

Cerebral near-infrared spectroscopy monitoring versus treatment as usual for extremely preterm infants. A protocol for the SafeBoosC randomised clinical phase III trial

Mathias Hansen (✉ mathias.luhr.hansen@gmail.com)

Rigshospitalet <https://orcid.org/0000-0003-1957-7005>

Adelina Pellicer

Hospital Universitario La Paz

Christian Gluud

Rigshospitalet

Eugene Dempsey

University College Cork National University of Ireland

Jonathan Mintzer

Stony Brook Children's Hospital

Simon Hyttel-Sørensen

Rigshospitalet

Anne Marie Heuchan

Royal Hospital for Children Glasgow

Cornelia Hagmann

Universitäts-Kinderspital Zurich

Ebru Ergenekon

Gazi Universitesi

Gabriel Dimitriou

University General Hospital of Patras

Gerhard Pichler

Medizinische Universität Graz

Gunnar Naulaers

Katholieke Universiteit Leuven Universitaire Ziekenhuizen Leuven

Guoqiang Cheng

Children's Hospital of Fudan University

Hercilia Guimarães

Centro Hospitalar de Sao Joao EPE

Jakub Tkaczyk

Fakultni nemocnice v Motole

Karen B. Kreutzer

Universitätsklinikum Tübingen Klinik für Kinder- und Jugendmedizin

Monica Fumagalli

Ospedale Maggiore Policlinico

Olivier Claris

Hospices Civils de Lyon

Petra Lemmers

UMC Utrecht Wilhelmina Kinderziekenhuis

Siv Fredly

Oslo universitetssykehus Ullevål

Tomasz Szczapa

Uniwersytet Medyczny imienia Karola Marcinkowskiego w Poznaniu

Topun Austin

Cambridge University Hospital NHS Foundation Trust

Janus Christian Jakobsen

Rigshospitalet

Gorm Greisen

Rigshospitalet

Study protocol

Keywords: Randomized clinical trial; preterm; near infrared spectroscopy; protocol

Posted Date: November 7th, 2019

DOI: <https://doi.org/10.21203/rs.2.490/v2>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published on December 30th, 2019. See the published version at <https://doi.org/10.1186/s13063-019-3955-6>.

Abstract

Background: Cerebral oxygenation monitoring may reduce the risk of death and neurologic complications in extremely preterm infants, but no such effects have yet been demonstrated in preterm infants in sufficiently powered randomised clinical trials. The objective of the SafeBoosC-III trial is to investigate the benefits and harms of treatment based on near-infrared spectroscopy (NIRS) monitoring compared with treatment as usual for extremely preterm infants.

Methods/Design: SafeBoosC III is an investigator-initiated multinational randomised, pragmatic phase III clinical trial. Inclusion criteria will be infants born below 28 weeks postmenstrual age and parental informed consent (unless the site is using 'opt-out' or deferred consent). Exclusion criteria will be no parental informed consent (or if 'opt-out' is used, lack of record that clinical staff have explained the trial and the 'opt-out' consent process to parents and/or a record of parents' decision to opt-out in the infants clinical file); decision not to provide full life support; and no possibility to initiate cerebral NIRS oximetry within 6 hours after birth. Participants will be randomised 1:1 into either the experimental or control group. Participants in the experimental group will be monitored during the first 72 hours of life with a cerebral NIRS oximeter. Cerebral hypoxia will be treated according to an evidence-based treatment guideline. Participants in the control group will not undergo cerebral oxygenation monitoring and will receive treatment as usual. Each participant will be followed up at 36 weeks postmenstrual age. The primary outcome will be a composite of either death or severe brain injury detected on any of the serial cranial ultrasound scans that are routinely performed in these infants up to 36 weeks postmenstrual age. Severe brain injury will be assessed by a person blinded to group allocation. To detect a 22% relative risk difference between the experimental and control group, we intend to randomise a cohort of 1600 infants.

Discussion: Treatment guided by cerebral NIRS oximetry has the potential to decrease the risk of death or survival with severe brain injury in preterm infants. There is an urgent need to assess the clinical effects of NIRS monitoring among preterm neonates.

Trial registration: ClinicalTrial.gov NCT03770741 (registered 10/12-2018),
[https://clinicaltrials.gov/ct2/show/NCT03770741?](https://clinicaltrials.gov/ct2/show/NCT03770741?recrs=b&cond=cerebral+near+infrared+spectroscopy&rank=3)
[recrs=b&cond=cerebral+near+infrared+spectroscopy&rank=3](https://clinicaltrials.gov/ct2/show/NCT03770741?recrs=b&cond=cerebral+near+infrared+spectroscopy&rank=3)

Background

Every year, approximately 50,000 extremely preterm infants (<28 weeks' postmenstrual age) are born in countries where they routinely will be offered neonatal intensive care (1). Extremely preterm birth carries a high risk of death or long-term cerebral impairment. With a current mortality of about 25% and a prevalence of psychomotor impairment in approximately 20% of survivors, more than 10,000 will die each year and a further 10,000 will suffer from cerebral palsy and/or moderate-to-severe cognitive impairment (2–4).

When an infant is born extremely preterm, all organs are immature and vulnerable (5,6). This is particularly relevant for the immature brain (7). Cerebral autoregulation is limited and believed to be fragile in extremely preterm infants (4). It is hypothesized that large fluctuations in cerebral blood flow may result in cerebral haemorrhage arising from immature blood vessels. These fluctuations in systemic blood flow are common during the transition from foetal to neonatal circulation during the first days of life, thus putting the immature brain in danger (8).

Neonatal brain injury may be diagnosed by cranial ultrasound (9). The most severe injuries, including grade III or IV intraventricular haemorrhage and the non-haemorrhagic white matter injury cystic periventricular leukomalacia, entail a high probability of death or cerebral palsy (10,11). Several pre- and postnatal factors have been shown or are thought to be associated with cerebral injury, including ascending infections (12), insufficient nutrition early in life (13), insufficient blood pressure, cardiac dysfunction, and suboptimal mechanical ventilation (14–16).

Among extremely preterm infants during their first days of life, current practice standards involve multiple parallel interventions including respiratory and haemodynamic support, intravenous fluids, antibiotics, nutrition, and monitoring of physiological parameters. Despite significant advances in the management of extremely preterm infants over the last three decades, many of these interventions are used with little evidence. Furthermore, an end-organ monitor with sufficient time resolution to guide evidence-based treatment is lacking. Near-infrared spectroscopy (NIRS) has the potential to function in this manner. Cerebral NIRS provides a real-time continuous estimate of the cerebral tissue oxygenation ($rStO_2$), expressed as a percentage. The normal ranges of $rStO_2$ in preterm infants have been determined and change somewhat with gestational age and post-natal age (17).

The evidence on the utility of NIRS monitoring in extremely preterm infants during the first days of life is sparse. Only one previous randomized clinical trial has assessed the effects of cerebral monitoring – the SafeBoosC phase-II feasibility trial (18). This trial was successful in showing that NIRS monitoring reduced the burden of cerebral hypoxia to less than half compared with treatment as usual and. There were also non-significant trends towards reduced incidence of severe brain injury and reduced mortality in the NIRS group though the trial was not powered to demonstrate effects on clinical outcomes (18). The clinical interventions used in the NIRS-open group included a significant number with likely beneficial effects on blood oxygen content and transport, blood pressure, cardiac output, and cerebral blood flow (19). Despite these promising results, it is theoretically possible that NIRS monitoring may cause harm. This includes skin marks from the sensors, inappropriate modifications in cardio-respiratory support based on hypoxic values, and unnecessary infant disturbance due to manipulation of the forehead-based NIRS sensor. Furthermore, the SafeBoosC II trial showed a higher prevalence of bronchopulmonary dysplasia and retinopathy of prematurity in the experimental group. As NIRS devices and sensors are also costly and monitoring confers additional nursing tasks, it would be unfortunate to incorporate NIRS monitoring into standard practice without clear evidence of clinical benefit.

To evaluate the potential benefits and harms of NIRS monitoring, large-scale randomized clinical trials are urgently warranted. Since the intervention is complex—NIRS monitoring itself in addition to evidence-based modification of cardio-vascular support, a pragmatic design is preferable to ensure relevance for routine neonatal intensive care. International participation is additionally necessary to achieve adequate subject numbers and ideally promote generalizability of the results.

Methods

This trial will be conducted in compliance with the guidelines of the Declaration of Helsinki in its latest form, the International Conference on Harmonization Good Clinical Practice guidelines (20), and applicable national regulations and directives. No clinical site will start randomization before their eligibility has been confirmed and the protocol has been approved by the relevant ethics committee. Any amendments to the protocol will need approval by the Steering Committee and ethical review before being implemented. Written informed consent will be obtained by a qualified physician or nurse connected to the trial, prior to randomization of any participant, unless the Neonatal Intensive Care Unit (NICU) uses deferred informed consent or prior assent as consent methods (see below). These consent procedures will be approved by local ethics committees or institutional review boards.

Objective

The objective of this trial is to examine the benefits and harms of treatment based on NIRS monitoring compared with treatment as usual (standard monitoring and treatment) to reduce cerebral hypoxia during the first 72 hours of life in extremely preterm infants. The hypothesis is that the application of treatment based on NIRS monitoring will decrease a composite outcome of severe brain injury or death at 36 weeks postmenstrual age.

Roles and responsibilities for committees

SafeBoosC -III is led by a Steering Committee comprising the coordinating investigator (GG), the national coordinators, and two representatives from the Copenhagen Trial Unit (CG and JCJ). Decisions will be by a simple majority. The executive committee will be responsible for the day-to-day management and will comprise the coordinating investigator, the trial manager (MLH), co-investigators (AP, GD, JM, SHS), and the two representatives from the Copenhagen Trial Unit (CG and JCJ).

There will be one principal investigator in each department, responsible for obtaining ethical approval, organize local Good Clinical Practice Monitoring, inform clinical staff members on the web-based training and certification program, recruitment of patients, and data entry into the patientCase rReport fForms. Copenhagen Trial Unit will be responsible for randomization, development of the patientCase rReport fForms and central monitoring.

Trial design

This is an investigator-initiated multinational randomized, pragmatic phase III clinical trial with a two-parallel group design that will enrol 1,600 extremely preterm infants from 20 countries (Austria, Belgium, China, Czech Republic, Denmark, England, France, Germany, Greece, India, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Switzerland, Scotland, Spain, Turkey, USA). A list of all study sites will be available at www.safeboosc.eu before enrolment. It is an open label trial, but parts will be conducted blinded to intervention (see '*Blinding*').

The trial has been designed according to the SPIRIT guidelines (see figure 1 and appendix 1) (21).

Inclusion criteria

The inclusion criteria will be consist of infants born before 28 weeks postmenstrual age and signed parental informed consent, unless the NICU has chosen to use 'opt-out' or deferred consent as their consent method.

Exclusion criteria

The exclusion criteria will be consist of missing signed parental informed consent (or if the 'opt-out' method is used, lack of a record that the clinical staff have explained the trial and the 'opt-out' consent process to parents, and/or a record in the infant's clinical file of parents' decision to opt-out in the infant's clinical file); decision not to provide full life support; and no possibility to initiate cerebral NIRS monitoring within six hours after birth.

Participation in other trials

Participants included in the SafeBoosC-III trial can participate in any other study or intervention on the condition, that the trial does not 1) allow clinical staff access to cerebral oximetry in the control group, from inclusion in SafeBoosC III, to the end of intervention period 72 hours after birth, and/or 2) exclude a treatment that would be clearly indicated by the SafeBoosC-III evidence-based treatment guideline during the intervention period. All partners are encouraged to design ancillary studies and draw on data collected by SafeBoosC -III, if not compromising the blinding of assessors or the equipoise of the trial. Ancillary studies must seek approval by the SafeBoosC Steering Committee.

Participant discontinuation and withdrawal

The participants' parents are free to withdraw their infant's participation from the intervention or from the SafeBoosC-III trial entirely at any time, and this will not have any consequences for the infant's further

treatment. Reasons for discontinuation, if provided offered by the parents, will be documented. When possible, the parents will be asked if they will allow their child's data to be used in the analysis.

The attending clinician can withdraw the 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.

Recruitment

In this phase III trial, we have prolonged the enrolment period from three hours, as used in SafeBoosC II, to six hours after birth, although we recommend that monitoring is be started as early as possible to help decision-making when cardio-respiratory support is established. This six-hour window is similar to what is currently used for another neonatal intervention—therapeutic hypothermia for hypoxic-ischaemic encephalopathy after birth asphyxia (22). We believe this will make the trial relevant in settings where antenatal transfer to a perinatal centre is used less often, and thereby increase recruitment feasibility without compromising the effect of NIRS monitoring.

Extremely preterm infants are expected to be included at about 50 NICUs in about 20 countries. The 93 units that took part in a previous funding application for the SafeBoosC- III trial had, have rates of admission of between 15 and 90 extremely preterm infants per year. The total admissions were estimated to be 3,000 infants per year. We The trial should therefore, have a good chance of recruiting 1,600 participants within two years. Sites that expect to enroll at least 15 participants per year within the two-year recruitment period will take part. Inclusion of new NICUs after the common start date will be done ad hoc, considering expected contributions and time remaining.

Randomization

Infants will be centrally randomized to either the experimental or control group with a 1:1 allocation ratio at the Copenhagen Trial Unit using a web-based randomization application. The allocation sequence will be computer-generated with varying block sizes. It will be concealed for all investigators, as the web-based program will not release the randomisation until the patient has been included in the trial and stratified by NICU and gestational age group (lower gestational age (<26 weeks) compared to higher gestational age (≥ 26 weeks)). Twin couples will be randomized to the same group, either intervention or control. In centres, where only one or two NIRS devices are available, it may not be possible to include all infants from twin births. Thus, only one of a pair of twins may be included. The sibling enrolled will be the one born last.

Blinding

Due to the nature of the experimental intervention, it is not possible to blind the clinical staff, the infant, and the parents to study group allocation. Outcome assessment of mortality will not primarily be blinded but the mortality data will be checked by Good Clinical Practice via source data verification in all patients. The diagnosis and classification of brain injury along with the entry of these data into the patient record online Case Report Form will be conducted by an assessor blinded to study group allocation. Data entry procedures will depend on local factors and will be agreed on between the principal investigator at each NICU and the coordinating investigator. The data managers, statisticians, and those drawing conclusions will be blinded to study group treatment allocation. Details on this will be described in a report on the statistical analysis plan (23) (see 'statistical analysis plan').

Intervention

Experimental group participants will undergo cerebral NIRS monitoring applied as soon as possible after arrival in the NICU and always within six hours after delivery and receive treatment based on NIRS monitoring during the first 72 hours of life. These treatments will be based on the same evidence-based guideline as used in the SafeBoosC- II trial (see below) (24).

The control group participants will not receive any cerebral NIRS monitoring and will be monitored and treated according to local guidelines and clinical practices.

Treatment guideline based on NIRS monitoring

An evidence-based treatment guideline recommending modification of cardio-respiratory support or interventions aiming at increasing blood oxygen transport capacity, will be followed in order to maintain cerebral oxygenation above 55% (see *Appendix 2*) (24). As the SafeBoosC- II trial showed a low burden of hyperoxia unaffected by monitoring-based interventions, the SafeBoosC- III trial will not target cerebral hyperoxia and therefore the interventions for hyperoxia have been removed from this trial's treatment guidelines. The same SafeBoosC- III treatment guideline will be used in all participating centres.

Devices

All commercially available cerebral oximeters that are approved for clinical use in newborns may be used. The aim is to use several different devices to generate results of generic value. There are now seven commercially available devices that are approved for clinical use in different countries: INVOS (Medtronic, Minneapolis, MN, USA); NIRO (Hamamatsu, Hamamatsu City, Japan); Fore-Sight (CAS Medical, Branford, CT, USA); Sensmart (Nonin Medical, Plymouth, MN, USA); O3 (Masimo, Irvine, CA, USA); Egos (Enginmed, Suzhou, China); and Oxyprem 1.4 (Oxyprem, Zürich, Switzerland). The normal range of rStO₂ was determined with the INVOS adult sensor (17) and defined the rStO₂ thresholds for intervention used in the SafeBoosC- II trial. Each eligible device in SafeBoosC III will be compared with the

INVOS adult sensor in a blood lipid phantom and device-specific thresholds will be determined (25), before being used in the SafeBoosC- III trial.

Training and certification

Clinical staff will be offered a web-based training and certification program consisting of short modules covering the trial rationale; NIRS and monitoring of cerebral oxygenation; the treatment guideline; cerebral ultrasound and classification of brain injury; and Good Clinical Practice (www.safeboosc.eu). The use of these modules and the completion rate will be monitored and reported with the results of the trial. Sites with low compliance may be selected for subgroup analyses.

Trial duration

NIRS monitoring will start within six postnatal hours and the intervention will last until 72 hours of life. Each participant will be followed up at 36 weeks postmenstrual age.

Explanatory variables

To allow comparisons between intervention groups, additional baseline clinical data will be obtained, including birth weight, gestational age, mechanical ventilation, and use of cardiovascular support. Data will be drawn from clinical records at 72 hours of age, and 36 weeks postmenstrual age, the same time as the primary and exploratorysecondary outcomes are assessed and documented. The majority of these selectedchosen variables are usually reported to neonatal network databases such as the Vermont Oxford Network (26).

Outcomes

Primary and exploratory outcomes will be assessed at 36 weeks postmenstrual age as documented in the infants' clinical files. If the infant in question has been discharged to a step-down unit, data will be sought from that unit, and if this is not possible, data will be used until the date of discharge to the step-down unit. In case in which the last entry in an infant's clinical file is prior to 36+0 weeks postmenstrual age, for example due to discharge home, the date of discharge will be reported in the online patient Case rReport fForm.

The primary outcome is a composite of either death or severe brain injury detected on any one of a series of cranial ultrasound scans that are routinely performed in extremely premature infants. Severe brain injury is defined as grade III or IV intraventricular haemorrhage (IVH), cystic periventricular leukomalacia (cPVL), cerebellar haemorrhage, post-haemorrhagic ventricular dilatation, or cerebral atrophy. The exploratory outcomes will be bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP) stage 3+, necrotiz

sing enterocolitis (NEC) stage 2 or higher using the modified Bell's staging system and/or focal intestinal perforation, and late-onset sepsis (>72 hours after birth) defined as being treated with antibiotics for a minimum of five days, and a count of the presence of three major neonatal morbidities (BPD, ROP and severe brain injury). All diagnoses, except severe brain injury, are made as per routine in each NICU.

Statistical plan and data analysis

Full details regarding statistical considerations and detailed statistical plan and data analysis will be outlined in a separate report (23), which will be published before the analysis phase begins, without knowledge of any data collected.

Sample size

We have calculated our sample size based on the composite primary outcome, with an alpha of 5%, a power of 90%, and a ratio of experimental trial participants to control trial participants of 1:1.

In the 2009 EuroNeoNet report, the mortality among extremely preterm infants was 33% and severe intracranial haemorrhage was observed in 15%. In the SafeBoosC-II trial, the proportion of participants with the composite primary outcome was approximately 34% in the control group and 26% in the experimental group (27).

Based on the above, a total of 1600 infants would be required to demonstrate a similar relative risk reduction of 22%, with an alpha of 5%, and a power of 90%.

In SafeBoosC II, the intra-class correlation coefficient (ICC) of the burden of hypoxia within pairs of twins was negligible. The ICC for death before discharge and for intraventricular haemorrhage grade 3 or 4 have previously been estimated to 0.00 (95% confidence interval (CI) -0.04 to 0.02) and -0.01 (95% CI -0.05 to 0.01) (28). These values correlate to a design effect very close to one (28). Based on this, we have not included twin ICC in the sample size estimation.

Analysis of the primary outcome

The primary outcome analysis will be made on the intention-to-treat population, and we will use mixed-effect logistic regression. 'Site' will be included as a random effect (intercept) and the remaining stratification variables, age and intervention groups, will be included as fixed effects. In addition, we will perform a range of pre-defined sensitivity analyses to inform the interpretation of the results of the primary analysis (23)

Safety

Predefined serious adverse reactions (SAR) will be reported at 72-hours after birth and serious adverse events (SAE) will be reported at 36 weeks' postmenstrual age. Expedited reporting will not be used. An independent data monitoring and safety committee is established to monitor mortality, neonatal morbidity, and SARs with 'certain' or 'probably/likely' relationships with the cerebral NIRS oximeter and/or the application of the evidence-based treatment guideline or any of its interventions. They include two neonatologists and a biostatistician. The charter for the data monitoring and safety committee will be written prior to the enrolment of trial participants. The trial will not be stopped early because of futility, and Lan-DeMets sequential monitoring boundaries will be used at each interim analysis to assess if thresholds for statistical significance of benefits or harms have been crossed (29). Only one interim analysis is planned, after one-third of trial participants have been randomised. Additional analyses will be decided by the data monitoring and safety committee members (23). Based on primarily safety considerations, the data monitoring and safety committee will make recommendations to the steering group to continue, change, hold, or terminate the trial. The recommendations will be guided by the statistical monitoring guidelines, which is defined in the data monitoring and safety committee charter (available from www.safeboosc.eu).

The preterm population is at high risk for serious adverse events and most adverse events may be of a serious nature with or without relevance to the SafeBoosC-III trial interventions. Both groups of the trial are expected to have a high proportion of serious adverse events. It is therefore neither feasible, nor meaningful, to record and report all adverse events. Therefore, we have decided only to record and report predefined SAEs and SARs. The SAEs include any event of death, severe brain injury, necrotizing enterocolitis, bronchopulmonary dysplasia, retinopathy of prematurity, or sepsis as defined under primary and exploratory outcomes. These predefined SAEs have been chosen since they cover the major neonatal morbidities seen in this study population. The SARs are defined as any adverse reaction related to the trial intervention that results in death, is life-threatening, requires prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or requires intervention to prevent permanent impairment or damage. This includes physical mishaps associated with managing the oximeter and sensors, such as severe skin damage, critical displacement of endotracheal tubes or endovascular lines, and clinical mismanagement based on cerebral oximetry monitoring data, such as interventions aiming at improving cardiovascular status, respiratory status and/or oxygen transport.

Data management

All participants' data are protected in accordance with the Danish Act on the processing of personal data and the Danish Health Act. The Copenhagen Trial Unit will provide central, web-based data entry through an online patient Case Report Form, in the open open-source clinical trials software OpenClinica[®]. This will handle the inclusion procedure, the documentation of the stratification and randomization process, the severe adverse reactions, and the relevant clinical data from enrolled subjects, including primary and exploratory secondary outcomes and explanatory variables. The data will be entered into the online patient Case Report Form directly by the medical staff. FA forms for randomization/inclusion, end-of-

monitoring at 72 hours of age, and the 36 weeks follow-up will be created. Data will be stored in accordance with guidelines issued by the Danish Data Protection Agency, with whom approval of the trial will be sought. Only NICU numbers and study numbers will be used to identify participants (i.e. the data kept at Copenhagen Trial Unit is pseudo-anonymized), while lists of study numbers and personal identifying information (e.g. to allow Good Clinical Practice, data cleansing, and later follow-up) will be kept at the NICUs. Six months after the acceptance of the publication that presents the primary outcome, the dataset will be transferred to the Danish data archive. Before transfer, subject study numbers will be removed, NICU numbers will be replaced, sex/gender documentation removed, and birth weight and gestational age recoded into binary variables to minimize the risk of re-identification. 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. Trial data will be handled according to regulations of data protection agencies in the respective countries.

Monitoring

Internal monitoring will be conducted by the Copenhagen Trial Unit, who will monitor 1) patient recruitment, and 2) quality, completeness, and timeliness of data entry. In case of problems, the principal investigator will be contacted.

External monitoring will be conducted by a Good Clinical Practice person assigned by the principal investigator at each site. The Good Clinical Practice person will perform monitoring according to the monitoring plan, which will be developed and available at www.safeboosc.eu before inclusion of trial participants.

Ethical considerations

To obtain evidence-based knowledge on the potential benefit and harms of NIRS-based cerebral monitoring in the clinical management of premature infants, a large-scale randomized clinical trial is required. The SafeBoosC-II trial served as a feasibility trial for the present large-scale SafeBoosC-III trial.

In most NICUs, there is still clinical equipoise regarding the use of NIRS monitoring, meaning there is genuine uncertainty over whether cerebral oximetry monitoring and subsequent monitoring-based treatments are clinically beneficial or harmful. Nevertheless, some NICUs have started to use cerebral oxygenation monitoring as part of routine clinical management. Thus, there might be a limited time-window for this trial, since it may be more difficult to test an intervention that is already in clinical use (30). Therefore, we aim at a pragmatic trial, rather than doing a proof-of-concept trial first.

Extremely preterm infants demonstrate stress reactions during routine manipulation. Positioning and repositioning of cerebral NIRS sensors can result in such reactions. There are, however, no data to support

substantially more risk or discomfort as compared with no intervention or compared with current routine care. All interventions proposed in the evidence-based treatment guideline are commonly used in this patient group (21).

'Treatment as usual' defined as treatment according to participating hospital's standard procedures, will be provided to the control group. Also, this will be the care provided to any participant that withdraws consent, in addition to infants who are not included in the trial. Multiple births will be randomised together and undergo allocation to the same study group. This is to avoid parents ascribing differences in their infants' clinical courses and outcomes based on group allocation resulting from participation in this trial.

Publication plan

The trial protocol is registered at clinicaltrials.gov (NCT03770741) and all versions are available at www.safeboosc.eu. Following trial completion, summary trial data will additionally be entered at www.clinicaltrials.gov. Further summary data of main outcomes will be entered after statistical analyses are conducted. Attempts will be made to publish all results, positive, neutral, as well as negative, in a peer-reviewed international journals. Authorship will be determined according to the International Committee of Medical Journal Editors. An additional requirement is one author per NICU completing at least 30 participants. Ancillary studies with results potentially affecting equipoise regard to the value of NIRS, shall not be published before the main publication of the SafeBoosC-III trial. After the publication of trial results, depersonalised individual patient data will be uploaded at Zenodo.

Discussion

In this pragmatic trial, we plan to test the hypothesis, that the application of treatment based on cerebral NIRS monitoring in extremely preterm infants will decrease a composite outcome of either death or survival with severe brain injury at 36 weeks postmenstrual age.

A Cochrane systematic review concluded that it is not possible, based on the currently available literature, to determine the specific benefits or harms of NIRS monitoring in extremely preterm infants (27). The conclusion of this review was that NIRS monitoring should only be used in randomized clinical trials (31). Despite this, NIRS is routinely used in extremely preterm infants during the first days of life in numerous NICUs in multiple countries (32). It is likely that this monitoring approach will become more common as evidence in other patient groups becomes more convincing (33). Therefore, to prevent a non-evidence-based, large-scale clinical uptake of NIRS monitoring, a robust randomized clinical trial, such as the SafeBoosC-III trial, is urgently required.

As described in the '*Blinding*' section, it is not possible to blind the clinical staff, the infant, and the parents of participants in this trial. This circumstance introduces risks of bias. Several previous studies have shown, that inadequate blinding of participants, personnel, and outcome assessors in randomized

trials often result in overestimation of treatment effects for a given intervention for all outcome types, including mortality and subjective outcomes such as radiologic image interpretation (34–37). A meta-epidemiologic study showed a high variability of treatment effect measured on unblinded subjective outcomes, indicating that for trials including subjective outcomes, the magnitude of bias due to lack of blinding is unpredictable (34). But again, non-blinded trials compared to similar blinded trials again showed overestimation of intervention effects (30). This meta-epidemiologic study included randomised trials across all clinical fields. A meta-analysis, including 361 intensive- care randomised trials, evaluated the effect of adequate blinding on effect estimates of mortality and found no statistically significant difference between blinded and unblinded trials, suggesting that there may be little, if any, effect of adequate blinding on mortality effect estimates in intensive- care trials (38). No meta-epidemiologic studies, meta-analysis, or systematic reviews have evaluated the effect of adequate/inadequate blinding on intervention effects in neonatal randomised trials. In conclusion, previous results suggest there is a risk of biased results due to lack of blinding even on mortality results. The design of the SafeBoosC III trial strives to minimize the risks regarding the primary outcome.

The pragmatic methodology of this trial also has some limitations. Cranial ultrasound-based diagnoses will be performed locally rather than centrally as was done in SafeBoosC II (18). This may potentially raise concerns in SafeBoosC III since discrepancies between local readers in different centres could be expected. However, when comparing local and central interpretations of cranial ultrasound images in preterm infants in previous clinical trials, the sensitivity and specificity for local interpretations of severe brain injury were quite robust (39). Furthermore, we have developed a web-based training program for staff members caring for trial participants. Among other topics, this web program includes a cranial ultrasound module for the purpose of decreasing interobserver variability and heightening data quality.

As in all trial populations of extremely preterm infants, a large number of participants will be twins, which can cause statistical concerns arising from intra-class correlation coefficients (ICC) (28). We cannot with certainty estimate the ICC for the composite outcome of death or severe brain injury for this present trial. However, the ICC of the burden of hypoxia within pairs of twins in SafeBoosC II was negligible (ICC = 0.027) (27). Additionally, the twin ICC for pre-discharge death and grade III or IV intraventricular haemorrhage have been estimated in a previous study to 0.00 and –0.01 respectively, which correlates to a negligible design effect (28). The details of how the twin issue will be statistically accounted for will be outlined in the later publication of the SafeBoosC. III statistical and data analysis plan (23).

The interventions in this trial are complex and rely on a number of separate but interacting components, all relevant for the potential success of the intervention. When NIRS monitors show hypoxic values, neonatologists must evaluate the participant's clinical status by taking additional measures into consideration and deciding on a possible modification of cardio-respiratory support and interventions to increase blood oxygen transport capacity, based on the treatment guideline. This complexity will result in difficulty interpreting specific results, as it cannot be ascertained what exactly causes a potential effect at

36 weeks postmenstrual age. Furthermore, reproducing and generalizing complex interventions may be difficult for future clinicians assessing the results of this trial (40). However, since this is a pragmatic effectiveness trial evaluating outcomes related to NIRS-based cerebral oxygenation monitoring in routine practice, and not the specific treatment choices per se, this concern will not affect the purpose of the trial. The Medical Research Council Framework has developed CONSORT guidelines, in order to help trialists develop clearly defined and reproducible complex interventions (41,42). We believe that the methodology in the SafeBoosC- III trial is in agreement with these guidelines, which is a major strength of this trial.

Obtaining prior informed consent from parents of critically ill neonates within the first hours following birth is difficult and may challenge important standards of information delivery, comprehension, competence, and voluntariness (43–45), and can also restrict the population studied with the effect of impairing the generalisability of results. Furthermore, since monitoring of cerebral oxygenation has been used clinically for several years in other patient groups, and now has entered neonatology to a significant degree, the SafeBoosC- III trial can be considered comparative effectiveness research rather than a test of an experimental intervention (46). Therefore, the protocol allows and encourages principal investigators at each NICU to consider and potentially to seek approval from research ethics boards for one of two other consent forms, i.e. deferred informed consent (43) and prior informed assent (opt-out with enrolment as default) (47). We believe this offers appropriate flexibility in an international trial in an area where legitimate ethical considerations are in conflict. For the purpose, we have developed parental information sheets specific for each consent method (see appendix 3)

Though extremely preterm infants constitute only 0.5% of all births (1), they represent an extremely high-risk population, and thus their contribution to infant mortality and to the prevalence of cerebral palsy exceeds 10% (48–50). There is accumulating evidence, that cerebral hypoxia is a significant cause of mortality as well as brain injury in this population. Thus, monitoring of cerebral oxygenation levels during the first days after birth has the potential to address a significant health problem. Although the overall risk in this population is high, there are many other relevant contributing factors to mortality and brain injury, and thus only a moderate risk reduction can be expected. Therefore, a trial to address this therapeutic question must be large in scope. If the experimental intervention proves successful, we may save 2,000 extremely preterm infants or more every year from death or a life with handicap due to brain injury in high-income countries. The ensuing health economics impact may thus be quite robust.

In conclusion, there is an urgent need for a randomized clinical trial to assess the effects of cerebral NIRS monitoring compared with treatment as usual in extremely preterm infants.

Trial status

Protocol The protocol is registered at www.clinicaltrials.gov NCT03770741 (registered 10/12–2018). The first infant was enrolled in June–2019 and Anticipated date of enrolment of the first participant is 30

April 2019 and anticipated date of study completion is Oct 30 July 2021. Recruitment status can be accessed at www.safeboosc.eu, when enrolment has begun.

Declarations

Ethics approval and consent for participation

By 3101-OctoberFebruary–2019, the study has been approved in 51 NICUs from Austria, China, Czech Republic, Denmark, Greece, Ireland, Italy, Norway, Poland, Portugal, Spain, Switzerland and Turkey.by Etik Kurul, Gazi Üniversitesi Tıp Fakültesi Dekanlığı. National coordinators from additional participating countries have started the ethics approval application processes.. No sites will start randomising participants before ethics approval have been granted. Status on ethical approval for all participating sites can be found at www.safeboosc.eu.

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests.

Funding

The sponsor/coordinating investigator, pProfessor of nNeonatology Gorm Greisen, is the initiator of the SafeBoosC-III project. He has no financial interest in the results of the trial, nor in the NIRS-devices. The Elsass Foundation and Svend Andersen Foundation supported this work through an unconditional and unrestricted grant of DKK 2,700,000 and DKK 1,000,000. Theseis funding sources had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results. We seek additional local and central funding, including funding from industry sponsors., Ssuch sources will not get any influence on the methodology, data, analysis, reporting, or conclusions of the trial. Furthermore, any participating department 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.

Author’s contributions

MLH, GG, SHS, JCJ, and CG contributed to the conception and design of the protocol, drafted the main protocol, drafted the manuscript, and will give final approval of the version to be published. AP and ED contributed to the conception and design of the protocol, drafted the main protocol, revised the manuscript critically for important intellectual content, and will give final approval of the version to be published. JM, AMH, CH, EE, GD, GP, GN, GC, HG, JT, KBK, MF, OC, PL, SF, TS, and TA contributed to the conception and design of the protocol, revised the main protocol critically for important intellectual content, revised the manuscript critically for important intellectual content, and will give final approval of the version to be published.

Acknowledgements

We would like to thank the Elsass Foundation and Sven Andersen Foundation for making the conduct of the SafeBoosC III trial possible, by covering central trial unit costs including trial coordination and data management. We would also like to thank Marie Isabel Rasmuseen for English language revision of the manuscript. Not applicable

List Of Abbreviations

BPD	Bronchopulmonary dysplasia
cPVL	Cystic periventricular leukolamacia
ICC	Intra-class correlation coefficients
IVH	Intraventricular haemorrhage
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
NIRS	Near-infrared spectroscopy
ROP	Retinopathy of prematurity
SAE	Severe adverse events
SAR	Severe adverse reactions

References

1. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller A-B, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012; 379:2162–72.
2. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, et al. Neonatal Outcomes of Extremely Preterm Infants From the NICHD Neonatal Research Network. Pediatrics 2010; 126:443–56.

3. Adams-Chapman I, Heyne RJ, DeMauro SB, Duncan AF, Hintz SR, Pappas A, et al. Neurodevelopmental Impairment Among Extremely Preterm Infants in the Neonatal Research Network. *Pediatrics* 2018; 141:e20173091.
4. Volpe JJ. Brain injury in the premature infant: neuropathology, clinical aspects and pathogenesis. *Semin Pediatr Neurol* 1998; 5:135–51.
5. Ward RM, Beachy JC. Neonatal complications following preterm birth. *BJOG An Int J Obstet Gynaecol* 2003; 110:8–16.
6. Behrman R, Butler AS. Preterm birth: Causes, Consequences and Prevention. Institute of Medicine. Washington, D.C.: National Academies Press; 2007.
7. Stephens BE, Vohr BR. Neurodevelopmental Outcome of the Premature Infant. *Pediatr Clin North Am* 2009; 56:631–46.
8. Kluckow M. Low systemic blood flow and pathophysiology of the preterm transitional circulation. *Early Hum Dev* 2005; 81:429–37.
9. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with birth weights less than 1,500 gm. *J Pediatr* 1978; 92:529–34.
10. Guzzetta F, Shackelford GD, Volpe S, Perlman JM, Volpe JJ. Periventricular intraparenchymal echodensities in the premature newborn: critical determinant of neurologic outcome. *Pediatrics* 1986; 78:995–1006.
11. Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. *Lancet Neurol* 2009; 8:110–24.
12. Cordeiro CN, Tsimis M, Burd I. Infections and Brain Development. *Obstet Gynecol Surv* 2015; 70:644–55.
13. Prado EL, Dewey KG. Nutrition and brain development in early life. *Nutr Rev* 2014; 72:267–84.
14. Perlman JM. White matter injury in the preterm infant: An important determination of abnormal neurodevelopment outcome. *Early Hum Dev* 1998; 53:99–120.
15. Greisen G, Vannucci RC. Is periventricular leucomalacia a result of hypoxic-ischaemic injury? Hypocapnia and the preterm brain. *Biol Neonate* 2001; 79:194–200.
16. Perlman M, Volpe J. Are Venous Circulatory Abnormalities Important in the Pathogenesis of Hemorrhagic and / or Ischemic Cerebral Injury ? *Pediatrics* 1987; 80:705–11.
17. Alderliesten T, Dix L, Baerts W, Caicedo A, van Huffel S, Naulaers G, et al. Reference values of regional cerebral oxygen saturation during the first 3 days of life in preterm neonates. *Pediatr Res* 2016; 79:55–64.
18. Hyttel-Sorensen S, Austin T, van Bel F, Benders M, Claris O, Dempsey E, et al. A phase II randomized clinical trial on cerebral near-infrared spectroscopy plus a treatment guideline versus treatment as usual for extremely preterm infants during the first three days of life (SafeBoosC): study protocol for a randomized controlled trial. *Trials* 2013; 14:120.

19. Riera J, Hyttel-Sorensen S, Bravo MC, Cabañas F, López-Ortego P, Sanchez L, et al. The SafeBoosC phase II clinical trial: an analysis of the interventions related with the oximeter readings. *Arch Dis Child - Fetal Neonatal Ed* 2016; 101:F333–8.
20. Guideline on Good Clinical Practice E6(R2). European Medicines Agency, Committee for Human Medicinal Products. 2017.
21. Chan A-W, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013; 346:e7586–e7586.
22. Davidson JO, Wassink G, van den Heuvel LG, Bennet L, Gunn AJ. Therapeutic Hypothermia for Neonatal Hypoxic–Ischemic Encephalopathy—Where to from Here? *Front Neurol* 2015; 6:198.
23. Hansen ML, Pellicer A, Gluud C, Dempsey E, Mintzer J, Hyttel-Sorensen S, et al. Detailed statistical analysis plan for the SafeBoosC III trial: a multinational randomised clinical trial assessing treatment guided by cerebral oxygenation monitoring versus treatment as usual in extremely preterm infants. *Trials*.
24. Pellicer A, Greisen G, Benders M, Claris O, Dempsey E, Fumagalli M, et al. The SafeBoosC Phase II Randomised Clinical Trial: A Treatment Guideline for Targeted Near-Infrared-Derived Cerebral Tissue Oxygenation versus Standard Treatment in Extremely Preterm Infants. *Neonatology* 2013; 104:171–8.
25. Kleiser S, Ostojic D, Andresen B, Nasseri N, Isler H, Scholkmann F, et al. Comparison of tissue oximeters on a liquid phantom with adjustable optical properties: an extension. *Biomed Opt Express* 2018; 9:86.
26. Vermont Oxford Network. Manual of Operations: Part 2 Data Definitions & Infant Data Forms. In 2018.
27. Hyttel-Sørensen S, Pellicer A, Alderliesten T, Austin T, Van Bel F, Benders M, et al. Cerebral near infrared spectroscopy oximetry in extremely preterm infants: phase II randomised clinical trial. *BMJ* 2015; 350:1–11.
28. Yelland LN, Sullivan TR, Collins CT, Price DJ, McPhee AJ, Lee KJ. Accounting for twin births in sample size calculations for randomised trials. *Paediatr Perinat Epidemiol* 2018; 32:380–7.
29. Jakobsen JC, Gluud C, Winkel P, Lange T, Wetterslev J. The thresholds for statistical and clinical significance—a five-step procedure for evaluation of intervention effects in randomised clinical trials. *BMC Med Res Methodol* 2014; 14:34.
30. Greisen G, van Bel F. Equipoise is necessary for randomising patients to clinical trials. *Acta Paediatr Int J Paediatr* 2016; 105:1259–60.
31. Hyttel-Sørensen S, Greisen G, Als-Nielsen B, Gluud C. Cerebral near-infrared spectroscopy monitoring for prevention of brain injury in very preterm infants. *Cochrane Database Syst Rev* 2017:1–25.
32. Hunter CL, Oei JL, Suzuki K, Lui K, Schindler T. Patterns of use of near-infrared spectroscopy in neonatal intensive care units: international usage survey. *Acta Paediatr* 2018; 107:1198–204.
33. Bevan PJW. Should Cerebral Near-infrared Spectroscopy be Standard of Care in Adult Cardiac Surgery? *Hear Lung Circ* 2015; 24:544–50.

34. Savović J, Turner RM, Mawdsley D, Jones HE, Beynon R, Higgins JPT, et al. Association Between Risk-of-Bias Assessments and Results of Randomized Trials in Cochrane Reviews: The ROBES Meta-Epidemiologic Study. *Am J Epidemiol* 2018; 187:1113–22.
35. Hróbjartsson A, Thomsen ASS, Emanuelsson F, Tendal B, Hilden J, Boutron I, et al. Observer bias in randomized clinical trials with measurement scale outcomes: a systematic review of trials with both blinded and nonblinded assessors. *Can Med Assoc J* 2013; 185:E201–11.
36. Hróbjartsson A, Thomsen ASS, Emanuelsson F, Tendal B, Rasmussen JV, Hilden J, et al. Observer bias in randomized clinical trials with time-to-event outcomes: systematic review of trials with both blinded and non-blinded outcome assessors. *Int J Epidemiol* 2014; 43:937–48.
37. Hróbjartsson A, Emanuelsson F, Skou Thomsen AS, Hilden J, Brorson S. Bias due to lack of patient blinding in clinical trials. A systematic review of trials randomizing patients to blind and nonblind sub-studies. *Int J Epidemiol* 2014; 43:1272–83.
38. Anthon CT, Granholm A, Perner A, Laake JH, Møller MH. No firm evidence that lack of blinding affects estimates of mortality in randomized clinical trials of intensive care interventions: a systematic review and meta-analysis. *J Clin Epidemiol* 2018; 100:71–81.
39. Hintz SR, Slovis T, Bulas D, Meurs KP Van. Interobserver reliability and accuracy of cranial ultrasound interpretation in premature infants. *J Pediatr* 2007; 150:592–6.
40. Campbell M. Framework for design and evaluation of complex interventions to improve health. *BMJ* 2000; 321:694–6.
41. Zwarenstein M, Treweek S, Gagnier JJ, Altman DG, Tunis S, Haynes B, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ* 2008; 337:a2390–a2390.
42. Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. *Ann Intern Med* 2017; 167:40.
43. Brierley J, Larcher V. Emergency research in children: options for ethical recruitment. *J Med Ethics* 2011; 37:429–32.
44. Beauchamp TL, Childress JF, Press. OU. Principles of biomedical ethics. 7th ed. Oxford: Oxford University Press; 2012.
45. Mason SA, Allmark PJ. Obtaining informed consent to neonatal randomised controlled trials: interviews with parents and clinicians in the Euricon study. *Lancet* 2000; 356:2045–51.
46. Gale C, Juszczak E. A paediatrician's guide to clinical trials units. *Arch Dis Child - Educ Pract Ed* 2016; 101:265–7.
47. Gale C, Hyde MJ, Modi N. Research ethics committee decision-making in relation to an efficient neonatal trial. *Arch Dis Child - Fetal Neonatal Ed* 2017; 102:F291–8.
48. Hafström M, Källén K, Serenius F, Maršál K, Rehn E, Drake H, et al. Cerebral Palsy in Extremely Preterm Infants. *Pediatrics* 2018; 141:e20171433.

49. Roberts G, Anderson PJ, De Luca C, Doyle LW. Changes in neurodevelopmental outcome at age eight in geographic cohorts of children born at 22–27 weeks' gestational age during the 1990s. Arch Dis Child - Fetal Neonatal Ed 2010; 95:F90–4.
50. Stanley F, Blair E, Alberman E. Cerebral palsies: epidemiology and casual pathways. In Cambridge: Cambridge University Press; 2000. p. 251.

Figures

Visit description	consent and randomisation	Intervention period: first 72 hours of life (Cerebral monitoring and treatment according to guideline versus 'treatment as usual')	Follow-up: two possible time points up to week 36+0 postmenstrual age	
Visit code	V0	V1	V2	
Time period	0-6 hours	0-72 hours	Discharge to home	36±1 weeks postmenstrual age
Assessing inclusion and exclusion criteria	X			
Informed consent (can be obtained before birth) *	X			
Allocation to experimental or control group	X			
SARs		X		
SAEs		X	X	
Explanatory variables		X	X	
Exploratory outcomes (NEC, ROP, BPD, Sepsis)			X	X
Severe brain injury (IVH grade III/IV, cPVL, post-haemorrhagic ventricular dilatation, cerebellar haemorrhage, cerebral atrophy)			X	X
All-cause mortality			X	X

Figure 1

Schedule for enrolment, intervention and assessment, based on the SPIRIT 2013 guidance for protocols of clinical trials. *if approved by local ethics committee, deferred informed consent or prior informed assent may be sought. Time to ask parents for deferred consent will be decided individually by clinical staff members.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Appendix1Spiritchecklist.doc](#)
- [Appendix2treatmentguideline.docx](#)