Safeguarding the Brain of our smallest Children

SafeBoosC-IIIv

Cerebral oximetry added to usual care versus usual care in mechanically ventilated newborns. An investigator-initiated, pragmatic, multinational randomised phase III clinical trial

Trial phase	Phase III
Protocol version and date	Version 1.0

Applicable protocol registration numbers (ClinicalTrials.gov identifier, ethics committee number, EudraCT number, etc.)

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Study centre:	Multicentre; international

1 Abstract

Background
Newborns in need of mechanical ventilation are at high risk of a detrimental outcome, not only due to the underlying condition, but also due to complications from the mechanical ventilation itself (1, 2). Such complications include pneumothorax, ventilation associated pneumonia, and hyperventilation causing vasoconstriction of the cerebral vasculature and possibly brain ischaemia (3). Summary data on outcomes is not easily available, but during 2019 death before discharge occurred in 41/500 (8.2%) newborns, born at more than 28 weeks of gestation and in need of mechanical ventilation during the neonatal period, in 10 neonatal units within the SafeBoosC consortium. A meta-analysis including 895 neonates from 23 non-randomised trials, undergoing surgery for non-cardiac congenital anomalies, found a deficit in intelligence quotient of 0.5 standard deviations below the population average (4). Additionally, data from a Danish national cohort, showed that 18% of children who underwent mechanical ventilation during the neonatal period, needed special educational support in primary school, which is 2.5 times more often than normal (Wiingreen et al. unpublished data).

Thus, mechanically ventilated newborns is a high-risk population. Given the instability of the newborn´s pulmonary and circulatory physiology, it is possible that the addition of measuring the oxygenation of the brain, by non-invasive near-infrared light technology (cerebral oximetry) plus a treatment guideline, as an addition to the complex treatment and monitoring regimes for these newborns, may increase the chance of surviving without neurodevelopmental impairment.

Objectives
The objective of the SafeBoosC-IIIv trial is to evaluate cerebral oximetry added to usual care versus usual care in mechanically ventilated newborns. The hypothesis is that the intervention will decrease a composite outcome of death or moderate to severe neurodevelopmental disability and/or increase the mean PARCA-R non-verbal cognitive score at two years of corrected age.

Trial design
SafeBoosC-IIIv will be an investigator-initiated, multinational, randomised, pragmatic phase III clinical trial. A total of 3000 newborns will be randomised in about 90 neonatal intensive care units across 18 countries. Data managers, statisticians, conclusion drawers, and the steering committee members will be blinded.

Inclusion – and exclusion criteria
Inclusion criteria will be:

- Newborns with gestational age more than 28+0 weeks
- Postnatal age less than 28 days
- Predicted to require mechanical ventilation for at least 24 hours

- Equipoise as regards the need for cerebral oximetry
- Prior informed consent or deferred parental informed consent or absence of opt-out

Exclusion criteria will be:

- No available cerebral oximeter
- Suspicion of or confirmed brain injury or disorder
- Congenital heart disease likely to require surgery.

Randomisation and interventions

Participants will be randomised through central web-based randomisation stratified by neonatal intensive care unit; gestational age (lower gestational age (≤ 34 weeks) / higher gestational age (> 34 weeks)), and surgery (newborns in need of mechanical ventilation due to a surgery (yes/no)) at the Copenhagen Trial Unit.

Participants in the experimental group will be monitored with cerebral oximetry, if possible before or, as soon as possible and within six hours after initiation of mechanical ventilation. Cerebral oximetry will be continued until the cardio-pulmonary function has been stabilised as indicated by the need for respiratory and circulatory support and evaluated by the responsible physician, until 28 days after birth, or until death. Cerebral oximetry may be restarted, if the cardio-pulmonary function becomes unstable again within the first 28 days of life, with the purpose of reducing the risk of cerebral damage as much as possible. Cerebral oximetry will be used to minimise cerebral hypoxia by modifying clinical care according to the SafeBoosC treatment guideline and monitoring as usual.

The control group will receive mechanical ventilation without access to cerebral oximetry and the SafeBoosC treatment guideline.

Outcomes

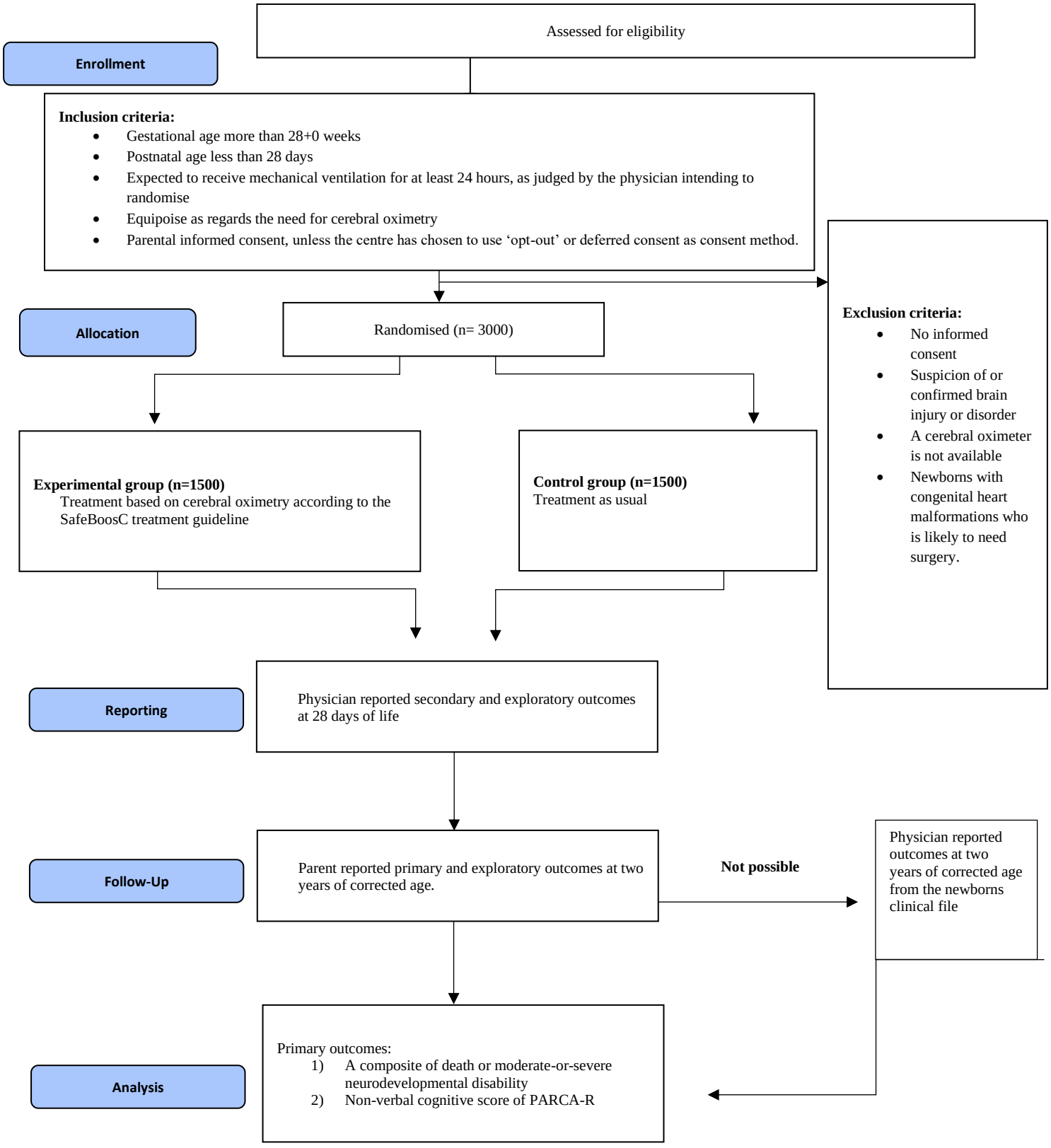
There will be two co-primary outcomes: 1) a composite of death or moderate-to-severe neurodevelopmental disability and 2) non-verbal cognitive score of Parent Report of Children's Abilities-Revised (PARCA-R). Both outcomes will be assessed by an online parental questionnaire, at two years of corrected age.

To test a reduction in death or moderate to severe neurodevelopment disability from 20% to 16% between the experimental and control group, at an alfa-level of 2.5% and a power of 80%, a total of 1500 participants in each group, i.e. a total of 3000, is needed. This corresponds to a relative risk reduction of 20%.

Trial duration

Recruitment is expected to begin in April 2022 and expected to be completed within 29 months.

2 SafeBoosC phase IIIv trial flow chart



Administrative information

Sponsor

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Coordinating investigator Gorm Greisen

Steering Committee

SafeBoosC-IIIv is led by a Steering Committee comprising the coordinating investigator/sponsor, the trial manager, the national coordinators and two representatives from the Copenhagen Trial Unit. Decisions will be by simple majority.

Executive Committee

The executive committee is responsible for day-to-day management and will comprise the Copenhagen SafeBoosC project team, including the coordinating investigator and the trial manager, as well as three national coordinators and two representatives from the Copenhagen Trial Unit.

National coordinators

To be appointed

Independent Data Monitoring and Safety Committee (DMSC)

To be appointed

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Introduction and background

2.1 The population and condition

Current standard of care of newborns in need of mechanical ventilation, involves several different interventions (5). The criteria for initiation of mechanical ventilation vary among neonatal intensive care units. In general, mechanical ventilation is initiated when respiratory failure occurs, usually indicated by one or more of the following: hypercapnia, hypoxia or severe apnoea (3). In surgical patients, pain and/or analgesia may contribute to the need for mechanical ventilation (6). It is commonly used for the following conditions in the near-term or term newborns: respiratory distress syndrome and pulmonary failure, congenital diaphragmatic hernia, other major congenital malformations and acute abdominal surgical conditions, sepsis, pneumonia, meningitis, persistent pulmonary hypertension, meconium aspiration syndrome, congenital cardiac anomalies, anticonvulsant treatment and hypoxic-ischaemic encephalopathy (5).

2.1.1 Current clinical management

Mechanically ventilated newborns are routinely monitored by continuous recording of heart rate, respiratory waveform, pulse oximetry, often invasive arterial blood pressure and often transcutaneous oxygen and carbon dioxide tension (7). The ventilator usually provides monitoring of respiratory pressures and volumes. Adjustments of the respiratory support is frequently needed and circulatory support may be needed with inotropes, vasopressors or volume expansion with saline, albumin or red blood cells(8).

2.2 Cerebral oximetry by near-infrared spectroscopy

Cerebral oximetry by near-infrared spectroscopy is a non-invasive technology that enables estimation of the tissue oxygenation in the brain (9). Cerebral oximetry uses the relative transparency of human tissue to light in the near-infrared region of the electromagnetic spectrum. Cerebral oximeters provide an absolute value of tissue oxygenation (rStO2), expressed as a ratio of oxygenated to total haemoglobin, in the tissue underlying a given monitoring sensor (10) . As the distance from the skin to the brain surface is less than 6 millimetres in newborns (11), cerebral oximetry is particularly suitable for monitoring cerebral oxygenation in these patients.

Cerebral oximetry is based on the same principles as the widely used pulse oximetry, but whereas pulse oximetry uses only a pulsatile signal and thereby selectively measures the oxygen saturation in arterial blood, cerebral oximetry measures the light attenuation of the tissue as a whole, and the estimate of oxygen haemoglobin saturation is influenced by the blood in all types of vessels. This means that venous blood contributes more to the cerebral oximetry signal than arterial blood, since anatomically, venous blood has a greater volume within tissues. The ratio of venous and arterial contribution is generally assumed to be 75:25, although this has been found to differ between and within newborns (12). Therefore, it is not surprising that cerebral tissue

oxygenation has shown only a fair correlation with the saturation in cerebral venous blood, drawn from the jugular bulb (13). The Bland-Altman limit of agreement is ±15% to 20% (14, 15). However, tissue oxygenation (rStO2) is volume-weighted across areas with high or low oxygen extraction, whereas jugular bulb saturation is flow-weighted, and therefore, venous oxygen saturation cannot be considered a 'gold standard'.

2.3 Tissue oxygenation as a measure of cardiac output

Monitoring of cardiac output or tissue blood flow is not routinely feasible in newborns. Monitoring of heart rate and blood pressure are indirect measures of cardiac function, but the correlation to cardiac output is weak. Clinician performed echocardiography may be used to judge cardiac function intermittently, depending on availability of time and competence (16). Electric cardiography can, in addition, potentially provide non-invasive continuous hemodynamic monitoring. However, there are no clinical evidence on clinically relevant outcomes yet (16).

Cerebral tissue oxygenation correlates with cardiac output (17). Therefore, apart from being an indicator of oxygen sufficiency of the brain, it may serve a dual purpose also as an indicator of cardiac output and thus, be of relevance for oxygen sufficiency of other organs, such as the liver, kidney and heart. Better management of low cardiac output may reduce the risk of dysfunction of these organs and thereby, reduce the risk of death.

2.4 Vascular reactions to circulatory stress

A mature autoregulation keeps the cerebral blood flow constant, despite fluctuations in perfusion pressure. It is accomplished by regulation of the arterial tone, so that low perfusion pressure results in vasodilation, and high perfusion pressure results in vasoconstriction (18). Autoregulation, however, may be impaired in ill newborns and thereby, operating at a reduced level (19). The characteristics of autoregulation in newborns is still not well defined but is affected by number of different factors, such as hypoxia or hypocapnia and circulatory stress (19).

On the systemic level, other organs such as the heart, and adrenal glands are also 'vital', and blood flow is maintained when systemic blood flow is low, while the arteries to non-vital organs, such as the skin and kidneys, vasoconstrict to maintain blood pressure, and direct circulating blood to the vital organs. This is partly mediated by the sympathetic nervous system (19). Sympathetic nerves, however, innervate the arteries of the immature forebrain (which is not vital to the immediate survival) more effectively compared to adults (20) and therefore, sympathetic activation by central hypovolemia and poor filling of the heart may potentially contribute to brain ischaemic hypoxia.

2.5 Mechanisms of brain damage in newborns in need of mechanical ventilation

Hypocapnia due to inadvertent hyperventilation causes vasoconstriction of the cerebral vasculature and may lead to cerebral ischaemia (21). This is an important cause of brain injury, in particularly periventricular leucomalacia and cerebral palsy in preterm infants (21). Although modern mechanical ventilators offer better control of ventilation, carbon dioxide tension is still often very variable during mechanical ventilation. Furthermore, cerebral vasoconstriction due to hypocapnia may interact with vasoconstriction due to circulatory stress, caused by the positive airway pressure during mechanical ventilation, which impairs venous return and filling of the heart (22). Finally, cerebral blood flow combines with the oxygen carrying capacity of the blood, as determined by blood haemoglobin concentration and shifts in the oxygen-haemoglobin dissociation curve, to determine the cerebral oxygen delivery (23). If this falls short of demand, tissue oxygenation falls.

Hypoxic-ischaemic brain injury is also common in term newborns (24). Typically, it occurs during delivery and can lead to death or neurodevelopmental deficits such as cerebral palsy, cognitive deficits, attention deficit disorder, and major psychiatric disorders, which have long-term consequences for the affected children (25). Stroke is also relatively common (26).

2.5.1 Trials of clinical benefit in mechanically ventilated newborns

To our knowledge, no randomised clinical trials have evaluated cerebral oximetry added to usual care versus usual care in mechanically ventilated newborns. The COSGOD (Cerebral regional tissue Oxygen Saturation to Guide Oxygen Delivery in preterm neonates during immediate transition after birth)-II and the SafeBoosC (Safeguarding the Brain of our smallest Children)-II randomised clinical trials have shown that it is possible to significantly reduce cerebral hypoxia, by adjusting intensive care based on cerebral oximetry in preterm infants (27, 28). Now, the larger COSGOD-III and SafeBoosC-III trials are testing the effect of cerebral oximetry on clinical relevant outcomes, i.e. survival without severe brain injury (29, 30). COSGOD includes preterm infants in the delivery room and SafeBoosC includes extremely preterm infants during the first three days of life.

It would be unfortunate, if cerebral oximetry was incorporated into routine intensive care of newborns without good evidence of benefits and harms. A meta-analysis by Hansen and colleagues (31) (to be submitted for publication) addresses the evidence of patient-relevant benefits of cerebral oximetry across all patient groups – extremely preterm infants to elderly adult patients undergoing cardiac surgery, and it concludes that there is yet insufficient data to confirm or reject the effects of cerebral oximetry on clinical relevant outcomes, and the addition of the coming results of COSGOD-III and SafeBoosC-III is unlikely to be decisive on this more general question. Thus, Trial Sequential Analysis shows a need for several thousand additional

participants, to conclude that the clinical effect on cerebral oxymetri is less than a 20% reduction of adverse outcomes. The SafeBoosC-IIIv trial can potentially fill this knowledge gab.

2.6 Benefits and risks

If the SafeBoosC-IIIv trial shows that cerebral oximetry will result in more newborns surviving without disabilities and with better cognitive outcome, the benefits will be obvious. Children with disabilities are costly to society: expenses to rehabilitation, hospitalisations, medicine, special educational support, loss of parental income, and in the long-term perspective fewer in employment. Moreover, better cognitive outcomes, i.e. higher IQ, will be a resource to society, since higher IQ correlates to higher education, higher income, and better social function (32).

On the other hand, cerebral oximetry monitoring may theoretically cause harm. First, hypoxic values may result in unnecessary and potentially dangerous changes in cardiorespiratory support. Second, although near-infrared light is safe, the sensor may cause skin marks by pressure. Third, the placement of yet another sensor to the small body of a newborn is disturbing, and these patients are already stressed by care procedures. Forth, if cerebral oximetry monitoring is without beneficial effects, it will result in waste of time and money that may be spent otherwise for the benefit of patients.

3 Trial objective and hypothesis

The objective of the SafeBoosC-IIIv trial is to evaluate cerebral oximetry added to usual care versus usual care in mechanically ventilated newborns. The hypothesis is that the intervention will decrease a composite outcome of death or moderate to severe neurodevelopmental disability and/or increase the mean PARCA-R non-verbal cognitive score at two years of corrected age.

4 Trial design

This is an investigator-initiated, multinational, randomised, pragmatic phase III clinical trial with a two parallel group design, that will enrol 3000 newborns from 18 countries.

4.1 Randomisation

Participants will be randomised into either the experimental group or the control group. The ratio of allocation will be 1:1. The allocation will be computer-generated with varying block sizes and the randomisation will be stratified by neonatal intensive care unit; gestational age (lower gestational age (≤ 34 weeks) / higher gestational age (≥ 34 weeks)), and surgery (newborns in need of mechanical ventilation due to a surgery (yes/no)) , and will be concealed for all investigators. Randomisation will be centralised and web-based at the Copenhagen Trial Unit.

Singleton newborns will be randomised individually. Multiple birth newborns will be

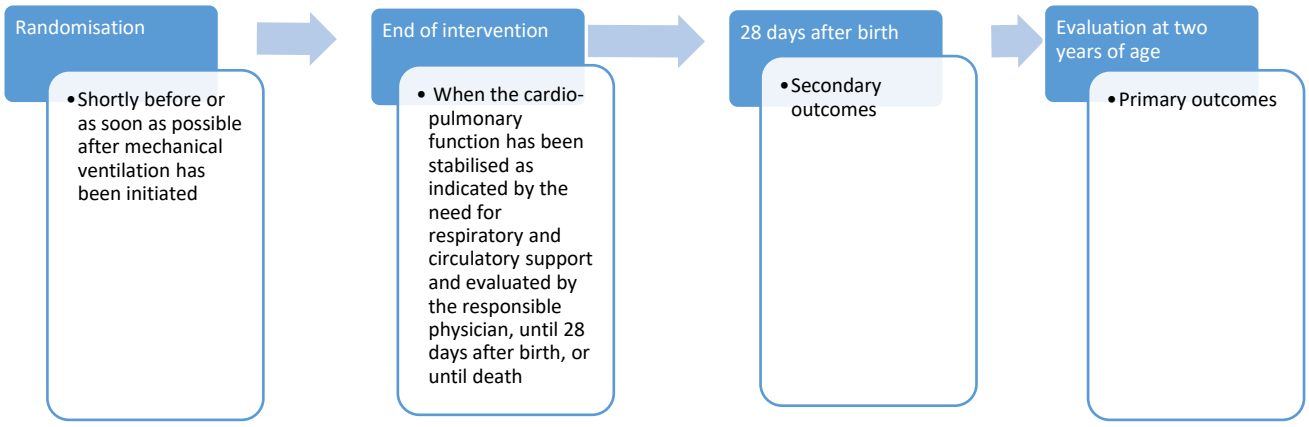
randomised individually, as it is not common that the twins or triplets will need mechanical ventilation at the same time. A second twin can be enrolled when it meets the inclusion criteria if the parents can accept a separate randomisation.

4.2 Blinding

Due to the nature of the experimental intervention, clinical staff and the parents will not be blinded to group allocation. Thus, the primary outcome will not be blinded in cases when it relies on parental reporting. If there is no contact with the parents, or if they do not return the questionnaire, data will be collected from health care records. All secondary outcomes will be assessed and reported at 28 days after birth by reviewing the newborn's health care records. Investigators reviewing the health care records will, if possible, be blinded to the allocated intervention.

Data managers, statisticians, conclusion drawers, and the steering committee members will be blinded. Furthermore, mortality status will be source data verified for all participants at 28 days after birth, during Good Clinical Practice (GCP) monitoring visits. Two blinded statisticians at The Copenhagen Trial Unit will independently perform all statistical analyses using different statistical software programs (R and STATA). Both reports and third fused final report will be presented to the Steering Group and all three reports will be published as supplemental material. Discrepancies between the two reports will be discussed by the Steering Committee.

4.3 Trial timeline



5 Participants

We will include newborns based on the following inclusion and exclusion criteria.

5.1 Inclusion criteria

- Gestational age more than 28+0 weeks

- Postnatal age less than 28 days
- Expected to receive mechanical ventilation for at least 24 hours, as judged by the physician intending to randomise
- Equipoise as regards the need for cerebral oximetry
- Parental informed consent unless the centre has chosen to use ‘opt-out’ or deferred consent as consent method.

5.2 Exclusion criteria

- No signed parental informed consent (if prior consent is used) and did not opt-out (if ‘opt-out’ is used,)
- Suspicion of or confirmed brain injury or disorder (e.g. perinatal asphyxia, cerebral haemorrhage, cerebral malformation, genetic or metabolic disease)
- A cerebral oximeter is not available
- Newborns with congenital heart malformations who is likely to need surgery.

5.3 Participation in other trials

Participants included in the SafeBoosC-IIIv trial can participate in any other trial, on the condition that the trial does not:

• allow clinical staff access to cerebral oximetry in the control group from inclusion in SafeBoosC-IIIv to the end of the intervention period or;

• exclude a treatment that would be clearly indicated by the SafeBoosC treatment guideline during the intervention period in the experimental group.

All partners are encouraged to design ancillary studies and draw on data collected by SafeBoosC-IIIv if such studies do not compromise the blinding of assessors or the equipoise of the trial. Ancillary studies must be approved by the SafeBoosC-IIIv Steering Committee, if presenting results analysed according to randomisation group.

5.3.1 Participant discontinuation and withdrawal

The participants’ parents are free to withdraw their newborn from the intervention at any time and to decline the use of any future data. For newborns included by deferred consent, the parents are also allowed to decline the use of previously registered data. A standard operating procedure, outlining when and how participant data should be deleted, if requested by the parents, will be developed before initiation of the trial. Withdrawal from the intervention or decline of data usage will not have any consequences for the newborn’s further treatment. Reasons for discontinuation, if offered by the parents, will be documented. The attending clinician can withdraw any participant from the trial intervention at any time, in case there are safety concerns. Reasons for withdrawal will be documented. There are no pre-specified criteria for discontinuation of participants from the trial. Discontinuation of participants from the trial will not result in replacement with new participants.

5.3.2 Recruitment feasibility

The feasibility of recruitment for a trial, evaluating the benefits and harms of cerebral oximetry combined with the SafeBoosC treatment guideline, was proven in the SafeBoosC-II trial, where 166 infants were recruited across eight European countries at eight neonatal intensive care units (33). In the SafeBoosC-III trial now being conducted, a total number of 1600 newborns needs to be recruited and the trial is in good progress. On average, 2.4 newborns per day are being randomised and as per August 2021, 1300 newborns have been randomised (safeboosc.eu).

During the conduct of SafeBoosC-III, the SafeBoosC consortium has been expanded and now includes neonatal intensive care units from more than 70 hospitals in 18 countries across the world, all recruiting infants into the SafeBoosC-III trial (34). In these hospitals, admission records indicate that the number of potential participants in SafeBoosC-IIIv is larger than for the current trial. Inclusion of new neonatal intensive care units after the common start date of SafeBoosC-IIIv, will be done ad hoc, considering expected contributions and time remaining.

6 Interventions

6.1 Experimental group

The experimental group will receive cerebral oximetry added to usual care, if possible before or, as soon as possible and within six hours after mechanical ventilation has been initiated, and continuing until the cardio-pulmonary function has been stabilised as indicated by the need for respiratory and circulatory support and evaluated by the responsible physician, until 28 days after birth, or until death. Cerebral oximetry will be used to modify clinical care according to the SafeBoosC treatment guideline (see section 8.1 treatment based on near-infrared spectroscopy monitoring) to minimise cerebral hypoxia.

6.1.1 Monitoring by cerebral oximetry

Cerebral hypoxia will be defined as a value below 55% by the INVOS adult sensor or the corresponding value with another oximeter or sensor, as calibrated in the blood-lipid phantom (35, 36). Decisions on change of clinical management will be based on the SafeBoosC treatment guideline in combination with other clinical information.

Cerebral oximetry may be restarted within 28 days after birth if the cardio-pulmonary function becomes unstable again, as evaluated by the responsible physician, with the final purpose of reducing the risk of cerebral damage as much as possible. If the newborn is cared for outside the neonatal unit at any time, e.g. during surgery, cerebral oximetry may or may not be used, as decided by the responsible physician.

7 Devices

Any oximeter and sensor combination that is approved for clinical use in newborns, and which has been calibrated in the blood-lipid phantom, may be used (37).

7.1 Treatment based on adding cerebral oximetry to usual care

The SafeBoosC treatment guideline recommending adjustments of respiratory and cardiovascular support will be used to keep cerebral oxygenation above 55% as measured by the oximeter. The SafeBoosC treatment guideline is detailed in **Appendix A** and will be used in all centres. Clinical staff will be offered web-based training and certification prior to caring for trial participants. As this is a pragmatic trial, we will not require a specific certification rate, before a neonatal intensive care unit can participate in the trial. However, we will aim at a 70% certification rate in all participating neonatal intensive care units. Since the web-based training and certification program is a trial quality measure, to ensure quality of data and patient care, data on certification rates will be collected and published in a paper regarding the development and implementation of the web-based training and certification program for SafeBoosC-IIIv. The principal investigator at each neonatal intensive care unit is responsible for listing relevant clinical staff, that are expected to use the web-based training and certification program, as well as providing trial information, supervision, and support.

7.1.1 Usual care

Usual care offered to newborns in the control group (see below) will be offered equally in the experimental group (e.g. antibiotics; nutrition; etc.). There will be no attempt to standardize ’usual care’ among centres.

7.2 Control group

The control group will receive mechanical ventilation without access to cerebral oximetry and the SafeBoosC treatment guideline. If the newborn is cared for outside the neonatal unit at any time, e.g. during surgery, cerebral oximetry may or may not be used, as decided by the responsible physician there.

7.3 Concomitant medication/treatment

There is no specified ‘per-protocol’ concomitant medication or treatment. The treatment options listed in the SafeBoosC treatment guideline, is per choice of the treating physician and the treating team, as based on a comprehensive evaluation of the clinical situation of the individual newborn and local protocols and guidelines.

8 Outcomes

8.1 Primary outcome

There will be two co-primary outcomes, a composite dichotomized outcome and a continuous outcome:

A composite of death from any cause or moderate to severe neurodevelopmental disability at two years of corrected age. Moderate to severe neurodevelopmental disability will be defined as one or more of the following

1) cerebral palsy with Global Motor Function Classification System level 2 or higher;
2) a PARCA-R non-verbal cognitive function score below -2 standard deviations (SD);
3) hearing loss corrected with aids or worse; or
4) vision impairment defined as moderately reduced vision of one eye, or only being able to perceive light or light reflecting objects; or blind in one eye with good vision in the contralateral eye.

Parental questionnaires completed between 18-30 months' corrected age as well as available data from at least 12 months' corrected age from health care records, including standardised neurodevelopmental assessments, will be used to assess mortality and neurodevelopment.

- Non-verbal cognitive score of PARCA-R, a parental questionnaire, at two years of corrected age.

8.2 Secondary outcomes

1. One or more Serious Adverse Events after randomisation and within the 28 first days of life, i.e. one or more of the following

    - Death from any cause
    - Any brain injury diagnosed by imaging
    - Seizures treated with antiepileptic medicine
    - Necrotising enterocolitis (NEC) Bells grade 2 or more
    - Sepsis (confirmed or suspected infection treated with antibiotics for 5 days or more)
    - Extra Corporal Membrane Oxygenation (ECMO)
    - Renal replacement therapy
    - Use of vasopressor/inotropes

- Nitric Oxygen treatment
- On mechanical ventilation at 28 days of life

2. Days alive without mechanical ventilation within the 28 first days of life.

8.3 Exploratory outcomes

- Individual Serious Adverse Events as listed in the secondary outcome
- Days alive outside hospital within the 28 first days of life.
- Cerebral palsy, defined as Global Motor Function Classification System level 2 or above, at two years of corrected age.
- Sensory deficit, defined as any degree of vision or hearing impairment, at two years of corrected age.
- Mortality at two years of corrected age.
- Use of medication during the last two months, at two years of corrected age.

8.4 Outcome assessment tools

All primary outcomes, as well as all exploratory outcomes evaluated at two years of corrected age, will be assessed by an online parental questionnaire. Parents of included newborns will be invited to complete the questionnaire one month before the newborn reaches two years of corrected age. A digital solution will be built for parents to fill out the questionnaires. Data can also be obtained by other means, i.e. consultations in person or by telephone. If it is not possible to obtain data from the parents, the local blinded assessor will review the participants' clinical records and complete outcome assessment, as described in Appendix C.

The secondary outcomes "one or more serious adverse events within the 28 first days of life, "days alive without mechanical ventilation within the 28 first days of life" and the exploratory outcome "days alive outside hospital within the 28 first days of life" will be assessed by the investigator, by reviewing the newborn's clinical records.

Based on the SafeBoosC-III Good Clinical Practice data monitoring model (38), a pragmatic system of local and central Good Clinical Practice data monitoring will be developed and used.

8.4.1 PARCA-R

The Parent Report of Children's Abilities-Revised, PARCA-R, is a parent completed questionnaire that can be used to assess children's cognitive and language development at 24 months corrected age (39). The questionnaire has been used as a two-year outcome measure in multiple clinical trials (40) and has been translated into several languages.
In the SafeBoosC-IIIv trial, the parents of the participating children will be invited to complete the non-verbal part of the PARCA-R questionnaire on an online platform, used in the SafeBoosC-III follow up study (to be published) and modified for the SafeBoosC-IIIv trial. The

PARCA-R questionnaire must be completed between 23,5 and 27,5 months of corrected age. The non-verbal part of the PARCA-R questionnaire consists of 34 forced-choice items, zero or one, from which a total score is derived.

9 Data collection and trial assessment schedule

9.1 Collection of trial data

9.1.1 Participant report form

Trial data will be collected using an electronic participant report form (ePRF) as the primary data entry point. The ePRF will be designed in collaboration between the trial manager, data manager at the Copenhagen Trial Unit and the coordinating investigator.

9.2 Trial assessment schedule

When a newborn has been enrolled in the trial, this must be documented in the newborn's clinical file. The physician enrolling the participant in the trial must also be responsible for prescribing cerebral oximetry monitoring, if the participant is randomised to the experimental group. There will be three time points for ePRF data entry: 1) consent/randomisation; 2) after the first 28 days of life, where there the physician should report the secondary outcomes, based on the newborn's health care record. The data entry system OpenClinica, will send a reminder to the principal investigators, after the first 28 days of the newborns life; 3) Parent-reported outcomes at two years of age. If there is no contact with the parents, or if they do not return the questionnaire, the local principal investigator will be asked for supplementary data (as defined in Appendix C from the newborn's health care records and requested to provide an informal assessment of the primary outcomes.

10 Assessment of Safety

10.1 Adverse events and reactions

10.1.1 Definitions

Adverse Event (AE): any undesirable medical event occurring to a participant during a clinical trial, whether or not considered related to the trial intervention.

Adverse Reaction (AR): any adverse event related to the trial intervention.

Serious Adverse Event (SAE): any adverse event that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or

significant disability or incapacity (41, 42). The predefined individual Serious Adverse Events are listed under “8.2 Secondary outcomes”.

Serious Adverse Reaction (SAR): any adverse reaction to the experimental intervention that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity (42): including:

- Physical mishaps associated with managing the oximeter and sensors
    - Severe skin damage
    - Critical displacement of endotracheal tubes caused by cerebral oximetry monitoring
    - Critical displacement of endovascular lines caused by cerebral oximetry monitoring
- Clinical mismanagement based on data from the cerebral oxygenation monitoring
    - Interventions aiming at improving respiratory status
    - Interventions aiming at improving cardiovascular status
    - Interventions aiming at improving oxygen transport

10.1.2 Reporting of adverse events and reactions

Serious Adverse Reactions and Serious Adverse Events will not be reported separately, and expedited reporting will not be used.

10.1.3 Justification for recording and reporting

The patient population of newborns in need of mechanical intervention is a seriously ill group. Both intervention groups are expected to have a high proportion of adverse events, the intervention is already in widespread clinical use, and the aim of this trial is to estimate any net benefit of harm at a level of statistical significance. It is therefore not feasible, nor meaningful, to record and report all adverse events. Therefore, predefined Serious Adverse Reactions and Serious Adverse Events are described in the protocol.

10.1.4 Timing for recording and reporting

Expedited reporting will not be used. The centre investigators will report the Serious Adverse Reactions and Serious Adverse Events through the ePRF after 28 days of the newborns life. The sponsor will inform all investigators in the case of unexpected patterns of Serious Adverse Reactions and Serious Adverse Events, as evaluated by individual investigator reporting, central data monitoring and interim analyses. Ethics committees will be informed as required.

10.2 Cerebral oximetry monitoring device

The devices used are approved for clinical use in newborns and will be used according to the user manuals provided by the manufacturers. Furthermore, all clinical staff will be offered web-

based training and certification that covers the principles of cerebral oximetry, practical application, as well as pathophysiology, and relevant interventions in the case of low cerebral oxygenation.

10.3 Data Monitoring and Safety Committee

A Data Monitoring and Safety Committee (DMSC) will be established to monitor mortality and neonatal morbidities at 28 days of life, including Serious Adverse Reactions and Serious Adverse Events. The charter for the DMSC will be written prior to inclusion of participants and prior to any analysis. The first pre-planned interim analysis will be conducted after 1000 participants have reached 28 days of life. Additional interim analyses will be decided by the DMSC. The DMSC will be given access to data by randomisation group. The DMSC may advice the trial steering committee to stop the trial early or if there is risk of important negative effects of the intervention. The trial will not be stopped early because of futility. Lan-DeMets boundaries will be used at each interim analysis to assess if the thresholds for statistical significance are crossed and if the trial should be stopped early because of evidence of benefit or harm (43).

10.4 Suspension or premature termination of the trial

The Steering Committee decides about trial discontinuation. If the Steering Committee terminates or suspends the trial, the relevant ethical committees will be provided with a detailed written explanation of the termination or suspension. The steering committee can, upon completion of the analysis of the reason(s) for a suspension, decide to lift the suspension when any necessary corrective actions have been implemented. The investigators and ethical committees will be notified and provided with the relevant data supporting the decision. Breaking of blinding for clinicians and parents will not be relevant in this trial, since group allocation is visible for them.

11 Ethical considerations

Due to the pathophysiology of newborns, the research question can only be answered in this critical ill population.

To obtain evidence-based knowledge on the benefit and harms of cerebral monitoring using cerebral oximetry as part of clinical management of mechanical ventilation in newborns, a large-scale randomised clinical trial is needed. The SafeBoosC phase II trial served as a feasibility trial for the large SafeBoosC-III trial that is now close to completion. These trials test the use of cerebral oximetry in extremely preterm infants during the cardio-respiratory transition from intra-uterine to extra-uterine life in the first three days of life. They provide a basis for the new SafeBoosC-IIIv trial that tests cerebral oximetry as an element of intensive care during mechanical ventilation at any time during the neonatal period. At the present time, there is clinical equipoise, which means that there is genuine uncertainty over whether the cerebral oximeter and subsequent treatments will be beneficial or may even be harmful to study

participants. There are no data to support substantially more risk or discomfort as compared with no intervention. All interventions proposed in the SafeBoosC treatment guideline are also commonly used in this patient group.

'Usual care', i.e. treatment according to each hospital's standard procedures will be given to the control group but without access to cerebral oximetry. Also, this will be the care given to any participant that is withdrawn, and newborns who are not included in the trial.

No clinical site will start randomisation before their eligibility has been confirmed, and the protocol has been approved by the relevant ethics committee. Any amendments to the protocol will be decided by the Steering Committee, and subject to ethical review before implemented. Written informed consent will be obtained prior to randomisation of any participant. However, the local neonatal intensive care units have the possibility to apply for the use of 'deferred consent', or 'opt-out' when obtaining approval of the protocol at their ethical committee. Parents can withdraw their consent for participation at any time. The trial will be conducted in compliance with the guidelines of the Declaration of Helsinki in its latest form and the International Conference on Harmonisation Good Clinical Practice guidelines (International Conference on Harmonization Good Clinical Practice) (44) and the applicable European Union regulations and directives. The trial protocol will be registered at www.clinicaltrials.gov, prior to participant enrolment, and, after completion of the trial, summary data will be uploaded.

11.1 Informed consent procedure for prior consent

Informed consent is required from one or both parents, according to local regulations. The investigator/investigator's delegate (qualified physician or nurse connected to the trial) will make contact, and parents will be informed of the trial and given the Parent information sheet **(**A template in English for adaptation to local requirement will be provided from the central trial unit in Copenhagen**)** for the trial. The information consultation will be held in an undisturbed setting as far as possible. The parents will be given time to consider as far as possible, given the need to begin the intervention as fast as possible after intubation and to ask questions before a written informed consent (a template in English will be available**)** will be obtained. Parents will be given a signed copy of the informed consent.

11.2 Deferred informed consent and opt-out

Due to the nature of the population and the sudden need for mechanical ventilation, it may be difficult to obtain prior informed consent from the parents in satisfactory way. Therefore, we allow the principal investigators at each neonatal intensive care unit, to seek approval for deferred informed consent and/or opt-out(30).

11.3 Risk of complications for participants

The following procedure will be implemented to prevent and/or minimise risk of complication for participants.

Related to devices

Correct reading of the monitor (since false readings may lead to wrong treatments) is critical. All clinical staff will be offered and expected to complete web-based training, and the investigators will train the local staff as appropriate, and trained staff will closely supervise all participants during the intervention. To minimise skin irritation related to the device, the care for sensor should follow the user manual.

Related to application of the SafeBoosC treatment guideline

The SafeBoosC treatment guideline used in this trial, has been tested in two trials (27, 30). The SafeBoosC treatment guideline is in harmony with current national clinical practices. All staff caring for trial participants will be offered the web-based training and certification programme.

11.4 Benefit for participant

The participants in both groups will receive careful attention from qualified physicians and hospital staff during the trial

12 Statistical plan and data analysis

12.1 Sample size estimation

A sample size calculation on the dichotomized, composite primary outcome shows that to test a reduction in death or moderate to severe neurodevelopment disability from 20% to 16% between the experimental and control group, at an alfa-level of 2.5% and a power of 80%, a total of 1500 participants in each group, i.e. a total of 3000, is needed. This corresponds to a relative risk reduction of 20%.

12.1.1 Power estimations

A power analysis for the continuous primary outcome, i.e. non-verbal cognitive score of PARCA-R, shows that, with a sample of 1500 in each group and an expected rate of death of 8%, and a standard deviation of the PARCA score of 18 points, the power will be more than 98% to detect a difference of 3 points, at an alfa of 2.5%.

For the secondary outcomes, assuming a risk of any serious adverse event of 20%, the power to detect a decrease to 16% will be 80% at an alpha of 2.5%, and the power to detect an increase in days alive without mechanical ventilation during the first 28 days of life of one day will be 99%, at an alpha of 2.5% (using a reduction of the sample size by 15% to compensate for non-parametric testing).

12.2 Data analysis and statistical methods

A fully detailed statistical analysis plan will be developed and published before enrolment is started. General principles are outlined below.

The primary analysis of all outcomes will be based on the intention-to-treat population and all data will be used, i.e. questionnaire data from the parents and the informal assessment based on health care records. A sensitivity analysis will be done using only parental information. Mixed-effect logistic regression and mixed-effect linear regression will be used to analyse the dichotomous and continuous co-primary outcomes, respectively. We will for all dichotomous outcomes calculate relative risks using the NLCOM STATA command. Data from all participating centres will be used in the primary analysis of all outcomes. In the regression models, 'centre' will be included as a random effect, while 'gestational age below or above 34 weeks of postmenstrual age', 'group allocation' and 'surgery' will be included as fixed effects. Multiples will be treated as independent observations and will, as mentioned, be randomised independently (45). We will use a five-step procedure to assess if the thresholds for statistical and clinical significance are crossed (43). To correct for multiple testing, the threshold for statistical significance will undergo Bonferroni adjustment, and thus a p-value of 0.025 for each primary outcome is chosen. Superiority of the intervention will only be claimed if at least one of the two co-primary outcomes is statistically significant. All other outcome results will be considered hypothesis-generating only.

12.2.1 Analysis of outcomes

Dichotomous outcomes will be summarised as numbers, percentages, risk ratios, and 95% confidence intervals. Continuous outcomes will be summarised by mean and standard deviation if normally distributed or by median and interquartile range if non-normally distributed.

12.2.2 Assessment of components of the dichotomised primary outcome

We will secondly assess each component of the dichotomised primary outcome, i.e. death and moderate to severe neurodevelopmental disability.

12.2.3 Threshold for significance

The thresholds for significance for the co-primary outcomes, will be assessed according to the 5-point procedure suggested by Jakobsen et al. (43, 46).

12.2.4 Missing outcomes

Missing data will be handled per the recommendation by Jakobsen et al. (47)
In short, we will consider using multiple imputation and present best-worst and worst-best case scenarios, if it is not valid to ignore missing data (47). Best-worst and worst-best case scenarios assess the potential range of impact of the missing data for the trial results (47). In the 'best-worst' case scenario, it is assumed that all participants lost to follow-up in the experimental

group have had a beneficial outcome, and all those with missing outcomes in the control group have had a harmful outcome (47). Conversely, in the ‘worst-best’ case scenario, it is assumed that all participants who were lost to follow-up in the experimental group have had a harmful outcome, and that all those lost to follow-up in the control group have had a beneficial outcome(48). We will consider using multiple imputation based on a flow chart (47).

13 Data management plan

13.1 Data handling and archiving

All participant data are protected in accordance with the EU General Data Protection Regulation (GDPR) regulations. The data flow is outlined in Appendix B.

The Copenhagen Trial Unit will provide central, web-based data entry (in the ePRF) using OpenClinica, an open source data management environment that was also used for SafeBoosC-II and III. Data will be managed and stored after approval by the Knowledge Centre on Data Protection Compliance, the Capital Region of Denmark. Only neonatal intensive care unit numbers and study numbers will be used to identify participants (i.e. the data kept at Copenhagen Trial Unit is pseudonymised), while lists of study numbers and personal identifying information (e.g. to allow GCP, data cleansing, and later follow-up) will be kept at the hospitals responsible for clinical care.

The dataset will be kept at the Capital Region of Denmark for 20 years. Six months after the acceptance of the publication that presents the primary outcome, the dataset can be shared with other researchers. Before sharing, subject study numbers, will be removed, neonatal intensive care unit numbers will be replaced, gender and twin status removed, birth weight and gestational age recoded into binary variables to minimize the risk of reidentification. Use by other researchers will depend on the permission of the trial Steering Group. The investigators permit trial-related monitoring, audits, and regulatory inspections by providing direct access to the source data and other relevant documents.

14 Quality assurance

The trial will be conducted in compliance with this protocol across all centres. Detailed instructions and Standard Operating Procedures will be developed for specific tasks, as needed. Any major or safety related deviations will be recorded, analysed and reported to the research ethics committees within seven workdays. If an investigator refuses to comply with the protocol, he/she will be disqualified.

14.1 Eligibility

14.1.1 Centres

Criteria for a centre can take part in the SafeBoosC-IIIv-trial

1. Can include at least 10 newborns per year
2. The centre has implemented or will implement the application of cerebral oximetry at a high level of clinical competence at all times during the trial.
3. The responsible physician and clinical staff are in equipoise as regards to the clinical value of cerebral oximetry in newborns on mechanical ventilation.

14.1.2 Trial personnel

Criteria for individuals who will perform the interventions

We will offer a web-based certification program, where trial personnel will be invited to participate. It will cover cerebral oximetry: the basic principles and device operation and the SafeBoosC treatment guideline; the possible clinical interventions and the rationale of the SafeBoosC treatment guideline. It will take place in a Moodle virtual learning environment (VLE). The setup will be based on the SafeBoosC-III web-based training and certification program.

14.2 Monitoring

14.2.1 Central monitoring

Central monitoring will consist of central daily check of recruitment to the trial, and the quality, completeness and timeliness of data entry in the ePRF by the trial manager, the coordinating investigator and Copenhagen Trial Unit. Statistics of the central monitoring will be published on the trial website. In case of problems, the national coordinators or principal investigators as relevant, will be contacted for verification/correction. The central monitoring will be conducted as described by Harboe Olsen et al. (38).

14.2.2 Local monitoring

The trial will be monitored according to the International Conference on Harmonization Good Clinical Practice guidelines, and a detailed monitoring plan will be developed. The following will be monitored locally

- All participants for existence of clinical file, existence of documented informed consent or absence of opt-out and entry of trial participation in clinical files and mortality.

14.3 Device quality control

Each centre is responsible for adhering to the quality control measures described in the oximeter manufacturer’s user’s guideline.

15 Trial timeframe

Trial stages	Time frame
Protocol development	Marts 2021 – October 2021
Protocol finalised	November 2021
Centre selection	Ongoing
Recruitment phase	To be decided
Assessment phase	To be decided
Final analysis	To be decided
Publication	To be decided

16 Legal aspects

16.1 Finance

The sponsor/coordinating investigator, Professor Emeritus of Neonatology Gorm Greisen, representing the Capital Region, Denmark, is the initiator of the SafeBoosC-IIIv project. He has no financial interest in the results of the trial, nor in the cerebral oximetry-devices. We seek central funding, including funding from industry sponsors, such sources will not get any influence on the methodology, data, analysis, reporting, or conclusions of the trial. Furthermore, any participating centre can seek local/national support from all sources, including dealers of devices, as long such sources will not get any influence on the methodology, data, analysis, reporting, or conclusions of the trial. No financial compensation is foreseen for hospitals participating in this trial.

16.2 Conflict of interest

The authors declare that they have no competing interest.

16.3 Participant insurance

Participants will, if needed, be insured in accordance with existing legislation in their respective countries. Individual neonatal intensive care units are obliged to finance the participants' insurances if relevant.

16.4 Publication plan

The trial will be registered on www.clinicaltrials.gov prior to the randomisation of the first participant. Summary data of the primary outcomes will be uploaded after statistical analyses are completed, if acceptable to the journal to which the manuscript is submitted. Attempts will be sought to publish all results, positive, neutral, as well as negative, in peer-reviewed international journals.

Ancillary studies with results potentially affecting equipoise regarding the value of cerebral oximetry, shall not be published before the main publication of SafeBoosC-IIIv.

16.5 Authorships

Authorship will be determined according to the International Committee of Medical Journal Editors.

- An additional requirement is one author per centre completing (randomise and complete data entry) at least 30 participants. The steering committee may allow more than one author from neonatal intensive care units that contribute more participants.

- The principal investigators, the Steering Committee and members from the SafeBoosC Copenhagen project team that are not principal investigators or Steering Committee members, will be stated as byline authors
- If there is a need for a blinded assessor for the two-year follow-up due to missing parent-reported outcomes, these will be stated as collaborators in the SafeBoosC-IIIv consortium

16.6 Statements of compliance

The randomised clinical trial will be conducted in accordance with this protocol, its Standard Operating Procedures and to the Good Clinical Practice.

17 Appendix

17.1 Appendix A: Treatment guideline

The SafeBoosC treatment guideline

Assessment of cerebral oxygen saturation
Regional cerebral tissue oxygen saturation (rStO2) is a composite measure of tissue oxygen saturation across arterial, capillary and venous beds and reflects a balance between cerebral oxygen delivery (CDO2) and cerebral metabolic rate (CMRO2). In preterm infants, the CMRO2 is unlikely to vary much and a change in rStO2 largely reflects changes in CDO2. The factors which influence CDO2 are arterial oxygen saturation (SaO2), haemoglobin concentration and cerebral blood flow (CBF).

Recommendation for clinical interventions
The threshold for intervention depends on the oximeter. If StO2 is predominantly below the hypoxic threshold over a 10-minute period or drops acutely and markedly under the threshold, the sensor should be inspected for any potential displacement, and possibly be repositioned. If this does not solve the problem, a decision regarding intervention (modification of cardio-respiratory support) should be made (identified in '•') as listed below and StO2 reassessed 30 to 60 minutes after the intervention. Generally, only one intervention should be chosen at a time. All the interventions proposed here are commonly used in this patient group.

For each intervention, the level of evidence (I-III) and strength of recommendation (A-E) are given (defined in Tables 1 and 2). For further explanation, see below.

Rationale/aim of interventions: A low rStO2 reflects a low CDO2. The interventions should be directed to increasing CBF, blood haemoglobin concentration, or SaO2.

<u>Assess cardiovascular status:</u>
Blood pressure below the normal range or low, even in the normal range, consider:

- Vasopressor-inotropes (I/B) (49, 50)
- Fluid bolus (normal saline) (I/C)(51, 52)
- Decrease mean airway pressure on ventilator or CPAP (III/B)(53-56)

Poor systemic circulation, consider if:
Echocardiography shows low cardiac output and/or low SVC flow, consider:

- Inotropes (I/B)(17, 52, 57-60)
- Fluid bolus (normal saline) (I/C) (51, 52)
- Decrease mean airway pressure (III/B) (53-56)

• Reduce vasopressor (III/ B) (61)

Echocardiography not available but has at least 2 of the following signs:
Lactate > 3.5 mmol/l
Capillary Refill Time > 3 seconds
Urine output < 1 ml/kg/hour consider:

- Inotropes (I/B) (17, 52, 57-60)
- Fluid bolus (normal saline) (I/C)(51, 52)
- Decrease mean airway pressure (III/B) (53-55)
- Reduce vasopressor (III/ B) (61)

Patent ductus arteriosus, consider:

- Medical treatment (II-2/B) (54, 56, 62, 63)

<u>Assess oxygen transport:</u>
Blood haemoglobin concentration below the normal range or low, even in the normal range, consider:

- Red blood cell transfusion (I/B)(64-66)

<u>Assess respiratory status:</u>
SaO2 below the normal range or low, even in normal range, consider:

- Increase FiO2 (II-1/A)(67)(ATTENTION: be careful not to exceed the upper target threshold of SpO2)
- Increase mean airway pressure (III/B) (53, 68, 69)

PCO2 below the normal range or low, even in normal range, consider:

- Decrease minute ventilation - (II/A) (64, 70-72)

Level of evidence and recommendation of intervention
The level of evidence (Table 1) and recommendation for a given intervention (in brackets and Table 2) were graded according to the U.S. Preventive Services Task Force system (73)

Table 1: Hierarchy of research design and level of evidence

Level of evidence	Type of study
I	Evidence obtained from at least one properly randomized controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomization
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group
II-3	Evidence obtained from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees

Table 2: Recommendation grid

	Net benefit			
Quality of evidence	substantial	moderate	small	zero/negative
Good	A	B	C	D
Fair	B	B	C	D
Poor	E	E	E	E
Standard recommendation language	A= Strongly recommended (good evidence that the intervention improves important health outcomes and benefits substantially outweigh harms). B= Recommended (at least fair evidence that the intervention improves important health outcomes and benefits substantially outweigh harms). C= No recommendation for or against routine provision of the intervention (fair evidence that the service can improve health outcomes but the balance of the benefits and harms is too close to justify a general recommendation). D= Recommends against routinely providing the intervention (at least fair evidence that the service is ineffective or that harms outweigh benefits). E= Insufficient to recommend for or against routinely providing the intervention (evidence that the intervention is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined).			

17.2 Appendix B: SafeBoosC-IIIv Data flow Web-based Case Report Form

The ePRF will be a web-based solution in the open source clinical trials software OpenClinica®. This will handle the inclusion procedure, the documentation of the stratification and randomisation process, the serious adverse reaction and events and the relevant clinical data from enrolled participants, including primary, secondary and exploratory outcomes as well as explanatory variables. The data will be entered into the ePRF directly by the principal investigator.

Data to be reported before randomisation

Date and time of birth --.--.----
Gestational age weeks and days
Indication for mechanical ventilation (two tick boxes)

- Respiratory insufficiency
- Surgery

Surgery for congenital heart disease is likely (y/n)
Major brain injury is likely (y/n)

Data to be reported at 28 days

Birth weight (0-9999 grams)
Apgar score at 1 min (0-10)
Apgar score at 5 min (0-10)
Major malformation or congenital disease (y/n)
Early onset sepsis (confirmed with culture from normally sterile fluid) (y/n)

At any time after randomisation until 28 days of life or first discharge home when ever come first

Supplementary oxygen above 50% for 24 hours or more (y/n)
Surfactant treatment (y/n)
Nitric oxide inhalation (y/n)
ECMO (y/n)
Renal replacement therapy (y/n)
NEC Bells grad 2 or more (y/n)

Brain imaging done
Cerebral ultrasound (y/n)
MRI (y/n)

Any brain injury on imaging (y/n) tick one or more:

- IVH grade 1
- IVH grade 2
- IVH grade 3
- PIVH (grade 4)
- Other parenchymal haemorrhage
- PHVD
- Cerebellar haemorrhage
- Stroke
- Other

Confirmed or suspected infection treated with antibiotics for 5 days or more (y/n)

Seizures treated with antiepileptic medicines (y/n)

Surgery performed (y/n)

- Acute (y/n)
- Reason for surgery (major malformation, NEC/intestinal perforation, other)

Durations of care and treatment

Completed days of admission
Completed days of tracheal intubation and mechanical ventilation

In the experimental group, only
Change in clinical management due to cerebral hypoxia (y/n)
Days of cerebral oxygenation monitoring
Serious adverse reactions y/n

- If yes: codes

Clinical status at 28 days (if not yet discharged home)

Respiratory support at 28 days

- Supplementary oxygen (y/n)
- CPAP or HF (y/n)
- Mechanical ventilation (y/n)

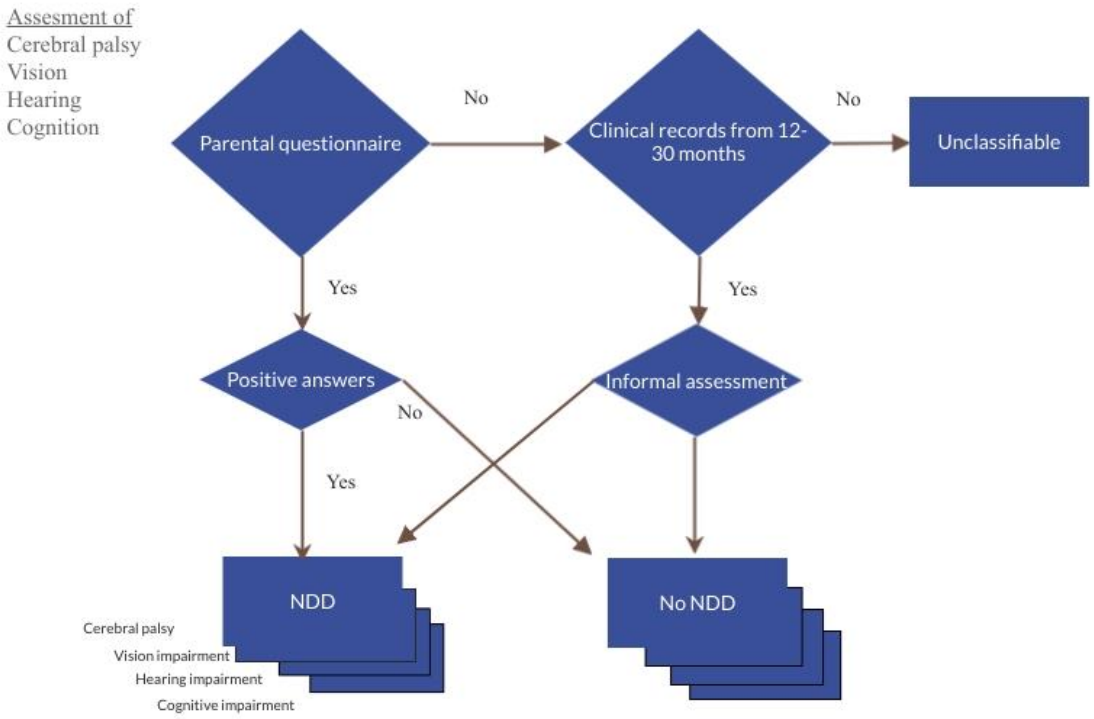
Nutrition (tick one)

- Full enteral feeds from breast or bottle
- Enteral feeding partly by tube
- Enteral feeding exclusively by tube
- Partly parenteral nutrition
- Full parenteral nutrition

Data to be reported at 2 years of age, corrected for preterm birth if it is not possible to complete the parental questionnaire

Weight
Height
Head circumference
Has the child been diagnosed with cerebral palsy?
(y/n)
Has the child been diagnosed with a visual impairment?
(y/n)
Has the child been diagnosed with a hearing impairment?
(y/n)
Has the child been diagnosed with any chronic health problems? Upper airways/ lungs/ heart/ gastro-intestinal /uninary / skin /orthopaedic / other
Has the child received any daily medication for the last two months?
(y/n)
Has the child been assessed with another standardised neurodevelopmental test? (y/n)

17.3 Appendix C: Prioritisation of data for the co-primary outcome moderate-or-severe NDD



NDD = moderate-or-severe neurodevelopmental disability = positive findings for at least one of the four components or NDD based on an informal blinded assessment of all available information
No NDD = no moderate-or-severe neurodevelopmental disability = no positive findings in any of the four components and no NDD based on an informal blinded assessment of all available information
Unclassifiable = if one or more components are unknown and none are positive and there is no informal assessment.

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