Safeguarding the Brain of our smallest Children

SafeBoosC-IIIv

Cerebral oximetry added to usual care versus usual care in newborns receiving invasive mechanical ventilation. An investigator-initiated, pragmatic, multinational randomised phase III clinical trial

Trial phase Phase III
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Sponsor Copenhagen Trial Unit, Centre for Clinical Intervention Research, The Capital Region of Denmark, Rigshospitalet, Denmark, Phone: +45 26186242, Email: janus.jakobsen@ctu.dk

Study centre: Multicentre; international

Abstract

Background
Newborns in need of invasive mechanical ventilation are at high risk of a detrimental outcome, not only due to the underlying condition, but also due to complications from the invasive 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 invasive 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 invasive 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 unpublished data).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, invasive mechanically ventilated newborns are 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 newborns receiving invasive mechanical ventilation. The hypothesis for step one is that the intervention will increase the number of hospital-free days within 90 days of randomisation. The hypothesis for step two 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. The trial will be conducted in two steps. In step one, 1,610 newborns will be randomised, and the outcomes will be assessed 90 days after randomisation. Funding has been obtained for step one. If further funding is obtained, we will continue to include newborns until a total of 3,000 newborns are randomised and then follow them up at two years of corrected age (step two). Randomisation will be performed in neonatal intensive care units across many countries. Data managers, statisticians, and conclusion drawers will be blinded.

Inclusion and exclusion criteria

Inclusion criteria will be:

- Newborns with gestational age more than or equal to 28+0
- Postnatal age less than 28 days
- Expected to receive mechanical ventilation (invasive, i.e., not including CPAP or BiPAP) for at least 24 hours, as judged by the physician intending to randomise
- Parental informed consent unless the centre has chosen to use ‘opt-out’ or deferred consent as consent method and a cerebral oximeter available so monitoring can be started within six hours after initiation of invasive mechanical ventilation

Exclusion criteria will be:

- Suspicion of or confirmed brain injury or disorder (e.g. perinatal asphyxia, cerebral haemorrhage, cerebral malformation, genetic or metabolic disease)
- Suspicion or diagnosis of congenital heart malformations 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 invasive 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 invasive mechanical ventilation. Cerebral oximetry will be continued until 1) the cardio-pulmonary function has been stabilised as indicated by the need for respiratory and circulatory support and evaluated by the responsible physician, 2) extubation, 3) until 28 days after birth, or 4) until death. Randomisation will only direct the use of cerebral oximetry during the first invasive mechanical ventilation episode. 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 invasive mechanical ventilation without access to cerebral oximetry (usual care).

Outcomes

The primary outcome for step one will be hospital-free days within 90 days of randomisation. This outcome will be assessed by a blinded investigator.

Based on a relative risk reduction of death of 5% and an absolute increase of 3 days in the estimate of hospital-free days of the surviving participants (considered clinically relevant) with an alpha of 0.05 and a power of 90% using the van Elteren test, we would need to include 1,610 participants.

There will be two co-primary outcomes for step two: 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).

To test a reduction in death or moderate to severe neurodevelopment disability from 20% to 16% between the experimental and control group, at an alpha-level of 2.5% and a power of 80%, a total of 1,500 participants in each group, i.e. a total of 3,000, is needed. This corresponds to a relative risk reduction of 20%.

Trial duration

Recruitment is expected to begin in December 2024 and expected to be completed within 29 months.

SafeBoosC phase IIIv trial flow chart

Enrolment

Assessed for eligibility

Inclusion criteria:

- Gestational age more than or equal to 28+0
- Postnatal age less than 28 days
- Expected to receive mechanical ventilation for at least 24 hours, as judged by the physician intending to randomise
- Parental informed consent unless the centre has chosen to use 'opt-out' or deferred consent as consent method and a cerebral oximeter available so monitoring can be started within 6 hours after initiation of mechanical ventilation

Exclusion criteria:

- Suspicion of or confirmed brain injury or disorder (e.g. perinatal asphyxia, cerebral haemorrhage, cerebral malformation, genetic or metabolic disease)
- Suspicion or diagnosis of congenital heart malformations who is likely to need surgery

Allocation

Randomised (n= 1610)

Experimental group (n=805)
Treatment based on cerebral oximetry according to the SafeBoosC treatment guideline

Control group (n=805)
Treatment as usual

Reporting

Outcomes for step one reported 90 days after randomisation

Outcomes for step two reported two years of corrected age if funding is obtained

Follow-up

Follow-up for outcomes from step one 90 days after randomisation.

Follow-up for outcomes from step two at two years of corrected age if funding is obtained.

Analysis

Primary outcome: Hospital-free days 90 days after randomisation.

Administrative information

Sponsor

Copenhagen Trial Unit, Centre for Clinical Intervention Research, The Capital Region of Denmark, Rigshospitalet, Denmark.
Phone: +45 26186242, Email: janus.jakobsen@ctu.dk

Steering Committee

SafeBoosC-IIIv is led by a Steering Committee comprising the Copenhagen SafeBoosC-IIIv project team, including Caroline Kamp (trial manager, Copenhagen Trial Unit)/Johanne Juul Petersen (alternate trial manager, Copenhagen Trial Unit), Gorm Greisen, all national coordinators, and Janus Christian Jakobsen (sponsor, Copenhagen Trial Unit). Decisions will be made by a simple majority.

Executive Committee

The executive committee is responsible for the day-to-day management and will comprise the Copenhagen SafeBoosC-IIIv project team, including Caroline Kamp (trial manager, Copenhagen Trial Unit)/Johanne Juul Petersen (alternate trial manager, Copenhagen Trial Unit), Gorm Greisen, Adelina Pellicer, Gunnar Naulaers, Eugene Dempsey, Gitte Hahn, and Janus Christian Jakobsen (sponsor, Copenhagen Trial Unit).

National coordinators

To be appointed

Independent Data Monitoring and Safety Committee (DMSC)

To be appointed

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1 Introduction and background

1.1 The population and condition

Current standard of care of newborns in need of invasive mechanical ventilation, involves several different interventions (5). The criteria for initiation of invasive mechanical ventilation vary among neonatal intensive care units. In general, invasive 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 invasive 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).

1.1.1 Current clinical management

Newborns receiving invasive mechanical ventilation 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).

1.2 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'.

1.3 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). Electrical cardiometry 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 and a low cerebral oxygenation might also be an indication to perform an echocardiography. Better management of low cardiac output may reduce the risk of dysfunction of these organs and thereby, reduce the risk of death.

1.4 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.

1.5 Mechanisms of brain damage in newborns in need of invasive 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 invasive mechanical ventilators offer better control of ventilation, carbon dioxide tension is still often very variable during invasive mechanical ventilation. Furthermore, cerebral vasoconstriction due to hypocapnia may interact with vasoconstriction due to circulatory stress, caused by the positive airway pressure during invasive 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).

1.5.1 Trials of clinical benefit in newborns receiving invasive mechanical ventilation

To our knowledge, no randomised clinical trials have evaluated cerebral oximetry added to usual care versus usual care in newborns receiving invasive mechanical ventilation. 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). The larger COSGOD-III and SafeBoosC-III trials have tested the effect of cerebral oximetry on clinical relevant outcomes, i.e. survival without severe brain injury (29, 30). COSGOD included preterm infants in the delivery room and SafeBoosC included extremely preterm infants during the first three days of life. Neither trial showed that treatment guided by cerebral oximetry monitoring was associated with a better clinical outcome.

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) 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 oximetry is less than a 20% reduction of adverse outcomes. The SafeBoosC-IIIv trial can potentially fill this knowledge gab.

1.6 Benefits and risks

If the SafeBoosC-IIIv trial shows that cerebral oximetry will result in more hospital-free days, the benefits will be obvious. First, hospital-free days have value to patients in itself; it must be considered important to patients and their relatives to spend as little time as possible in the hospital. It may also be a valid surrogate outcome for other patient-important outcomes, as a low number of hospital-free days will likely correlate with complications and abilities to breathe and feed. Second, results based on hospital-free days reflect both incidences of deaths and the cumulated hospital burden (patients who die in hospital will experience no hospital-free days).

If the SafeBoosC-IIIv trial shows that cerebral oximetry is without effects or is harmful, such results will also benefit patients. If cerebral oximetry monitoring is without beneficial effects, clinical use result in waste of time and money that may be spent otherwise for the benefit of patients. 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 on the small body of a newborn is disturbing, and these patients are already stressed by care procedures.

2 Trial objective and hypothesis

The objective of the SafeBoosC-IIIv trial is to evaluate cerebral oximetry added to usual care versus usual care in newborns receiving invasive mechanical ventilation. The hypothesis for step one is that the intervention will increase the number of hospital-free days within 90 days of randomisation. The hypothesis for step two 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.

3 Trial design

This is an investigator-initiated, multinational, randomised, pragmatic phase III clinical trial with a two parallel group design, that will enrol 1610 newborns in step one. If funding is obtained, randomisation will continue until 3000 newborns are enrolled (step two).

3.1 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 invasive 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.

A screening log will be kept at each site with a list of all admitted patients with gestational age more than or equal to 28+0, who were intubated and expected to be mechanically ventilated for more than 24 hours, at any time during the first 28 days after birth. The screening log will contain data on subject number, date of screening, gestational age (lower gestational age (<34 weeks) / higher gestational age (≥34 weeks)), expected surgery (yes/no), randomised (yes/no), and reason not randomised.

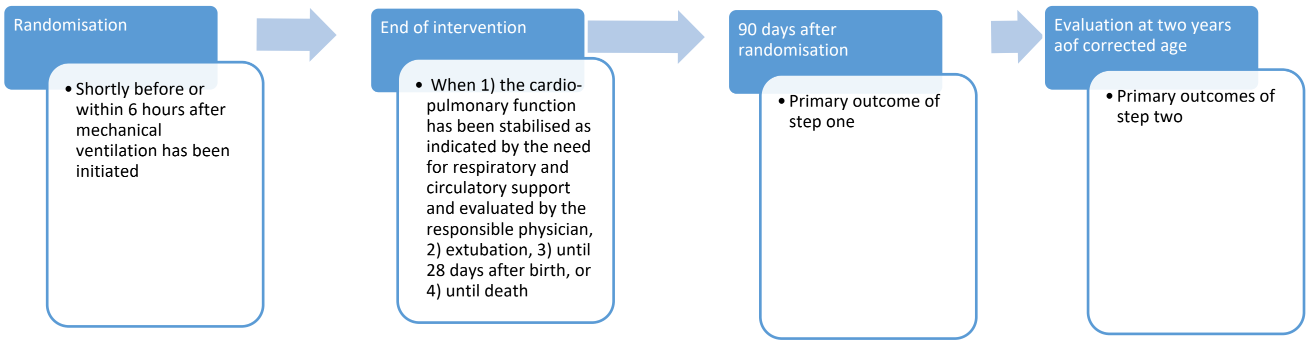
Singleton newborns will be randomised individually. Multiple birth newborns will be randomised individually, as it is not common that the twins or triplets will need invasive mechanical ventilation at the same time. A second twin can be enrolled when it meets the inclusion criteria if the parents can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

3.2 Blinding

Due to the nature of the experimental intervention, clinical staff and the parents will not be blinded to group allocation. Data will be collected from health care records, and parents will be consulted and, if necessary, contacted by phone and/or email. The primary outcome will be assessed by a blinded investigator. The principal investigator from each centre must develop a local blinding procedure, describing how blinding is achieved. Before the initiation of randomisation in each centre, the local blinding procedure must be approved by the coordinating investigator or the trial manager. To support the principal investigators in this work, a Standard Operation Procedure with suggestions for blinding procedures has been developed.

Data managers, statisticians, and conclusion drawers will be blinded. Furthermore, mortality status and hospital-free days will be source data verified for all participants at 90 days after randomisation, 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 Committee and all three reports will be published as supplemental material. Discrepancies between the two reports will be discussed by the Steering Committee.

3.3 Trial timeline



4 Participants

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

4.1 Inclusion criteria

- Gestational age more than or equal to 28+0
- Postnatal age less than 28 days
- Expected to receive mechanical ventilation (invasive, i.e., not including CPAP or BiPAP) for at least 24 hours, as judged by the physician intending to randomise
- Parental informed consent unless the centre has chosen to use 'opt-out' or deferred consent as consent method and a cerebral oximeter available so monitoring can be started within six hours after initiation of invasive mechanical ventilation

4.2 Exclusion criteria

- Suspicion of or confirmed brain injury or disorder (e.g. perinatal asphyxia, cerebral haemorrhage, cerebral malformation, genetic or metabolic disease)
- Suspicion or diagnosis of congenital heart malformations who is likely to need surgery

4.3 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.

4.3.1 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.

4.3.2 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 (32). In the SafeBoosC-III trial, a total number of 1601 newborns were randomised, with an average of 1.8 newborns randomised per day (safeboosc.eu). The results of SafeBoosC-III are published in New England Journal of Medicine (29).

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 recruited infants into the SafeBoosC-III trial (33). 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.

5 Interventions

5.1 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 invasive mechanical ventilation has been initiated and continuing until 1) the cardio-pulmonary function has been stabilised as indicated by the need for respiratory and circulatory support and evaluated by the responsible physician, 2) extubation, 3) until 28 days after birth, or 4) 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.

5.1.1 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 (34, 35). Decisions on change of clinical management will be based on the SafeBoosC treatment guideline in combination with other clinical information.

Randomisation will only direct the use of cerebral oximetry during the first invasive mechanical ventilation episode. 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.

6 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 (36).

6.1 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 the sensor-specific hypoxic threshold 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 information and training prior to caring for trial participants. The principal investigator at each neonatal intensive care unit is responsible for listing relevant clinical staff, that are expected to use the web-based information and training, as well as providing trial information, supervision, and support.

6.1.1 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.

6.2 Control group

The control group will receive invasive mechanical ventilation without access to cerebral oximetry (usual care). 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.

6.3 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.

7 Outcomes

7.1 Outcomes for step one

7.1.1 Primary outcome for step one

- Hospital-free days within 90 days of randomisation.

7.1.2 Secondary outcomes for step one

- One or more Serious Adverse Events within 90 days of randomisation (Appendix B), i.e. one or more of the following:
    - Death from any cause
    - Bronchopulmonary dysplasia (BPD)
    - Any brain injury diagnosed by imaging
    - Seizures treated with antiepileptic medicine
    - Haemodynamic insufficiency that needs cardiovascular support
    - Spontaneous bowel perforation or necrotising enterocolitis (NEC) Bells grade 2 or more
    - Nosocomial infection
    - Extra Corporal Membrane Oxygenation (ECMO)
    - Renal replacement therapy
- Invasive mechanical ventilation-free days within 90 days of randomisation.

7.1.3 Exploratory outcomes for step one

- Late-onset sepsis
- Invasive mechanical ventilation-related infection

7.2 Outcomes for step two

7.2.1 Primary outcomes for step two

There will be two co-primary outcomes for step two, 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.

7.2.2 Exploratory outcomes for step two

- 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.

7.3 Outcome assessment tools

7.3.1 Outcome assessment tools for step one

All outcomes for step one will be assessed within 90 days of randomisation. Data will be collected from health care records, and parents will be contacted and consulted by phone and/or email. Information from health care records will be prioritised regarding the index admission, while information from the parents will be used only as additional information (e.g., readmissions). A Standard Operation Procedure for assessment of primary outcome will be developed. The primary outcome will be assessed by a blinded investigator. The principal investigator from each centre must develop a local blinding procedure, describing how blinding is achieved. Before the initiation of randomisation in each centre, the local blinding procedure must be approved by the coordinating investigator or the trial manager. To support the principal investigators in this work, a Standard Operation Procedure with suggestions for blinding procedures will be developed.

7.3.2 Outcome assessment tool for step two

All primary outcomes for step two, 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 D.

Based on the SafeBoosC-III Good Clinical Practice data monitoring model (37), a pragmatic system of local and central Good Clinical Practice data monitoring will be developed and used.

7.3.2.1 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 (38). The questionnaire has been used as a two-year outcome measure in multiple clinical trials (39) 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.

8 Data collection and trial assessment schedule

8.1 Collection of trial data

8.1.1 Collection of trial data in step one

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

The assessment of the primary outcome is based on a review of clinical records and contact with the parents. We suggest the following:

- Review of clinical records: A colleague, unaware of group allocation, will be presented to the infant's clinical records to assess the number of hospital-free days from randomisation until discharge/last note in the available clinical records. Prior to the assessment, the principal investigator will identify any records that could reveal group allocation and ensure this information is not presented to the blinded colleague. Alternatively, the principal investigator could print the clinical records, exclude information that reveals group allocation, and let the blinded assessor review the remaining records in print.
- Contact with parents: after reviewing the clinical records, the blinded colleague must contact the infant's parents via phone or email to ask if the child has been admitted to any hospital since the date of first discharge. If the parents report that the infant has been admitted to a hospital since the date of first discharge, the parents must report the number of days in hospital to the blinded colleague.

Based on the described assessment, the blinded colleague will determine the total number of hospital-free days within 90 days from randomisation, add it to a primary outcome log, access OpenClinica, and report it. The blinded colleague will have access to a separate OpenClinica site without information on group allocation. The investigator may choose another method for blinded assessment of the primary outcome. However, if the chosen method is different than the one described above, the method must be approved by the Trial Manager on behalf of the Steering Committee. The investigator must report and describe the chosen method to the trial manager at caroline.kamp@ctu.dk before enrolment of participants.

8.1.2 Collection of trial data in step two

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

8.2 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 eCRF data entry: 1) consent/randomisation; 2) end of monitoring, and 3) 90 days after randomisation. The data entry system, OpenClinica, will send a reminder to the principal investigators 90 days after randomisation. If funding is obtained for step two, data will be entered for 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 D) from the newborn's health care records and requested to provide an informal assessment of the primary outcomes.

9 Assessment of Safety

9.1 Adverse events and reactions

9.1.1 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 (40, 41). 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 (41): 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

9.1.2 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.

9.1.3 Justification for recording and reporting

The patient population of newborns in need of invasive 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.

9.1.4 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 eCRF 90 days after randomisation. 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.

9.2 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.

9.3 Data Monitoring and Safety Committee

A Data Monitoring and Safety Committee (DMSC) will be established to monitor mortality and neonatal morbidities at 90 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 one-third of the participants have reached 90 days of life (537 participants). 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 (42).

9.4 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.

10 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 invasive 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 invasive 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) (43) 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.

10.1 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.

10.2 Deferred informed consent and opt-out

Due to the nature of the population and the sudden need for invasive 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 (44).

10.3 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, 44). 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.

10.4 Benefit for participant

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

11 Statistical plan and data analysis

11.1 Sample size estimation

11.1.1 Sample size estimation for step one

A sample size calculation on the primary outcome (hospital-free days) shows that to test a relative risk reduction of death of 5% and an absolute increase of 3 days in the estimate of hospital-free days of the surviving participants (considered clinically relevant) with an alpha of 0.05 and a power of 90% using the van Elteren test, we would need to include 1,610 participants (Appendix E).

11.1.1.1 Power estimations for step one

Based on data from Statistics Denmark and from Rigshospitalet (45, 46), we assume 20% of the newborns receiving invasive mechanical ventilation will experience one or more serious adverse events within 90 days of randomisation. With a relative risk reduction of 30% in the experimental group, we will be able to detect this difference between the experimental and control group with 89% power at a 5% significance level.

For invasive mechanical ventilation-free days, we defined a clinically relevant relative risk reduction of 5% and an absolute increase of 3 days in the estimate. Based on an alpha of 0.05 using the van Elteren test, we would have a power of 100% when including 1,610 participants.

11.1.2 Sample size estimation for step two

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 alpha-level of 2.5% and a power of 80%, a total of 1,500 participants in each group, i.e. a total of 3,000, is needed. This corresponds to a relative risk reduction of 20%.

11.1.2.1 Power estimations for step two

A power analysis for the continuous primary outcome, i.e. non-verbal cognitive score of PARCA-R, shows that, with a sample of 1,500 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 alpha of 2.5%.

11.2 *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. data from the health care records and from contact with parents.

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 (47). We will use a five-step procedure to assess if the thresholds for statistical and clinical significance are crossed (42). Our primary conclusions will be based on the primary outcome, and all remaining results will be considered hypothesis generating. Hence, we will consider a p-value of less than 0.05 as statistically significant.

11.2.1 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.

11.2.2 Assessment of components of the dichotomised primary outcome for step two

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

11.2.3 Threshold for significance

The thresholds for significance for the primary outcomes, will be assessed according to the 5-point procedure suggested by Jakobsen et al. (42, 48).

11.2.4 Missing outcomes

Missing data will be handled per the recommendation by Jakobsen et al. (49)
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 (49). Best-worst and worst-best case scenarios assess the potential range of impact of the missing data for the trial results (49). 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 (49). 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(50). We will consider using multiple imputation based on a flow chart (49).

12 Data management plan

12.1 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 C.

The Copenhagen Trial Unit will provide central, web-based data entry (in the eCRF) 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.

13 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.

13.1 Eligibility

13.1.1 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 invasive mechanical ventilation.

13.1.2 Trial personnel

Criteria for individuals who will perform the interventions

We will offer web-based information and training, 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.

13.2 Monitoring

13.2.1 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 eCRF 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. (37).

13.2.2 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, and entry of trial participation in clinical files. Data for group allocation, gestational age, survival or death at 90 after randomisation, hospital-free days and screening logs will be entered by the local investigator and source checks will be done by an independent monitor.

13.3 Device quality control

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

14 Trial timeframe

Trial stages	Time frame
Protocol development	February 2024 – July 2024
Protocol finalised	August 2024
Centre selection	Ongoing
Recruitment phase	To be decided
Assessment phase	To be decided
Final analysis	To be decided
Publication	To be decided

15 Legal aspects

15.1 Finance

The sponsor/coordinating investigator, Professor Janus Christian Jakobsen, 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 have received funding from the Independent Research Fund Denmark to cover central trial costs for step one. We will seek additional 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.

15.2 Conflict of interest

The authors declare that they have no competing interest.

15.3 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.

15.4 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. Results of step one will be published even if funding for step two is not obtained.

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

15.5 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 10 participants per year. 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

15.6 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.

16 Appendix

16.1 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) (51, 52)
- Fluid bolus (normal saline) (I/C)(53, 54)
- Decrease mean airway pressure on ventilator or CPAP (III/B)(55-58)

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

- Inotropes (I/B)(17, 54, 59-62)
- Fluid bolus (normal saline) (I/C) (53, 54)
- Decrease mean airway pressure (III/B) (55-58)

• Reduce vasopressor (III/ B) (63)

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, 54, 59-62)
- Fluid bolus (normal saline) (I/C)(53, 54)
- Decrease mean airway pressure (III/B) (55-57)
- Reduce vasopressor (III/ B) (63)

Patent ductus arteriosus, consider:

- Medical treatment (II-2/B) (56, 58, 64, 65)

<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)(66-68)

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

- Increase FiO2 (II-1/A)(69)(ATTENTION: be careful not to exceed the upper target threshold of SpO2)
- Increase mean airway pressure (III/B) (55, 70, 71)

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

- Decrease minute ventilation - (II/A) (66, 72-74)

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 (75)

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).			

16.2 Appendix B: Definitions of serious adverse events

One or more serious adverse events within 90 days of randomisation: death from any cause, bronchopulmonary dysplasia (BPD), any brain injury diagnosed by imaging (if both ultrasound and MRI are available, MRI will be prioritized), seizures treated with antiepileptic medicine, hemodynamic insufficiency that needs cardiovascular support, spontaneous bowel perforation or necrotizing enterocolitis defined as Bell's grade 2 or more, extracorporeal membrane oxygenation treatment, renal replacement therapy, and nosocomial infection)

The diagnoses of any of the serious adverse events will be made by the outcome assessor using health care records, however, the following definitions are recommended.

The following **neonatal outcomes** expressed as the **grades outlined below or above** (**adapted from: E**uropean **N**ewborn **S**tudy: **E**arly **M**arkers for a **B**etter **L**ife-ENSEMBLE; International Neonatal Consortium (doi: 10.1136/archdischild-2019-317399); European Standards of Care for Newborn Care (EFCNI))

Bronchopulmonary dysplasia (grade 2): Supplemental oxygen at 28 days AND need for 22-30% oxygen at 36 weeks PMA in infants born <32 weeks' gestation; need for 22-30% oxygen by 56 days postnatal age in infants born >32 weeks' gestation; need for 22-30% oxygen at discharge. [Note: For conversion of oxygen administered by different modalities to FiO2: see http://nicutools.org/MediCalcs/ActualO2.php3]).

Brain injury documented either by CUs, MRI, or TC

a) Peri-intraventricular hemorrhage (grade 2 or more): Hemorrhage occupying less than 50% of the ventricle volume
b) Periventricular haemorrhagic (venous) infarction
c) Post-haemorrhagic ventricular dilatation: ventricular dilatation with ventricular index > 4mm above the 97th percentile or anterior horn with > 6 mm or need of CSF removal (drain, shunt, reservoir, lumbal puncture)
d) Periventricular leukomalacia (grade 2) (CUs diagnosis): Transient periventricular echodensities evolving into small, localized frontal-parietal cysts or persistent diffuse echodensities.
e) Extensive punctate white matter injury (MRI diagnosis)
f) Perinatal ischemic stroke
g) Acute HI brain damage:
    i. (CUs diagnosis)*: i) brain swelling; ii) bilateral-symmetric basal ganglia-thalamic injury or focal (asymmetric) hyperechoic areas; iii) laminar cortical necrosis; iv) Periventricular and/or subcortical white matter injury
    ii. (MRI diagnosis): i) Central and/or peri-rolandic gray matter damage; ii) Hypoxic-ischemic injury in watershead areas
h) Cerebellar injury (ischemic-haemorrhagic) involving vermis or >1/3 of hemisphere
i) Big extra-axial bleeding or parenchymal bleeding/contusion with/without midline shift
j) Other: imaging findings related to CNS acquired infection

Neonatal seizures that need for treatment

a) Neonatal epileptic seizure (grade 2): electroencephalogram (EEG)-proven seizures that are controlled with one anti-seizure drug (no recurrence within three days after treatment).

b) Neonatal Convulsions (grade 3): Suspected seizures (no EEG) uncontrolled with one anti-seizure drug (recurrence within three days after treatment or requiring two or more anti-seizure drugs).

Hemodynamic insufficiency

a) Persistent hypotension (grade 3): hypotension affecting perfusion; requiring major care change (e.g., vaso-active drugs or hydrocortisone)

b) Clinical signs of compromised perfusion regardless blood pressure (raised serum lactate, poor urine output, central-to-peripheral temperature gap, prolonged skin refill-time, echocardiographic parameters) requiring major care change (e.g., vaso-active drugs or hydrocortisone)

Bowel AE

a) Neonatal spontaneous intestinal perforation (grade 3): presence of spontaneous intestinal perforation (SIP), non-urgent medical stabilization and surgical intervention indicated.

b) NEC (Bell's stage 2): confirmed NEC with lack of bowel sounds, pain, and tenderness in the abdomen, low or no intestinal movement, presence of gasfilled spaces in the intestinal walls, including stage 1 clinical signs (lethargy, vomiting, bloody stools abdominal bloating, slow heart rate and unstable temperature).

Renal replacement therapy

a) Infants receiving any of the following therapies: peritoneal dialysis, hemodialysis, or hemofiltration

Nosocomial infection

a) Late-onset sepsis: Defined as antibiotics prescribed after 72 hours and given for 5 days or more

b) Invasive mechanical ventilation (endotracheal or tracheostomy)-related infection

16.3 Appendix C: SafeBoosC-IIIv Data flow Web-based Case Report Form

The eCRF 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 eCRF directly by the responsible physician at randomisation or blinded assessor.

Data to be reported before randomisation

Date and time of birth --.--.---- --.--
Singleton or multiple birth
Number of babies to include in trial

- 1
- 2
- 3
- 4

Inclusion criteria:

Neonate born gestational age more than 28+0 weeks and expected to receive invasive mechanical ventilation for at least 24 hours (y/n)
Consent method

- Prior informed consent
- Deferred consent
- Opt-out

Exclusion criteria:

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

Stratification and allocation:

Gestational age

- Lower gestational age (≤ 34 weeks)
- Higher gestational age (> 34 weeks)

In need of invasive mechanical ventilation due to a surgery (y/n)
Site

Data to be reported end of monitoring

Gestational age weeks and days
Birth weight (0-9999 grams)
Sex

Male
Female
Race or ethnic group
White
Black or African American
Asian
Hispanic or Latino
Mixed
Other
Apgar score at 1 min (0-10)
Apgar score at 5 min (0-10)
Indication for invasive mechanical ventilation
Respiratory insufficiency
Surgery

NIRS monitoring (intervention group):
Did the newborn undergo NIRS monitoring during the index case (y/n)
Age in days when cerebral oximetry was started
Time from start invasive mechanical ventilation to NIRS monitoring (hours)
Did cerebral oximetry monitoring stop prematurely (before any of the four stop criteria)? (y/n)
If yes: What caused monitoring to stop prematurely?
Total days of cerebral oxygenation monitoring during the index case (days)
Did clinical staff change the medical management due to cerebral hypoxia? (y/n)
Which NIRS device did you use to monitor the baby?
INVOS
NIRO
Fore-Sight
Sensmart
O3 / Masimo
Egos
OxyPrem
Other
If other: Please write the name of the NIRS device
Severe adverse reaction during monitoring (y/n)
If yes: Severe adverse reaction specification
Severe skin damage
Date
Comment
Critical displacement of endotracheal tube threatening the life of the baby
Date
Comment
Critical displacement of endovascular line threatening the life of the baby

Date
Comment
Clinical mismanagement while trying to improve respiratory status
Date
Specification of mismanagement
Comment
Clinical mismanagement while trying to improve cardiovascular status
Date
Specification of mismanagement
Comment
Clinical mismanagement while trying to improve oxygen transport
Date
Specification of mismanagement
Comment

NIRS monitoring (control group):
Had the baby cerebral NIRS monitoring despite being in the control group? (y/n)
If yes: Was information on cerebral oxygenation available for clinical staff? (y/n)

Parental withdrawal:
Did the parents withdraw consent? (y/n)
If yes: What reason did the parents give?
If yes: Did the parents withdraw permission to use data form the baby's future clinical course?

Deferred consent:
Did the parents decline the baby's continuation in the trial? (y/n)
If yes: What reason did the parents give?
If yes: Did the parents decline permission to use data from the baby's future clinical course? (y/n)
If yes: Did the parents decline permission to use data up until time of exclusion? (y/n)

Treatment:
Surfactant treatment (y/n)
Did the baby receive cardiovascular support? (y/n)

Data to be reported at 90 days after randomisation
Follow-up date
Major malformation or congenital disease (y/n)
Beyond the index case, was the newborn reintubated? (y/n)
Did the baby receive treatment for patent ductus arteriosus (medical or surgical)? (y/n)

What was the last registered weight of the baby before follow-up?
Date of last weighing

Primary outcome
Hospital-free days within 90 days of randomisation based on review of health care records
Hospital-free days within 90 days of randomisation based on contact with parents

Serious adverse events
Any serious adverse event (y/n)
Death (y/n)
    If yes: Cause of death
    Congenital anomaly
    Respiratory distress syndrome
    Bronchopulmonary dysplasia
    Infection
    NEC
    CNS injury
    Immaturity
    Other
    Unknown
    If other: Please specify cause of death
Bronchopulmonary dysplasia (grade 2) (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
    Periventricular haemorrhagic (venous) infarction
    PHVD
    Other parenchymal haemorrhage
    Periventricular leukomalacia (grade 2)
    Extensive punctate white matter injury
    Acute HI brain damage
    Cerebellar haemorrhage
    Stroke
    Big extra-axial bleeding or parenchymal bleeding/contusion
    Other
Seizures treated with antiepileptic medicine

EEG-proven seizure controlled with one anti-seizure drug (y/n)
Suspected seizure uncontrolled with one anti-seizure drug (y/n)

Haemodynamic insufficiency
Persistent hypotension (y/n)
Clinical signs of compromised perfusion regardless of blood pressure (y/n)

ECMO (y/n)

Bowel adverse events
NEC Bells grade 2 or more (y/n)
Spontaneous intestinal perforation (grade 3) (y/n)

Renal replacement therapy (y/n)

Nosocomial infection
Confirmed or suspected late-onset sepsis treated with antibiotics after 72 hours for 5 days or more (y/n)
Confirmed or suspected invasive mechanical ventilation (endotracheal or tracheostomy)-related infection (y/n)

Other:

Invasive mechanical ventilation-free days

Clinical status at 90 days (if not yet discharged home):

Respiratory support at 90 days
Supplementary oxygen (y/n)
Non-invasive ventilation (CPAP included) (y/n)
Invasive 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

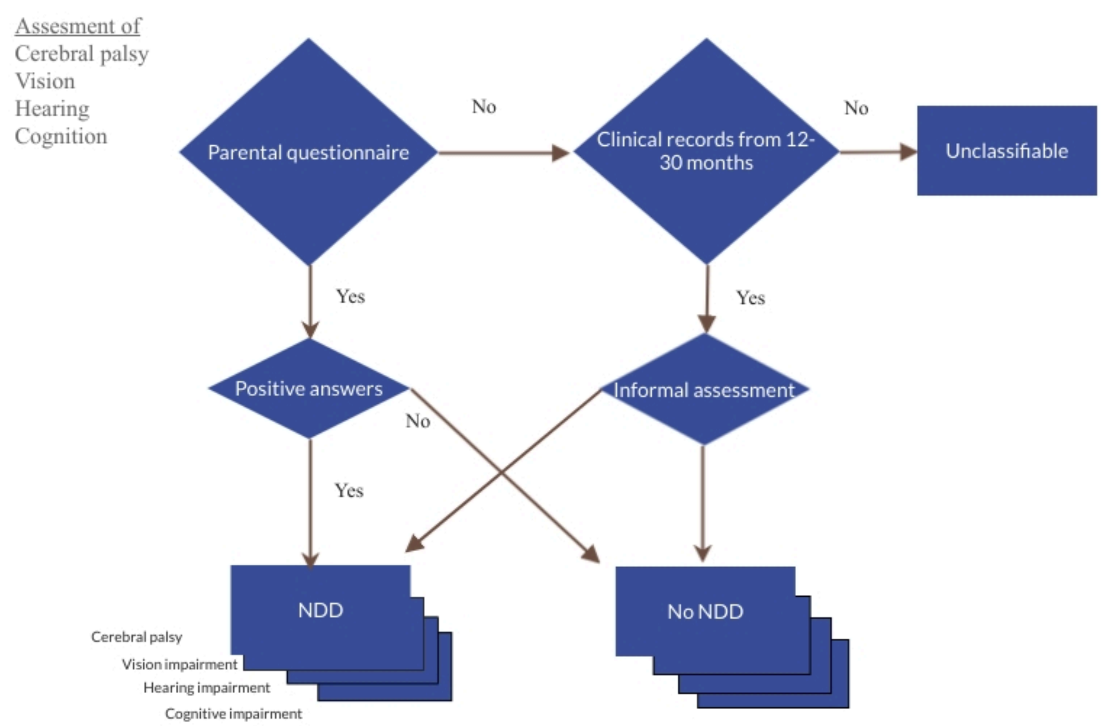
Head circumference

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 /urinary / 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)

16.4 Appendix D: Prioritisation of data for the co-primary outcome moderate-or-severe NDD for step two



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.

16.5 Appendix E: Sample size

Simulation of sample size for SafeBoosC-IIIv

Markus Harboe Olsen

08 december 2023

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Introduction

The SafeBoosC-IIIv is a randomised clinical trial designed as superiority trial to asses days alive and out-of-hospital. We chose to use statistical simulations to estimate the required sample size to achieve a power of 90%. This, using an alpha of 0.05.

Sample data

To carry out these simulations, we used data from the danish national registry. Between 2001 and 2018, 1,392 children were born who were in mechanical ventilator and did not have any heart defects. Pseudonymised data were assessed for days alive and out-of-hospital. Of those, 140 (10.1%) dies within 90 days.

The data below is used for the simulations:

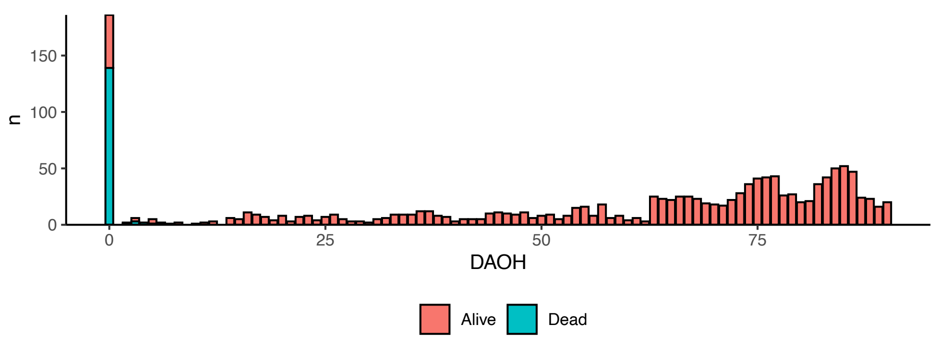
DAOH	All	Mortality	Alive	Dead
	n	n (%)	mean (SD)	mean (SD)
0	169	129 (76.3%)	-	.
1-10	33	9 (27.3%)	5.5 (2.8)	4.8 (2.8)

DAOH	All	Mortality	Alive	Dead
11-20	64	0 (0%)	16.2 (2.6)	-
21-30	52	0 (0%)	25.1 (2.9)	-
31-40	78	0 (0%)	35.8 (2.9)	-
41-50	88	0 (0%)	45.6 (3.1)	-
51-60	101	2 (1.4%)	55.6 (2.9)	-
61-70	173	0 (0%)	66.2 (2.7)	-
71-80	285	0 (0%)	75.8 (2.9)	-
81-89	344	0 (0%)	84.9 (2.4)	-
90	3	0 (0%)	-	-

Simulation procedure

For each trial, the above-shown table is simulated so the two missing participants who died in the 51-60 category is simulated to have the same distribution as the alive participants in the same category. Each participant is first classified as alive or dead, depending on the defined risk. The baseline risk is 10.1%. Next, the participant is assigned to one of the above defined groups based on the probability from the number of participants in the simulated assignment table. Finally, the participants specific DAOH is then assigned based on the mean and SD.

Here we present a graphical presentation of participants from one simulated trial with 1,392 participants without any intervention effect, stratified by alive or dead.



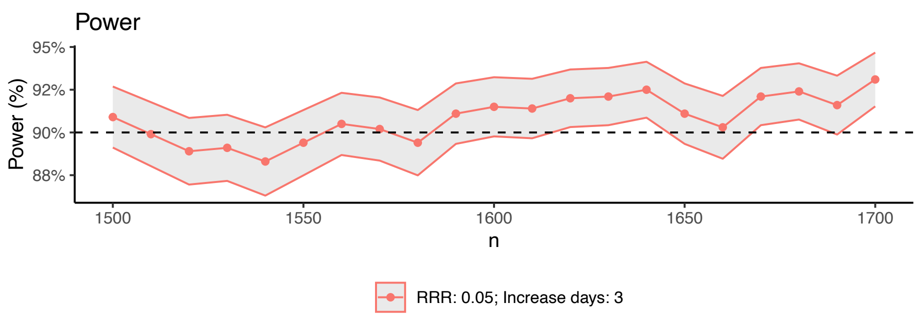
Planned statistical analysis

We aim to use Wilcox rank sum test to estimate median difference and 95% Hodghes-Lehmann confidence intervals. The primary analysis used for sample size calculation will be Van Elteren test. As sensitivity analyses, we will use mixed effect linear regression with site as a random effects covariate and gestational age (above or below 34 weeks) as a fixed effect covariate and also the Kryger Jensen and Lange test which was developed specifically for distributions of outcome results that show many patients with a value of zero, which would be the case for the number of days alive and out of the hospital. Here, the p-value will be used to estimate power for the different sample sizes.

Intervention effects

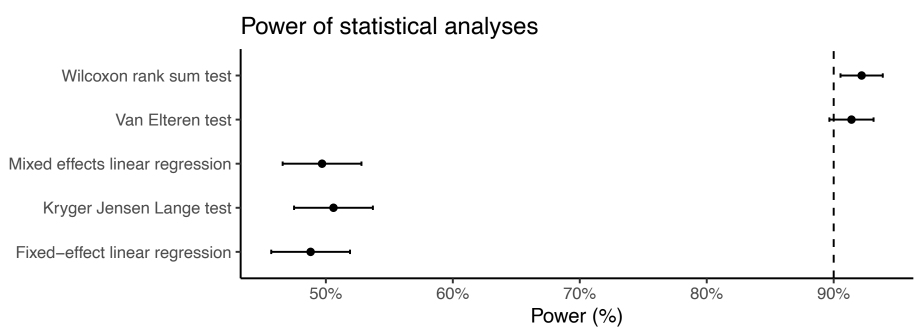
We proposed the intervention will have a relative risk reduction in mortality of 5%, i.e. an absolute decrease of 0.50%. This decreases the mortality from 10.06% to 9.55%. Furthermore, we propose an absolute increase of 3 days in the estimate of days out-of-hospital of the surviving participants.

Based on an alpha of 0.05, we investigate when the power of the Van Elteren analysis exceed 90%.



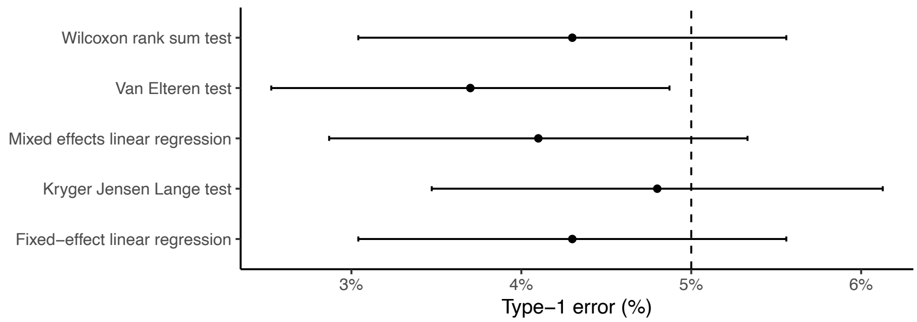
After inclusion of 1,610 participants the power of the analysis would reach a stable level of 90% or above.

Furthermore, we investigated the power of the sensitvity analyses when including 1,610 participants:



Statistical analysis	Estimate (95%CI)
Mixed effects linear regression	49.7 (46.6;52.8) %
Kryger Jensen Lange test	50.6 (47.5;53.7) %
Fixed-effect linear regression	48.8 (45.7;51.9) %
Wilcoxon rank sum test	92.2 (90.54;93.86) %
Van Elteren test	91.4 (89.66;93.14) %

As seen the power of the sensitivity analyses are under-powered for this exact outcome. Finally we need to ensure the Type-1 error does not exceed 5% for trial without any intervention effect.



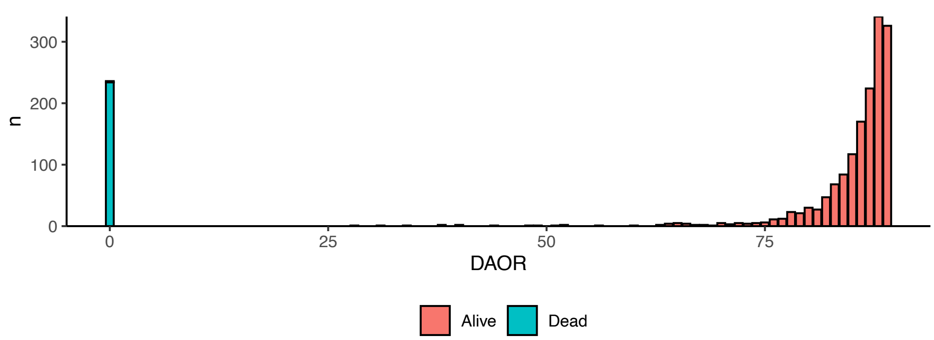
Statistical analysis	Estimate (95%CI)
Mixed effects linear regression	4.1 (2.87;5.33) %
Kryger Jensen Lange test	4.8 (3.47;6.13) %
Fixed-effect linear regression	4.3 (3.04;5.56) %
Wilcoxon rank sum test	4.3 (3.04;5.56) %
Van Elteren test	3.7 (2.53;4.87) %

For all analyses the type-1 error is below 5%.

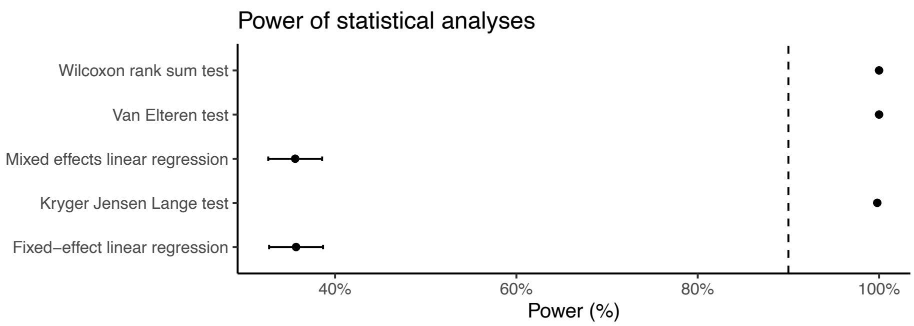
Power calculations

Days alive and out of mechanical ventilation

Days alive and out-of-respirator (DAOR) / mechanical ventilator is a secondary outcome. The simulations are carried out by using DAOR from 1,800 previous patients admitted to Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark:

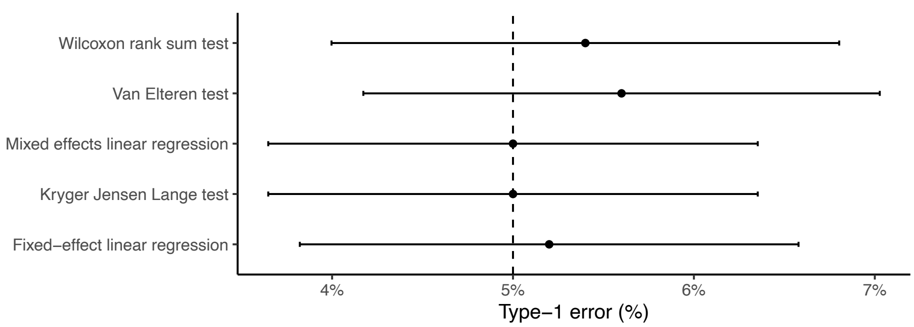


Based on a relative risk reduction of 5% in mortality (from the previously defined 10.1%) and a minimum relevant difference of 3 days in the surviving participants, we carried 1,000 simulations from a trial including 1,610 participants.



sa	Statistical analysis
Mixed effects linear regression	35.6 (32.63;38.57) %
Kryger Jensen Lange test	99.8 (99.52;100.08) %
Fixed-effect linear regression	35.7 (32.73;38.67) %
Wilcoxon rank sum test	100 (100;100) %
Van Elteren test	100 (100;100) %

Now we investigate the type-1 error:



sa	Statistical analysis
Mixed effects linear regression	5 (3.65;6.35) %
Kryger Jensen Lange test	5 (3.65;6.35) %
Fixed-effect linear regression	5.2 (3.82;6.58) %
Wilcoxon rank sum test	5.4 (4;6.8) %

sa	Statistical analysis
Van Elteren test	5.6 (4.17;7.03) %

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