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Treatment guided by cerebral oximetry in mechanically ventilated newborns: a statistical analysis plan for step one of the SafeBoosC-IIIv randomised clinical trial

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Abstract

Background Newborns requiring invasive mechanical ventilation are at high risk of neurodevelopmental impairment, prolonged hospitalisation, and increased mortality. Treatment guided by cerebral oximetry monitoring has been proposed to reduce morbidity and mortality.

Methods The SafeBoosC-IIIv trial is a multicentre, parallel-group, randomised clinical trial. The trial will be conducted in two steps. This is a statistical analysis plan for step one. The objective of step one is to assess whether treatment guided by cerebral oximetry monitoring, compared with usual care, increases the number of hospital-free days in newborns receiving invasive mechanical ventilation. Inclusion criteria are gestational age ≥ 28 + 0 weeks, postnatal age less than 28 days, expected to receive invasive mechanical ventilation (intubation) for at least 24 h, and a cerebral oximeter available so monitoring can be started within 6 h after initiation of invasive mechanical ventilation. Exclusion criteria are suspicion of or confirmed brain injury or congenital heart malformation likely to require surgery. A total of 1610 participants will be randomised 1:1 to treatment guided by cerebral oximetry monitoring or usual care. The primary outcome will be hospital-free days within 90 days of randomisation, which will be analysed with the van Elteren test stratified by 'centre'. This statistical analysis plan provides a detailed description of the planned analyses, including methods for handling missing data and assessing statistical assumptions. Analyses will follow the intention-to-treat principle and will be performed independently by two statisticians.

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Conclusion This statistical analysis plan describes the planned statistical analyses in detail for step one of the SafeBoosC-IIIv trial.

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Keywords Randomised clinical trial, Statistics, Neonatology, Cerebral oximetry monitoring, Mechanical ventilation

Background

Newborns requiring invasive mechanical ventilation are a high-risk population, not only due to their underlying conditions but also because of complications associated with the ventilation itself [1, 2]. Determining the optimal treatment to address the underlying condition while minimising complications, reducing the risk of neurodevelopmental impairment and hospitalisation, and lowering mortality is complex.

Treatment guided by cerebral oximetry monitoring has been proposed for newborns in the intensive care unit [3]. Cerebral oximetry may alert clinicians to low blood flow and potential organ ischaemia, allowing adjustments of interventions [3]. In theory, treatment guided by cerebral oximetry monitoring could improve the treatment of mechanically ventilated newborns, thus minimising the risk of organ damage and complications, and reducing admissions to hospital [3].

The SafeBoosC-IIIv trial is a multicentre, parallel-group, randomised clinical trial to study the effects of treatment guided by cerebral oximetry monitoring compared to usual care. The SafeBoosC-IIIv trial builds on the existing SafeBoosC consortium and draws on experience from the previous SafeBoosC-II and SafeBoosC-III trials [4, 5]. SafeBoosC-IIIv will be conducted in two steps. In step one, we aim to assess whether treatment guided by cerebral oximetry monitoring will increase the number of hospital-free days within 90 days of randomisation. In step two, we aim to assess whether treatment guided by cerebral oximetry monitoring 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 2 years of corrected age. Step one will include 1610 newborns with a follow-up of 90 days. Step two will include 3000 newborns with a follow-up of 2 years. Currently, funding has been obtained for step one.

This statistical analysis plan (version 1.0) will outline the statistical analyses for step one of the SafeBoosC-IIIv trial in detail.

Methods

The SafeBoosC-IIIv trial design has previously been described in detail in a published protocol [6]. This statistical analysis plan is reported in accordance with Guidelines for the Content of Statistical Analysis Plans in Clinical Trials [7]. All current and previous protocol versions, standard operating procedures, data monitoring plans, and additional trial data can be found at safeboosc.eu. In brief, the trial population will be newborns with a gestational age ≥ 28 weeks and postnatal age < 28 days undergoing invasive mechanical ventilation. Newborns will be eligible for enrolment if they meet the following eligibility criteria:

Inclusion criteria

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

Exclusion criteria

- Suspicion of or confirmed brain injury or disorder (e.g. severe hypoxic-ischaemic encephalopathy, intraventricular haemorrhage grade 3 or 4, cerebral malformation, genetic or metabolic disease)
- Suspicion or diagnosis of congenital heart malformations likely to require surgery

Randomisation and blinding

Participants will be randomised through central web-based randomisation at the Copenhagen Trial Unit. The ratio of allocation will be 1:1 with varying block sizes, and the randomisation will be stratified by centre, gestational age (≤ 34 weeks or > 34 weeks), and whether invasive mechanical ventilation was initiated due to surgery (yes or no).

A screening log will be kept in the electronic case report file (eCRF). The screening log will contain data

on subject number, date of screening, stratification variables, randomised (yes or no), and reason not randomised, if relevant.

Due to the experimental intervention's nature, clinical staff and parents will not be blinded to group allocation, but a blinded investigator will assess the primary outcome. Data will be collected from clinical records, and parents will be contacted (e.g. by phone or email). 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 trial manager.

The trial manager, sponsor, statisticians, and writers of the initial abstracts will be blinded (see the 'Statistical reports' section). Furthermore, survival status and hospital-free days will be source data verified for all participants 90 days after randomisation during local monitoring visits. Two blinded statisticians at Copenhagen Trial Unit will independently perform all statistical analyses using different statistical software programs (R and STATA). Both reports and the third fused final report will be presented to the Steering Committee, and all three reports will be published as supplemental material. The Steering Committee will discuss discrepancies between the two reports.

Trial intervention

Participants in the experimental group will receive treatment guided by monitoring with cerebral oximetry, if possible, before or as soon as possible and within 6 h after initiation of invasive mechanical ventilation. Treatment guided by cerebral oximetry will be continued until one of four stop criteria: (1) the cardiopulmonary function has been stabilised as indicated by the need for respiratory and circulatory support and evaluated by the responsible physician, (2) extubation, (3) 28 days after birth, or (4) 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 as suggested in the SafeBoosC treatment guideline and monitoring as usual [8].

The control group will receive usual care, i.e. invasive mechanical ventilation without access to cerebral oximetry.

Outcomes

The outcomes were defined as primary, secondary, and exploratory [6]. The sample size was based on the primary outcome, and our primary conclusions will be based on the results of the primary outcome.

Primary outcome

- Hospital-free days within 90 days of randomisation.

Hospital-free days are defined as the number of days during which the infant is neither admitted, under hospital observation, nor attending hospital appointments, measured from the date of randomisation up to 90 days thereafter. If the infant dies at any time within 90 days of randomisation, the number of hospital-free days will be analysed as 0, even if they were discharged and had hospital-free days before death.

Secondary outcomes

- One or more serious adverse events within 90 days of randomisation (Supplementary materials), i.e. one or more of the following:
  - Death from any cause
  - Bronchopulmonary dysplasia
  - Any brain injury diagnosed by imaging
  - Seizures treated with antiepileptic medicine
  - Haemodynamic insufficiency that needs cardiovascular support
  - Spontaneous bowel perforation or necrotising enterocolitis Bell's grade 2 or more
  - Nosocomial infection
  - Extracorporal membrane oxygenation
  - Renal replacement therapy
- Invasive mechanical ventilation-free days within 90 days of randomisation.

Exploratory outcomes

- Late-onset sepsis within 90 days of randomisation.
- Invasive mechanical ventilation-related infection within 90 days of randomisation.

Sample size and power estimations

Simulations were performed showing that to test a relative risk reduction of death of 5% (from an estimated mortality of 10.1%) 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 [9], we would need to include 1610 participants (Supplementary Materials).

Based on data from Statistics Denmark and from Rigshospitalet [10, 11], 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 groups 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 1610 participants.

General analysis principles

All analyses will be conducted according to the intention-to-treat principle (ITT), i.e. all randomised participants with available data will be included in all analyses.

We will assess whether the statistical and clinical significance thresholds are crossed (Bayes factor calculations will be reported in supplementary material) [12]. Our primary conclusion will be based on the primary outcome, so all tests of statistical significance (including subgroup analyses) will be two-sided with a threshold of 5% [12]. *P* values will only be reported for the primary outcome.

It is generally acknowledged that regression analyses ought to be adjusted for the stratification variables used in the randomisation [13–15]. The SafeBoosC-IIIv trial uses three stratification variables in the randomisation, i.e. 'centre', 'gestational age' (≤ 34 weeks or > 34 weeks), and 'initiation of invasive mechanical ventilation was due to surgery' (yes or no). Thus, we will adjust all regression analyses for 'centre', 'gestational age group', and 'initiation of invasive mechanical ventilation was due to surgery'.

We will perform the following subgroup analyses:

- Sex (male or female)
- Indication for invasive mechanical ventilation (respiratory insufficiency or surgery)
- Race or ethnic group (White, Black or African American, Asian, Hispanic or Latino, Mixed, or other)

Subgroup analyses will primarily be presented in forest plots. Additionally, subgroup comparisons will be conducted using tests of interaction. Subgroup analyses will be hypothesis-generating rather than confirmatory.

Statistical analyses

Outcomes

The primary outcome will be analysed as count data (number of hospital-free days). The secondary outcomes will be analysed as following: (i) serious adverse events will be analysed as a binary variable (one or more versus no serious adverse event), and (ii) invasive mechanical ventilation-free days will be analysed as count data. Additionally, each specific serious adverse event will be presented separately by risk ratios and 95% confidence intervals. The exploratory outcomes will be analysed as following: (i) late-onset sepsis will be analysed as a binary variable (late-onset sepsis versus no late-onset sepsis), and (ii) invasive mechanical ventilation-related infection will be analysed as a binary variable (one or more versus no invasive mechanical ventilation-related infection).

Count data

Count data will be presented as medians, median differences (Hodges–Lehmann), and 95% confidence intervals; and means, mean differences, and 95% confidence intervals will be reported in the supplementary materials. Count data will be analysed by the van Elteren test stratified by 'centre'. Two sensitivity analyses will be performed when analysing the primary outcome: (1) a mixed effects model with 'centre' as a random effect and the remaining stratification variables as fixed effects and (2) a van Elteren test, in which the number of hospital-free days up until death will be included, even if the infant dies within 90 days of randomisation.

Dichotomous data

Dichotomised outcomes will be presented as proportions of participants in each group with the event, as well as relative risks with 95% confidence intervals. Dichotomous outcomes will be analysed using mixed effects generalised linear models using a log-link function with 'centre', as random intercept using an exchangeable covariance matrix. If the analysis does not converge, mixed effects logistic regression will be used to analyse dichotomised data, and relative risks will be obtained using either G computation in R (R Core Team, Vienna, Austria)—or an equivalent methodology—or the NLCOM command in Stata (StataCorp, College Station, TX, USA).

Handling of missing data

The primary analysis will include all randomised participants with available data. Missing data will be handled according to the recommendation by Jakobsen et al. [16]. In short, missing data will be considered negligible if the amount of missing data is less than 5%. If the amount of missing data is more than 5%, we will apply multiple imputation and best–worst/worst–best analyses to evaluate the potential impact of missing data on the results, depending on the amount of missing data, as specified [16].

Assessment of underlying assumptions

We will systematically assess underlying statistical assumptions for all statistical analyses [17, 18]. The non-parametric van Elteren test will be performed without

additional assumption testing. For all regression analyses, both primary, secondary, and exploratory, we will test for major interactions between each covariate and the intervention variable. When assessing for major interactions, we will, in turn, include each possible first-order interaction between included covariates and the intervention variable. For each combination, we will test if the interaction term is significant and assess the effect size. We will only consider that there is evidence of an interaction if the interaction is statistically significant after Bonferroni adjusted thresholds, which is 0.05 divided by the number of possible interactions (treatment variable interaction with 'centre', 'gestational age group', and 'initiation of invasive mechanical ventilation was due to surgery' = 0.0167), and if the interaction shows a clinically important effect. If it is concluded that the interaction is significant, we will consider both presenting an analysis separately for each (e.g. for each centre if there is a significant interaction between the trial intervention and 'centre') and an overall analysis including the interaction term in the model [17, 18].

Assessments of underlying statistical assumptions for dichotomous outcomes

We will assess if the deviance divided by the degrees of freedom is significantly larger than 1 to assess for relevant overdispersion. Overdispersion is the presence of greater variability (statistical dispersion) in a data set than expected based on a given statistical model. Relevant overdispersion will be handled using a maximum likelihood estimate of the dispersion parameter. To avoid analytical problems with few events or problems with all participants dying at a given centre, we have only included centres planning to randomise 10 participants (rule of thumb). We will consider pooling data from smaller centres if the number of participants is too low [18].

Assessments of underlying statistical assumptions for linear regression

We will visually inspect quantile–quantile plots of the residuals to assess if the residuals are normally distributed and use residuals plotted against covariates and fitted values to assess for homogeneity of variances [19, 20]. If the plots show deviations from the model assumptions, we will consider transforming the outcome, e.g. using log transformation or square root and/or use robust standard errors [18–20].

Sensitivity analysis for secondary composite outcome

The secondary outcome 'serious adverse events' is a composite of nine items. This will be analysed using a win-ratio approach as an exploratory analysis [21]. The patients will be unmatched, meaning each patient in the intervention group will be compared with all patients of the usual care group ($805 \times 805 = 648{,}025$ unmatched pairs classified into 18 categories of the composite outcome: death of treatment guided by cerebral oximetry first; death of usual care first; bronchopulmonary dysplasia of treatment guided by cerebral oximetry first; bronchopulmonary dysplasia of usual care first; etc.) [21]. Items of the secondary outcome are ranked hierarchically: death; bronchopulmonary dysplasia; any brain injury diagnosed by imaging; seizures treated with antiepileptic medicine; haemodynamic insufficiency that needs cardiovascular support; spontaneous bowel perforation or necrotising enterocolitis Bells grade 2 or more; nosocomial infection; Extra Corporal Membrane Oxygenation; renal replacement therapy during 90-days follow-up. The win ratio is the odds that the intervention of treatment guided by cerebral oximetry wins for any randomly chosen patient pair in the usual care group. A win ratio, therefore, describes the ratio of the proportion of win pairs to the proportion of losses, and a win ratio with a lower 95% confidence limit above 1 indicates that treatment guided by cerebral oximetry is worse than usual care. Further, win difference (%wins − %losses) will be calculated in order to quantify the absolute and relative risk of the win ratio [22]. The win ratio depends on the duration of follow-up and the censoring distribution, e.g. if the patient dies, but the other patient is censored earlier, a 'win' cannot be determined for this pair, which introduces a tie. Thus, we will plot the win ratio with a 95% confidence interval as well as the proportion of wins and losses [21].

Statistical reports

Blinded data on all outcomes will be analysed by two independent statisticians (JCJ and MHO) [18]. CBK is the chief investigator, and JCJ is the senior responsible statistician. Two independent statistical reports will be sent to the trial manager and shared with the Steering Committee and author group. In case of discrepancies between the two primary statistical reports, possible reasons for those will be identified, and the Steering Committee will decide which is the most correct result. A final statistical report will be prepared, and all three statistical reports will be published as supplementary material [18].

Reporting of CONSORT flow diagram, baseline data, and outcome data

Information to be included in the CONSORT flow diagram is presented in Supplementary materials 'CONSORT flow diagram'. Baseline data will primarily be presented as described in Supplementary materials

'Baseline table'. Data on primary and secondary outcomes will primarily be presented as described in Supplementary materials 'Outcome table'.

Discussion

This is the statistical analysis plan for step one of the SafeBoosC-IIIv trial, a pragmatic, multicentre, parallel-group, randomised clinical trial to study treatment guided by cerebral oximetry monitoring compared to usual care. The SafeBoosC-IIIv trial builds on the existing SafeBoosC consortium and draws on experience from the previous SafeBoosC-II and SafeBoosC-III trials [4, 5]. In step one of the SafeBoosC-IIIv trial, we aim to assess whether treatment guided by cerebral oximetry monitoring will increase the number of hospital-free days within 90 days of randomisation. This predefined statistical analysis plan aims to minimise the risk of reporting biased and data-driven results and thus increase the validity of our results.

This statistical analysis plan has several strengths, and the SafeBoosC-IIIv trial has been designed to minimise both systematic and random errors. The methodology is predefined and thoroughly detailed to prevent data-driven analyses and reduce the risk of outcome reporting bias. All outcomes were prespecified in the trial protocol [6], thereby minimising the risk of selective outcome reporting. The primary, secondary, and exploratory outcomes are all clinically relevant, and the primary conclusions will be drawn from the primary outcome to address concerns related to multiplicity [12]. Data will be analysed according to the intention-to-treat principle. Depending on the amount of missing data, we will apply multiple imputation and best–worst/worst–best analyses to evaluate the potential impact of missing data on the results, as specified [16]. Furthermore, we will systematically assess whether the underlying statistical assumptions are met for almost all analyses.

This statistical analysis plan also has limitations. While the primary conclusions will be based on the main outcome, we will also include secondary outcomes, exploratory outcomes, and perform subgroup analyses. We have not adjusted the thresholds for significance for these multiple comparisons, recognising that this increases the risk of type I errors. However, these analyses are intended to be hypothesis-generating rather than confirmatory.

Conclusion

This statistical analysis plan describes the planned statistical analyses in detail for the SafeBoosC-IIIv trial to minimise the risk of reporting bias and data-driven results.

Abbreviations

SafeBoosC	Safeguarding the Brain of our smallest Children
eCRF	Electronic case report form

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-025-09387-4.

Supplementary Material 1

Supplementary Material 2. SAP 2019 Checklist

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Authors' contributions

JJP, CBK, and JCJ drafted the initial manuscript. MHO, MLH, KT, AP, GN, ED, GHH, MISR, GP, GD, TS, MLO, SN, GM, LC, MDM, JL, RSP, JT, HF, MC, CH, HP, JF, LW, GS, MF, SPB, RM, PZ, KS, MAC, NBS, LSL, EG, EH, SA, TD, and GG contributed to revisions, critically reviewed the content, and approved the final version of the manuscript.

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Data availability

Not applicable.

Declarations

Ethics approval and consent to participate

The protocol is approved by the Danish Research Ethics Committees (2402572). All neonatal intensive care units must have their eligibility confirmed, and the protocol should be approved by the relevant ethics committee before randomisation can begin. Prior informed consent, deferred consent, or absence of opt-out to participate will be obtained from all participants.

Consent for publication

Not applicable.

Competing interests

TS is the president of the Polish Neonatal Society. He has received speakers' honoraria from the following companies: Masimo, Medtronic, AstraZeneca, Sanofi. All other authors declare that they have no competing interests.

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