Protocol title: Effect of cerebral NIRS monitoring in ventilated neonates on the frequency of early cardiovascular interventions: an ancillary study of the SafeBoosC-IIIv Trial

Short Title: *c*NIRS monitoring and cardiovascular interventions in ventilated neonates

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Introduction

Cardiovascular compromise, most commonly presenting as arterial hypotension, is a frequent problem, particularly in critically ill very preterm infants [1–3] but also occurs in a substantial proportion of late preterm and term neonates receiving mechanical ventilation [2,4]. Hemodynamic instability in neonates arises from multiple and complex mechanisms [5]. Interventions such as mechanical ventilation—both invasive and non-invasive—via well-established cardiopulmonary interactions [6], as well as the use of medications (e.g., analgesics and sedatives) [7], may significantly affect cardiovascular stability.

Ensuring adequate perfusion and oxygen delivery to vital organs is a key objective in the management of these infants. Cardiovascular support commonly involves volume expansion, vasoactive agents such as inotropes and vasopressors, and corticosteroid therapy [5]. Nevertheless, hemodynamic assessment in neonates still largely relies on clinical and laboratory indicators with limited diagnostic value, such as heart rate, capillary refill time >3 seconds, central-to-peripheral temperature difference [8], metabolic acidosis, elevated blood lactate, urine output, and arterial blood pressure measurement [9], although echocardiography is increasingly utilized to assess cardiovascular status and guide management [10]. Cerebral near-infrared spectroscopy (cNIRS) may assist in the detection of cerebral hypoperfusion, prompting initiation cardiovascular support, despite the fact that cNIRS does not consistently correlate with arterial blood pressure values [11,12]. In a single-center observational study of neonates <30 weeks gestational age and <1500 grams, treatment with dopamine increased mean arterial pressure but did not improve cerebral oxygenation [13].

On the other hand, evidence from previous studies suggests that cNIRS monitoring may influence clinical management. In smaller trials, cNIRS-guided care prompted additional diagnostic evaluations such as echocardiography, and adjustments in respiratory or transfusion strategies, although consistent effects on cardiovascular support were not demonstrated. In the SafeBoosC phase II trial, only 25% of cNIRS alarms led to protocol-defined interventions, most of which were respiratory rather than cardiovascular [14]. More recently, in the SafeBoosC-III trial of extremely preterm infants, a numerically higher proportion of neonates in the cNIRS group received cardiovascular support compared with controls (36.9% vs 30.2%), although this difference was not statistically significant [3]. Similarly, in a large randomized trial, vasopressor or inotrope use was comparable between groups (20 vs 19 patients), while fluid bolus administration was higher in the cNIRS group [mean (SD) 0.9 (1.9) vs 0.6 (1.2)][15].

Taken together, these findings suggest that cNIRS monitoring may influence clinical decision-making and potentially affect the frequency of cardiovascular interventions, although this has not been systematically evaluated as a primary outcome. Importantly, it remains unclear whether such changes reflect appropriate responses to cerebral hypoperfusion or represent alterations in clinician behavior driven by access to cNIRS data.

Patients and methods

1. Study Population

All infants enrolled in the SafeBoosC-IIIv trial who have not received cardiovascular intervention prior to randomization will be eligible for inclusion in this ancillary study.

* Cardiovascular intervention: defined as any of the following—fluid bolus administration, initiation of inotropes, vasopressors or corticosteroid therapy.

2. *Study hypothesis and objectives*

We hypothesize that neonates monitored with cerebral NIRS receive more frequent and/or more intensive cardiovascular interventions compared with infants managed without visible NIRS monitoring.

Primary Objective

To compare the **overall exposure to cardiovascular interventions during the first 72 hours** after randomization between infants randomized to treatment guided by cerebral NIRS monitoring and those receiving standard care without NIRS monitoring.

Secondary Objectives

- To compare the **time from randomization to first cardiovascular intervention** between groups.
- To compare the **type of cardiovascular intervention** administered.

Exploratory objective:

- To evaluate whether cardiovascular support is initiated in the presence of predefined indicators of circulatory compromise.
- To quantify the relative contribution of clinical parameters, echocardiographic findings, and cNIRS values to decisions to initiate cardiovascular interventions.

3. Additional data to be collected for* the *ancillary study

In addition to data collected as part of the SafeBoosC-IIIv trial, participating centers will extract routinely recorded clinical data from medical records **for the first 72 hours after randomization.**

Participating centers will first confirm whether no cardiovascular intervention was performed prior to randomization (yes/no).

The following data will subsequently be recorded in eligible infants:

1. **Occurrence and timing**
   - Occurrence of any cardiovascular intervention (yes/no)
   - Time of first cardiovascular intervention (HH:MM, DD-MM-YYYY)

2. **Type of intervention** *(select all that apply)*

   - Fluid bolus administration
   - Vasoactive medications (inotropes and/or vasopressors)
   - Corticosteroids

3. **For the exploratory analysis:**

Indication for initiation of cardiovascular support *(if applicable; select all that apply)*

- Compromised circulation indicated by clinical parameters (e.g., arterial hypotension, elevated blood lactate, capillary refill time >3 seconds, urine output <1 mL/kg/h)
- Compromised circulation as assessed by echocardiography (cardiac-POCUS)
- cNIRS values *(intervention group only)*

Contribution of each factor to the decision to initiate cardiovascular interventions (as assessed by the attending physician(s) in charge during the study period)

(1 = no contribution, 5 = major contribution)

- Clinical parameters: 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐
- Echocardiography findings: 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐
- cNIRS values *(intervention group only)*: 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

Statistical analysis

Sample Size and Power

As this is an ancillary study embedded within a randomized trial, all eligible infants will be included. The statistical power of the study will depend on the incidence of cardiovascular interventions in the parent cohort.

Analysis plan

1 Descriptive statistics will be used to summarize the frequency and types of cardiovascular interventions in both groups. All data will be analyzed centrally by Copenhagen Trial Unit.
2. The primary analysis of all outcomes will be performed on the intention-to-treat population.

Ethics

Participating centers must comply with local regulations regarding the need for new or updated ethical approval. As this ancillary study only involves the collection of additional routinely recorded clinical data, and parental consent for the neonate's participation has already been obtained for the SafeBoosC-IIIv trial (Protocol version 1.0 – 19 February 2025), no additional ethical approval is expected to be required, subject to local regulations.

Timeline

Expected date of registration of the study protocol on clinicaltrials.gov

Once the protocol has been approved by the Steering Committee, it will be submitted to ClinicalTrials.gov and to the local Ethics Committee within the following three months.

Expected date of manuscript submission

Data will be analyzed and a manuscript prepared after recruitment is complete, with submission planned following publication of the primary SafeBoosC-IIIv trial results.

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Additional authors

Authorship will follow the criteria outlined in the SafeBoosC-IIIv Standard Operating Procedure, "SOP: Substudies and Subsequent Publications," available at safeboosc.eu. Principal investigators from sites participating in this ancillary study will be invited to co-author the publication. To be listed as a co-author, principal investigators must meet the Vancouver criteria

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