend to register babies were NIRS monitoring was stopped prematurely due to death in the intervention period, data entry has now been corrected. One baby had NEC and due to treatment of this, monitoring was stopped. NIRS was stopped for more than 14 hours. No correction is needed.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	rN	One baby was 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 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)	kT	Two babies were registered with premature stop of NIRS	Yes	For one baby, the investigator experienced technical problems with the monitor. For one baby, NIRS monitoring did not work well during phototherapy and therefore, monitoring was stopped. For both babies, monitoring was missing for more than 14 hrs. Data entries are valid, no correction needed.

Quality deficiency	Blinded site	Comment	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)	vc	One baby was registered with premature stop of NIRS	No	NIRS monitoring was stopped due to death after 48 hrs of life, i.e. 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)	yC	One baby was registered with premature stop of NIRS	Yes	In OpenClinica the cause of premature NIRS stop is described as due to "Exitus" meaning that the baby died. Investigator have been asked to confirm, that monitoring was stopped due to death within the 72 hrs. Still awaiting answer from investigator.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	hh	Two babies were registered with premature stop of NIRS	Yes	For one baby, NIRS monitoring was stopped due to death after 50 hrs of life, i.e. within the 72 hrs intervention period. Therefore, the baby should not be registered as having had premature NIRS stoppage. Data entry has been corrected. For one baby, monitoring was never initiated due to that the head was too small for monitoring with the NIRS sensor. Data entry is valid, no correction is needed.
Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)	el	One baby was registered with premature stop of NIRS	Yes	The sensor was removed due to a minor skin redness. The sensor was removed for 16,5 hrs. Therefore, data entry is valid (more than 14 hrs of missing monitoring), no correction is needed.

Quality deficiency	Blinded site	Comment	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)	lf	Three babies were registered with premature stop of NIRS	Yes	For one baby, the sensor was removed for six hours by mistake. Two babies died within 13 hrs of life and thus, NIRS monitoring was stopped. Since the first baby had stoppage of NIRS monitoring for less than 14 hrs and the two additional babies had NIRS monitoring terminated due to death, none of them should be registered as having had premature NIRS stop. Data entries have been corrected.
Proportion of participants where consent was withdrawn or declined by the parents	yC	For one baby, consent was withdrawn/declined.	Yes	The baby was randomised with deferred consent. When consent was sought later, the parents declined participation. Data has now been deleted, according to the SOP: deletion of data in situations with missing or withdrew consent. Investigator has been informed.
Proportion of participants where consent was withdrawn or declined by the parents	Ok	For two babies, consent was withdrawn/declined.	Yes	The babies were randomised with deferred consent. When consent was sought later, the parents declined participation. Data has now been deleted according to the SOP: deletion of data in situations with missing or withdrew consent. Investigator has been informed.

Quality deficiency	Blinded site	Comment	Any course of action be taken?	Summary of course of action
Proportion of participants where consent was withdrawn or declined by the parents	oD	For one baby, consent was withdrawn/declined.	No	The baby was randomised with deferred consent. When consent was sought immediately after randomisation, the parents declined participation. Data had already been deleted according to the SOP: deletion of data in situations with missing or withdrew consent. Investigator was already informed.
Proportion of participants in the control group that underwent unblinded cerebral oximetry monitoring	Ok	Two babies were registered as such.	Yes	Both babies underwent cerebral NIRS monitoring. It was a decision by the attending physician in the beginning of the trial, despite that it conflicted with the trial protocol. This has been discussed in the physician group and the investigator has informed, that it will not happen again. Data entries are valid. No corrections are needed.
Proportion of participants in the control group that underwent unblinded cerebral oximetry monitoring	AD	Two babies were registered as such.	Yes	Both babies underwent cerebral NIRS monitoring for the first 24 hours of life. No adjustment of treatment was made due to the cerebral StO ₂ values. Investigators have been informed that no babies in the control are to be monitored with cerebral NIRS. Data entries are valid. No corrections are needed.
Proportion of participants in the control group that underwent unblinded cerebral oximetry monitoring	OA	Three babies were registered as such.	Yes	Investigator was contacted an asked for an elaboration. 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
Randomisation age in minutes	Ox	One suspected outlier due to an age of 800 minutes, when the baby was randomised	Yes	Due to uncertainty regarding the randomisation process, the baby was included in the trial within six hours from birth. The baby started NIRS immediately after birth. When the randomisation was completed in OpenClinica after 13 hrs of life, the baby was randomised to the control group and NIRS monitoring was terminated. Investigator is aware of the protocol, and all other babies have been monitored according to group allocation. Status regarding “NIRS monitoring despite being in control group” and “NIRS monitoring available for clinical staff” have been changed to YES for this participant.

Statistical outlier identification by Mahalanobis distance

The Mahalanobis distance was between 10.7 and 11.1, which is due to the number of centres included were only one higher than the number of variables analysed. This results in a successful analysis, but a result which is not able to interpret outliers.

Changes to the central monitoring report setup for November meeting

- Deletion of figure 1A “Time for cranial ultrasound”
- Name change of figure 1C from “NIRS monitoring stopped prematurely” to “Significant amount of missing monitoring”
- Change in order of figure 1, so that it follows the central monitoring plan: 1B, 1F, 1C, 1D, 1E
- Deletion of figure 4C “NIRS in the control group” and 4D “NIRS data available for clinical staff”
- 4E “Cardiovascular support” must include trial participants in both experimental and control group
- 5B “Last registered weight of the infant” must only include survivors at follow-up
- 6B phrasing edited so that the question is positively weighted
- Deletion of figure 8A “The baby was scanned”
- Textual change of E07 to “If the baby survived until 72 hours of age, was cerebral oximetry monitoring stopped for more than 14 hours during this time period?”. This is due to that this data point only intends to explore whether it is possible to complete the intervention when available

NOTA

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

An ad hoc analysis revealed that five trial participants 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 that 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 investigators have been contacted for an elaboration and errors will be corrected. During the next monitor meeting, we will test whether these errors have been corrected at the next central monitoring meeting.

Corrected per site

- Site zT, three babies: The registration of NO to “NIRS data available for clinical staff” was a an error, corrected
- Site hh, one baby: The registration of NO to “NIRS data available for clinical staff” was a an error, corrected
- Sita OA, one baby: still awaiting answer from investigator

Wrongly registration of consent method

During the central monitoring meeting, we identified that rf had registered the use of deferred consent for several participants, despite not being allowed to use this consent method by their local ethics committee. The investigator has elaborated that this were data entry errors. We suspect that this could have happened at other hospitals as well. Therefore, we have sent an e-mail to all participating centres, explained the issue and asked them to report which consent methods they use. Following this, the Copenhagen Trial Unit will change the eCRF so that sites not allowed to use deferred consent, cannot randomise by deferred consent.

If we identify centres where the wrong consent method has been used for randomisation (we will urge PIs to double check randomisation in their centre) we will correct this in the eCRF.

The following changes has been done so far per site

- Rf, five babies: change from deferred consent to prior informed consent
- Ox, seventeen babies: change from deferred consent to prior informed consent