



University of Southern Denmark

Cerebral Oximetry Monitoring in Extremely Preterm Infants

Hansen, Mathias L.; Pellicer, Adelina; Hyttel-Sørensen, Simon; Ergenekon, Ebru; Szczapa, Tomasz; Hagmann, Cornelia; Naulaers, Gunnar; Mintzer, Jonathan; Fumagalli, Monica; Dimitriou, Gabriel; Dempsey, Eugene; Tkaczyk, Jakub; Cheng, Guoqiang; Fredly, Siv; Heuchan, Anne M.; Pichler, Gerhard; Fuchs, Hans; Nesargi, Saudamini; Hahn, Gitte H.; Piris-Borregas, Salvador; Širc, Jan; Alsina-Casanova, Miguel; Stocker, Martin; Ozkan, Hilal; Sarafidis, Kosmas; Hopper, Andrew O.; Karen, Tanja; Rzepecka-Weglarz, Beata; Oguz, Serife S.; Arruza, Luis; Memisoglu, Asli C.; Del Rio Florentino, Ruth; Baserga, Mariana; Maton, Pierre; Truttmann, Anita C.; De Las Cuevas, Isabel; Agergaard, Peter; Zafra, Pamela; Bender, Lars; Lauterbach, Ryszard; Lecart, Chantal; De Buyst, Julie; El-Khuffash, Afif; Curley, Anna; Vaccarello, Olalla O.; Miletin, Jan; Ppathoma, Evangelia; Vesoulis, Zachary; Vento, Giovanni; Cornette, Luc; Lopez, Laura S.; Yasa, Beril; Klamer, Anja; Agosti, Massimo; Baud, Olivier; Mastretta, Emmanuele; Cetinkaya, Merih; McCall, Karen; Zeng, Shujuan; Hatzidaki, Eleftheria; Bargiel, Agata; Marciniak, Sylwia; Gao, Xiaoyan; Huijia, Lin; Chalak, Lina; Yang, Ling; Rao, Shashidhar A.; Xu, Xin; Gonzalez, Begoña L.; Wilinska, Maria; Yin, Zhaoqing; Sadowska-Krawczenko, Iwona; Serrano-Viñuales, Itziar; Krolak-Olejniak, Barbara; Ybarra, Marta M.; Morales-Betancourt, Catalina; Korček, Peter; Teresa-Palacio, Marta; Mosca, Fabio; Hergenhan, Anja; Koksal, Nilgun; Tsoni, Konstantia; Kadri, Munaf M.; Knöpfli, Claudia; Rafinska-Wazny, Elzbieta; Akin, Mustafa S.; Nordvik, Tone; Peng, Zhang; Kersin, Sinem G.; Thewissen, Liesbeth; Alarcon, Ana; Healy, David; Urlesberger, Berndt; Baş, Münevver; Baumgartner, Jana; Skylogianni, Eleni; Karadyova, Veronika; Valverde, Eva; Bergon-Sendin, Elena; Kucera, Jachym; Pisoni, Silvia; Wang, Le; Smits, Anne; Sanchez-Salmador, Rebeca; Rasmussen, Marie I.; Olsen, Markus H.; Jensen, Aksel K.; Gluud, Christian; Jakobsen, Janus C.; Greisen, Gorm

Published in:
New England Journal of Medicine

DOI:
10.1056/NEJMoa2207554

Publication date:
2023

Document version:
Final published version

ORIGINAL ARTICLE

Cerebral Oximetry Monitoring in Extremely Preterm Infants

M.L. Hansen, A. Pellicer, S. Hyttel-Sørensen, E. Ergenekon, T. Szczapa, C. Hagmann, G. Naulaers, J. Mintzer, M. Fumagalli, G. Dimitriou, E. Dempsey, J. Tkaczyk, G. Cheng, S. Fredly, A.M. Heuchan, G. Pichler, H. Fuchs, S. Nesargi, G.H. Hahn, S. Piris-Borregas, J. Širc, M. Alsina-Casanova, M. Stocker, H. Ozkan, K. Sarafidis, A.O. Hopper, T. Karen, B. Rzepecka-Weglarz, S.S. Oguz, L. Arruza, A.C. Memisoglu, R. del Rio Florentino, M. Baserga, P. Maton, A.C. Truttmann, I. de las Cuevas, P. Agergaard, P. Zafra, L. Bender, R. Lauterbach, C. Lecart, J. de Buyst, A. El-Khuffash, A. Curley, O.O. Vaccarello, J. Miletin, E. Papathoma, Z. Vesoulis, G. Vento, L. Cornette, L.S. Lopez, B. Yasa, A. Klamer, M. Agosti, O. Baud, E. Mastretta, M. Cetinkaya, K. McCall, S. Zeng, E. Hatzidaki, A. Bargiel, S. Marciniak, X. Gao, L. Huijia, L. Chalak, L. Yang, S.A. Rao, X. Xu, B.L. Gonzalez, M. Wilinska, Z. Yin, I. Sadowska-Krawczenko, I. Serrano-Viñuales, B. Krolak-Olejnik, M.M. Ybarra, C. Morales-Betancourt, P. Korček, M. Teresa-Palacio, F. Mosca, A. Hergenhan, N. Koksál, K. Tsoni, M.M. Kadri, C. Knöpfli, E. Rafinska-Wazny, M.S. Akin, T. Nordvik, Z. Peng, S.G. Kersin, L. Thewissen, A. Alarcon, D. Healy, B. Urlesberger, M. Baş, J. Baumgartner, E. Skylogianni, V. Karadyova, E. Valverde, E. Bergon-Sendin, J. Kucera, S. Pisoni, L. Wang, A. Smits, R. Sanchez-Salmador, M.I. Rasmussen, M.H. Olsen, A.K. Jensen, C. Glud, J.C. Jakobsen, and G. Greisen

ABSTRACT

BACKGROUND

The use of cerebral oximetry monitoring in the care of extremely preterm infants is increasing. However, evidence that its use improves clinical outcomes is lacking.

METHODS

In this randomized, phase 3 trial conducted at 70 sites in 17 countries, we assigned extremely preterm infants (gestational age, <28 weeks), within 6 hours after birth, to receive treatment guided by cerebral oximetry monitoring for the first 72 hours after birth or to receive usual care. The primary outcome was a composite of death or severe brain injury on cerebral ultrasonography at 36 weeks' postmenstrual age. Serious adverse events that were assessed were death, severe brain injury, bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, and late-onset sepsis.

RESULTS

A total of 1601 infants underwent randomization and 1579 (98.6%) were evaluated for the primary outcome. At 36 weeks' postmenstrual age, death or severe brain injury had occurred in 272 of 772 infants (35.2%) in the cerebral oximetry group, as compared with 274 of 807 infants (34.0%) in the usual-care group (relative risk with cerebral oximetry, 1.03; 95% confidence interval, 0.90 to 1.18; $P=0.64$). The incidence of serious adverse events did not differ between the two groups.

CONCLUSIONS

In extremely preterm infants, treatment guided by cerebral oximetry monitoring for the first 72 hours after birth was not associated with a lower incidence of death or severe brain injury at 36 weeks' postmenstrual age than usual care. (Funded by the Elsass Foundation and others; SafeBoosC-III ClinicalTrials.gov number, NCT03770741.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Hansen can be contacted at mathias.luhr.hansen@gmail.com or at the Department of Neonatology, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark.

A complete list of the authors' contributions is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2023;388:1501-11.

DOI: 10.1056/NEJMoa2207554

Copyright © 2023 Massachusetts Medical Society.

 A Quick Take
is available at
NEJM.org

IN COUNTRIES WITH ACCESS TO NEONATAL intensive care, more than 50,000 infants are born extremely preterm every year.¹ Of these infants, approximately 25% die² and 20% survive with substantial neurologic or cognitive deficits.³ In the first days after birth, low arterial blood pressure and low systemic blood flow are common,⁴ and impairment of cerebral autoregulation may jeopardize consistent blood flow to the brain.⁵ Respiratory distress usually necessitates intensive care⁶; mechanical ventilation carries a risk of hypocapnia and decreased cerebral blood flow with subsequent brain injury.⁷⁻⁹

Monitoring of cerebral oxygenation has been proposed as a means of alerting clinicians to low cerebral blood flow and risk of cerebral ischemia, as well as to low systemic blood flow and ischemia of other organs, so that therapy can be adjusted to minimize the risk of damage.^{10,11} In the Safeguarding the Brains of our Smallest Children (SafeBoosC)-II trial,¹² a total of 166 extremely preterm infants underwent randomization to receive treatment guided by cerebral oximetry monitoring during the first 72 hours after birth or to receive blinded cerebral oximetry monitoring (the cerebral oxygenation values were not visible to staff) and usual care. The occurrence of primary outcome events — cerebral hypoxia and hyperoxia (total duration and magnitude of cerebral oxygenation, <55% or >85%) — was reduced by 58% in the cerebral oximetry group, primarily owing to a reduction in hypoxia.¹² However, SafeBoosC-II was not powered to detect a difference in clinical outcomes,¹² and evidence has been lacking to determine the clinical benefit or harm.¹³ Despite this lack of evidence, the clinical use of cerebral oximetry monitoring in neonatal intensive care is growing.¹⁴ We conducted a phase 3 trial to assess whether treatment guided by cerebral oximetry for the first 72 hours after birth in extremely preterm infants would result in a lower incidence of death or survival with severe brain injury at 36 weeks' postmenstrual age than usual care.

METHODS

TRIAL DESIGN

The SafeBoosC-III trial was an investigator-initiated, pragmatic, superiority, open-label, multi-

national, phase 3, randomized clinical trial. The design and statistical analysis plan have been published previously,^{15,16} as described in the protocol (available with the full text of this article at NEJM.org). Before the trial launch, the protocol was approved by the relevant ethics committees at each trial site. An independent data and safety monitoring committee conducted one preplanned, blinded interim analysis after one third of the infants had reached 36 weeks' postmenstrual age (data and safety monitoring are described in the Supplementary Appendix, available at NEJM.org). The trial was conducted in compliance with the International Council for Harmonisation guidelines for Good Clinical Practice,¹⁷ including local monitoring visits and central data monitoring conducted during the trial.¹⁸

PATIENTS

Infants were eligible for enrollment if they were less than 28 weeks' gestational age at birth (as estimated at each site according to local guidelines), if a decision had been made to provide full life support, and if the initiation of cerebral oximetry monitoring within 6 hours after birth was possible. Inclusion in the trial in most cases required previous written informed consent from the parents; an opt-out or deferred consent process was used at some sites (Section S18 and Fig. S4 in the Supplementary Appendix).^{19,20}

RANDOMIZATION

Infants were randomly assigned in a 1:1 ratio to receive monitoring with cerebral oximetry or to receive usual care. Randomization was performed centrally by the Copenhagen trial unit with the use of a computer-generated assignment sequence with varied block sizes. Stratification variables were site and gestational age (<26 weeks or ≥26 weeks). The assignment sequence was concealed for all investigators. Infants who were multiple-birth siblings were assigned to the same trial group. In cases in which it was not possible for all multiple-birth siblings to undergo randomization owing to a lack of available cerebral oximeters, the last-born sibling (or siblings, if oximeters were available) underwent randomization.

BLINDING

Parents and health care professionals were aware of group assignments. The determination of se-

vere brain injury was performed in a blinded fashion (Section S12). Assessment of the outcome of death was not blinded, but source data verification was conducted during monitoring visits. Assessments of other exploratory outcomes were not blinded. Statisticians, data managers, and authors were unaware of group assignments, which were identified as group A and group B. An abstract was written for each of the two treatment scenarios and agreed to by the authors before the randomization code was revealed.¹⁶

INTERVENTIONS

Infants in the oximetry group underwent cerebral oximetry monitoring for the first 72 hours after birth. A probe with near-infrared light sources and sensors was fixed to the infant's head with the use of an elastic bandage, and a signal indicating the hemoglobin oxygen saturation percentage was continuously displayed. The signal primarily displayed information from veins in the cortex and subcortex directly beneath the probe.²¹

If an infant's cerebral oxygenation level dropped below the threshold for hypoxia, treatment was considered. Interventions were based on the SafeBoosC-III treatment guideline,¹⁵ which includes commonly used potential clinical interventions for the purpose of normalizing cerebral oxygenation (Fig. S1).²² Any oximetry device and sensor approved for clinical use in neonates was allowed for use in the trial. Consistent with the measurements used in the SafeBoosC-II trial, the hypoxic threshold for interventions was 55% as measured with the INVOS small adult sensor.¹² Because devices and sensors differ in measurement of absolute oxygenation values, the oxygenation value corresponding to 55% as measured with the INVOS small adult sensor was determined with the use of a blood-lipid phantom for 13 different combinations of cerebral oximeters and sensors (Table S1).²³ Adherence to the intervention was defined as less than 14 hours of missing oximetry monitoring data during the 72-hour intervention period.

Infants in the usual-care group did not undergo monitoring with cerebral oximetry but received treatment and monitoring as usual. To familiarize staff members with the intervention and trial design, a Web-based training and certification program was developed and

offered to relevant clinical staff (Section S15 and Fig. S2).²⁴

OUTCOMES

Outcomes were assessed at 36 weeks' postmenstrual age or the time of death or discharge to home, whichever came first. Outcomes other than severe brain injury were extracted from the clinical records by individual site investigators. Severe brain injury was assessed by means of a review of all cerebral ultrasound scans and imaging reports available in each infant's clinical record. If an infant was discharged to another hospital before 36 weeks' postmenstrual age, the principal investigator sought data from the relevant hospital; if data from the transfer hospital were not obtained, data obtained until the date of discharge at the site hospital were used.

The primary outcome was a composite of death or survival with severe brain injury. Severe brain injury was defined as one or more of the following: intraventricular hemorrhage of grade 3 or 4, cystic periventricular leukomalacia, post-hemorrhagic ventricular dilatation, cerebellar hemorrhage, and cerebral atrophy (Section S13).

The exploratory outcomes were death at any time up to 36 weeks' postmenstrual age or bronchopulmonary dysplasia (defined as any respiratory support or use of supplementary oxygen at 36 weeks' postmenstrual age or both) and the following outcomes that occurred at any time up to 36 weeks' postmenstrual age: death or retinopathy of prematurity stage 3 or above (as categorized according to the International Classification of Retinopathy of Prematurity²⁵), death or late-onset sepsis (defined as initiation of antibiotic therapy >72 hours after birth for at least 5 days), and death or necrotizing enterocolitis stage 2 or higher (as scored with the use of the modified Bell's staging system) or focal intestinal perforation (or both). To account for the competing risk of death, the exploratory outcomes were redefined post hoc as composite outcomes including death.¹⁶ The definitions of and results from the original exploratory outcomes (not accounting for the competing risk of death) are shown in Table S2.

SERIOUS ADVERSE EVENTS AND REACTIONS

The components of the primary outcome and the exploratory outcomes constituted serious

adverse events. Serious adverse reactions included severe skin damage, physical injury associated with managing the device and sensors (critical displacement of endotracheal tubes or endovascular lines caused by cerebral oximetry monitoring), and clinical mismanagement (i.e., interventions aimed at improving respiratory or cardiovascular status and oxygen transport) that occurred on the basis of oximetry monitoring.¹⁵

STATISTICAL ANALYSIS

Using data from SafeBoosC-II,¹² we estimated that a sample group of 1600 infants would provide the trial with 90% power to detect a reduction in the risk of death or severe brain injury from 34.0% in the usual-care group to 26.5% in the oximetry group (22.0% relative risk reduction), with a two-sided alpha level of less than 0.05.¹⁶

Statistical analyses were conducted independently by two of the authors. The results of the analyses were compared for discrepancies before unblinding; no significant discrepancies were found. Primary analyses were based on the intention-to-treat principle. Dichotomous outcomes were analyzed with the use of mixed-effect logistic regression.¹⁶ In all regression models, the trial site was included as a random effect, and group allocation and gestational age group were included as fixed effects. A two-sided P value of 0.05 was considered to indicate statistical significance for the primary outcome.

We considered it unlikely that data were missing entirely at random. The potential influence of missing data was assessed by using best-worst and worst-best case analyses.¹⁶ Assuming that data were missing at random, we also conducted post hoc analyses with the use of multiple imputation to further investigate the potential influence of missing data.²⁶

Three prespecified sensitivity analyses were conducted for the primary outcome, including a per-protocol analysis, a random-effects meta-analysis, and a generalized-estimation-equation analysis to allow for nonindependence of the primary outcome in multiple births¹⁶; the per-protocol analysis was redefined after publication of the statistical analysis plan but before the data were unblinded (Section S20).¹⁶ Confidence intervals for the exploratory outcomes and sensitivity analyses were not adjusted for multiple

testing and cannot be used in place of hypothesis testing.

RESULTS

PATIENTS

A total of 1601 infants underwent randomization between June 2019 and December 2021 (785 to the oximetry group and 816 to the usual-care group) across 70 sites in Asia, Europe, and North America (Fig. 1 and Section S8). The parents of 18 infants who were enrolled under the terms of deferred consent did not eventually provide written informed consent and declined the use of their infants' data. For three infants who were enrolled under the terms of prior informed consent, the parents withdrew their consent and, for two of the three infants, also withdrew consent for the use of their infants' data. Two infants from one site were lost to follow-up because the site withdrew from the trial shortly after the start of data collection.

The characteristics of the infants were similar in the two groups (Table 1). The types of oximetry devices and sensors used in the trial are described in Table S3.

Nonadherence to the assigned intervention was documented in 36 of 772 infants (4.7%) in the oximetry group (who each had more than 14 hours of missing oximetry monitoring data) and in 20 of 807 infants (2.5%) in the usual-care group (who underwent oximetry monitoring) (Table 1 and Table S4). The representativeness of the trial population is described in Table S5.

OUTCOMES

At 36 weeks' postmenstrual age, 272 of 772 infants (35.2%) in the oximetry group and 274 of 807 (34.0%) in the usual-care group had died or survived with a severe brain injury (relative risk with cerebral oximetry, 1.03; 95% confidence interval [CI], 0.90 to 1.18; P=0.64) (Table 2). In the oximetry and usual-care groups, 27 and 26 infants, respectively, were discharged to home or to another hospital before 36 weeks' postmenstrual age. Causes of death are shown in Table 3, and subsets of severe brain injury are described in Table S6. Data regarding the primary outcome were missing for 22 infants (13 in the oximetry group and 9 in the usual-care group).

The results of the best-worst and worst-best case analyses and multiple imputation analyses

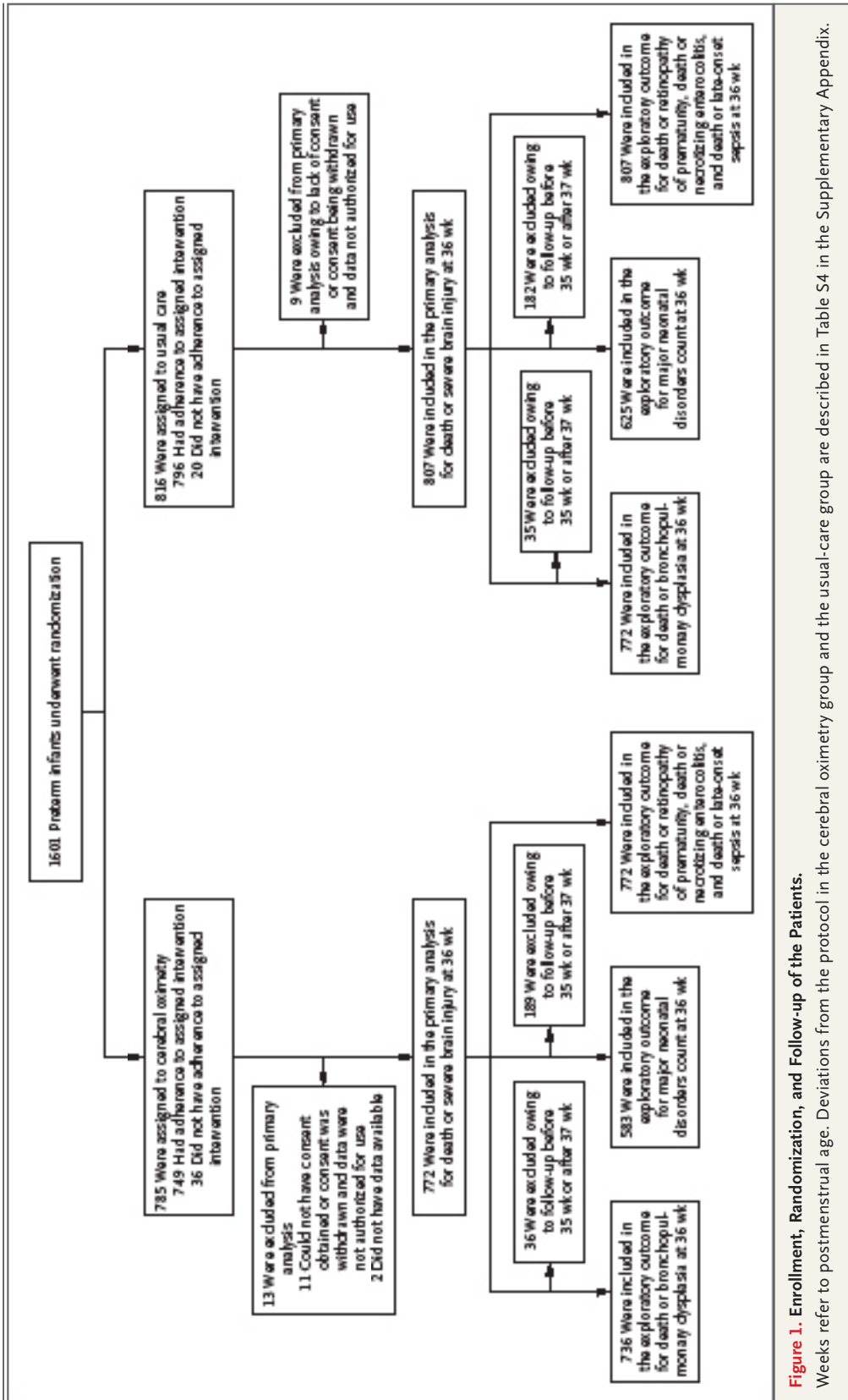


Figure 1. Enrollment, Randomization, and Follow-up of the Patients.

Weeks refer to postmenstrual age. Deviations from the protocol in the cerebral oximetry group and the usual-care group are described in Table S4 in the Supplementary Appendix.

Table 1. Characteristics of the Intention-to-Treat Population.*

Variables	Cerebral Oximetry (N=772)	Usual Care (N=807)
Baseline characteristics		
Median birth weight (IQR) — g	815 (670–976)	814 (670–960)
Median gestational age (IQR) — wk	26.1 (25.0–27.1)	26.1 (25.0–27.1)
Gestational age >26 wk — no. (%)	431 (55.8)	453 (56.1)
Twins or triplets — no. (%)	192 (24.9)	230 (28.5)
Male sex — no. (%)	418 (54.1)	425 (52.7)
Median Apgar score (IQR)		
At 1 min	5 (3–7)	5 (3–7)
At 5 min	7 (6–8)	7 (6–8)
Clinical and treatment characteristics		
Surfactant treatment — no. (%)	632 (81.9)	666 (82.5)
Cardiovascular support ≤72 hr after birth — no. (%)	285 (36.9)	244 (30.2)
Major congenital anomaly — no. (%)	17 (2.2)	20 (2.5)
Mechanical ventilation — no. (%)†	612 (79.3)	630 (78.1)
Median days using mechanical ventilation (IQR) — no.	10.0 (3.0–24.0)	10.0 (3.0–26.8)
Treatment for patent ductus arteriosus — no. (%)	330 (42.7)	376 (46.6)
Treatment for retinopathy of prematurity — no. (%)	66 (8.5)	67 (8.3)
Cerebral ultrasonography — no. (%)‡		
Early and late	588 (76.2)	638 (79.1)
Early only	158 (20.5)	150 (18.6)
Late only	6 (0.8)	3 (0.4)
Only between days 8 and 35	7 (0.9)	1 (0.1)
No ultrasound	13 (1.7)	15 (1.9)
Cerebral oximetry		
Median age at initiation of cerebral oximetry monitoring (IQR) — hr	3 (2–4)	—
Cerebral oximetry monitoring discontinued >14 hours — no. (%)	36 (4.7)	—
Change of medical management due to cerebral hypoxia — no. (%)	222 (28.8)	—
Cerebral oximetry monitoring in control group — no. (%)		
Total	—	52 (6.4)
Unmasked	—	20 (2.5)

* IQR denotes interquartile range.

† Mechanical ventilation is defined as invasive mechanical ventilation delivered by means of an endotracheal tube or tracheostomy tube.

‡ Early cerebral ultrasonography is defined as a cerebral ultrasound scan between 3 and 8 days of life. Late cerebral ultrasonography is defined as a cerebral ultrasound scan between 35 days of life and until 36 weeks' postmenstrual age, death, or discharge to home. A total of nine infants were reported as never scanned but had results of cerebral ultrasonography. This discrepancy was not detected before the database lock. Therefore, 1551 infants were registered as having undergone a cerebral ultrasound scan (759 in the cerebral oximetry group and 792 in the usual-care group), although 1560 infants (763 in the cerebral oximetry group and 797 in the usual-care group) have a data record noting severe brain injury. In one of the nine infants reported as never scanned in the usual-care group, an intraventricular hemorrhage was reported; in the other eight infants, no severe brain injury was reported. Of the nine infants reported as never scanned, four were in the cerebral oximetry group and five were in the usual-care group; all nine infants died shortly after birth.

Table 2. Outcomes at 36 Weeks' Postmenstrual Age.*

Outcome	Cerebral Oximetry (N=772)	Usual Care (N=807)	Relative Risk (95% CI) [†]
Primary			
Death or severe brain injury — no. (%)‡	272 (35.2)	274 (34.0)	1.03 (0.90–1.18)
Components of the primary outcome			
Death — no. (%)	164 (21.2)	160 (19.8)	1.07 (0.89–1.28)
Severe brain injury — no./total no. (%)‡	185/763 (24.2)	188/797 (23.6)	1.02 (0.85–1.21)
Exploratory			
Death or bronchopulmonary dysplasia — no./total no. (%)§	484/736 (65.8)	524/772 (67.9)	0.96 (0.89–1.02)
Death or retinopathy of prematurity — no. (%)¶	235 (30.4)	228 (28.3)	1.08 (0.94–1.24)
Death or late-onset sepsis — no. (%)	565 (73.2)	598 (74.1)	0.98 (0.93–1.03)
Death or necrotizing enterocolitis — no. (%)**	232 (30.1)	209 (25.9)	1.16 (1.00–1.35)

* Plus-minus values are means \pm SD.

[†] The confidence intervals were not adjusted for multiple testing and cannot be used in place of hypothesis testing.

[‡] Severe brain injury is defined as one or more of the following diagnoses: intraventricular hemorrhage grade 3 or 4, cystic periventricular leukomalacia, posthemorrhagic ventricular dilatation, cerebellar hemorrhage, or cerebral atrophy shown on any routine cerebral ultrasound scan conducted until follow-up. $P=0.64$.

[§] Bronchopulmonary dysplasia was defined as the receipt of any respiratory support or supplementary oxygen (or both) at 36 weeks' postmenstrual age. Missing data were mainly owing to death before follow-up. Only 38 infants were discharged before 35 weeks' postmenstrual age.

[¶] Retinopathy of prematurity was defined as stage 3 or above (as classified according to the International Classification of Retinopathy of Prematurity) at any time point until follow-up.

^{||} Late-onset sepsis was defined as the initiation of antibiotics later than 72 hours from birth for at least 5 days.

^{**} Necrotizing enterocolitis was defined as stage 2 or higher based on the modified Bell's staging system or focal intestinal perforation at any time point until follow-up (or both).

showed that missing data did not have the potential to substantively affect results (Tables S7 and S8). Results of a post hoc analysis that excluded surviving infants who did not undergo late cerebral ultrasonography were similar to those of the primary analysis (Table S9). The results of the per-protocol analysis were consistent with the intervention effect in the primary analysis (Table S10), and heterogeneity was small enough to be ignored in a random-effects meta-analysis of site-specific effects ($I^2=0\%$) (Fig. S3). The results of the generalized-estimation-equation sensitivity analysis were also consistent with those of the primary analysis (Table S10). There was no interaction between the stratification variables and the intervention effect for the primary outcome. Estimates of marginal effects are reported in Table S11.

Incidences of exploratory-outcome events did not materially differ between the oximetry and usual-care groups (Table 2). For each exploratory outcome, the numbers of infants who had

the outcome and survival status are shown in Table S12.

SERIOUS ADVERSE EVENTS AND REACTIONS

In the oximetry group, one or more serious adverse events occurred in 657 of 772 (85.1%) infants, as compared with 698 of 807 (86.5%) infants in the usual-care group (relative risk with oximetry, 0.98; 95% CI, 0.94 to 1.01) (Table S2). There were no appreciable differences between the oximetry and usual-care groups in the incidence of individual serious adverse events. Four serious adverse reactions, all severe skin injuries, occurred in the oximetry group.

DISCUSSION

In this randomized trial, the incidence of death or severe brain injury at 36 weeks' postmenstrual age did not differ significantly between infants assigned to receive monitoring with cerebral oximetry during the first 72 hours af-

Table 3. Causes of Death at 36 Weeks' Postmenstrual Age.*

Cause	Cerebral Oximetry (N=164)	Usual Care (N=160)
	number (percent)	
Congenital anomaly	3 (1.8)	0
Respiratory distress syndrome	14 (8.5)	13 (8.1)
Bronchopulmonary dysplasia	5 (3.0)	3 (1.9)
Infection	39 (23.8)	38 (23.8)
Necrotizing enterocolitis	13 (7.9)	28 (17.5)
Central nervous system injury	31 (18.9)	20 (12.5)
Immaturity†	17 (10.4)	19 (11.9)
Other causes	39 (23.8)	37 (23.1)
Unknown	3 (1.8)	2 (1.2)

* Causes of death were determined according to local guidelines at the individual participating sites.

† Deaths occurred despite initial decision to provide full life support.

ter birth and those assigned to receive usual care. Incidences of the other serious adverse events did not materially differ between the two groups, and there were few serious adverse reactions. The results of sensitivity analyses were consistent with those of the primary analysis.

Assessment of the causes of death revealed fewer deaths from necrotizing enterocolitis in the oximetry group than in the usual-care group and more deaths attributed to severe brain injury in the oximetry group than in the usual-care group. These differences are probably chance findings; notably, the overall frequency of necrotizing enterocolitis was not lower in the oximetry group than in the usual-care group.

Our trial has several limitations. Exploratory outcomes were assessed in an unblinded manner, which could have introduced a bias favoring treatment.²⁷ However, our findings did not suggest any benefit to cerebral oximetry. The diagnosis of severe brain injury by cerebral ultrasonography was based on routine scans and imaging reports; magnetic resonance imaging was not used, and there was no central adjudication of cerebral ultrasound images. Less than 80% of infants underwent scans both early and late in their clinical course. However, results

were not materially different in a post hoc analysis that excluded surviving infants who did not undergo a late scan. We did not collect data on the results of cerebral oxygenation monitoring. Our report includes only short-term follow-up; follow-up at a corrected age of 2 years is ongoing to assess neurodevelopmental and other outcomes.

The lack of difference between groups in the incidence of the primary outcome event may have several possible explanations. First, using cerebral oximetry in an intensive care setting is a complex intervention. Although we developed a Web-based training program as a tool for clinical staff to establish basic competence, training was not mandatory, and it is possible that our pragmatic trial involving hospitals with little or no experience with cerebral oximetry did not realize the potential for reduction of cerebral hypoxia shown in the SafeBoosC-II trial.¹² Second, monitoring in the intervention group was not performed in the delivery room or during the first few hours in the neonatal intensive care unit and was performed for only 72 hours; it therefore covered only a small portion of a clinical course that typically lasts several months for survivors. Third, the target of cerebral oximetry is hypoxic–ischemic brain injury, so other factors that are not detectable by oximetry may have been responsible for death or severe brain injury in many of these extremely preterm infants.²⁸

In this randomized trial involving extremely preterm infants, treatment guided by cerebral oximetry monitoring in the first 72 hours after birth did not lead to a lower incidence of death or severe brain injury at 36 weeks' postmenstrual age than usual care.

Supported by the Capital Region of Denmark; grants from the Elsass Foundation, the Svend Andersen Foundation, and the Aage and Johanne Louis-Hansen Foundation; and financial and technological contributions from businesses and institutions in the trial-center countries (Table S13 in the Supplementary Appendix).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the families who consented to have their newborns participate in the trial; the nurses, doctors, and additional staff from all participating sites who cared for and treated the newborns in the trial; and data and safety monitoring committee members Andrew Whitelaw, James Boardman, and Theis Lange.

APPENDIX

The authors' full names and academic degrees are as follows: Mathias L. Hansen, M.D., Ph.D., Adelina Pellicer, M.D., Ph.D., Simon Hyttel-Sørensen, M.D., Ph.D., Ebru Ergenekon, M.D., Ph.D., Tomasz Szczapa, M.D., Ph.D., Cornelia Hagmann, M.D., Ph.D., Gunnar Nauelaers, M.D., Ph.D., Jonathan Mintzer, M.D., Monica Fumagalli, M.D., Ph.D., Gabriel Dimitriou, M.D., Ph.D., Eugene Dempsey, M.D., Ph.D., Jakub Tkaczyk, M.D., Guoqiang Cheng, M.D., Siv Fredly, M.D., Ph.D., Anne M. Heuchan, M.D., Gerhard Pichler, M.D., Hans Fuchs, M.D., D.M.Sc., Saudamini Nesargi, D.N.B., Gitte H. Hahn, M.D., Ph.D., Salvador Piris-Borregas, M.D., Ph.D., Jan Širc, M.D., Ph.D., Miguel Alsina-Casanova, M.D., Ph.D., Martin Stocker, M.D., Hilal Ozkan, M.D., Kosmas Sarafidis, M.D., Ph.D., Andrew O. Hopper, M.D., Tanja Karen, M.D., Beata Rzepecka-Weglarz, M.D., Serife S. Oguz, M.D., Luis Arruza, M.D., Ph.D., Asli C. Memisoglu, M.D., Ruth del Río Florentino, M.D., Mariana Baserga, M.D., Pierre Maton, M.D., Anita C. Truttmann, M.D., Isabel de las Cuevas, M.D., Ph.D., Peter Agergaard, M.D., Ph.D., Pamela Zafrá, M.D., Lars Bender, M.D., Ryszard Lauterbach, M.D., Ph.D., Chantal Lecart, M.D., Julie de Buyst, M.D., Aff El-Khuffash, M.D., Anna Curley, M.D., Olalla O. Vaccarello, M.D., Jan Miletin, M.D., Ph.D., Evangelia Papatoma, M.D., Ph.D., Zachary Vesoulis, M.D., Giovanni Vento, M.D., Ph.D., Luc Cornette, M.D., Ph.D., Laura S. Lopez, M.D., Beril Yasa, M.D., Anja Klamer, M.D., Massimo Agosti, M.D., Olivier Baud, M.D., Ph.D., Emmanuele Mastretta, M.D., Merih Cetinkaya, M.D., Ph.D., Karen McCall, M.D., Shujuan Zeng, M.D., Eleftheria Hatzidaki, M.D., Ph.D., Agata Bargiel, M.D., Sylwia Marciniak, M.D., Xiaoyan Gao, M.D., Lin Huijia, M.D., Lina Chalal, M.D., Ling Yang, M.D., Shashidhar A. Rao, M.D., D.M., Xin Xu, M.D., Begoña L. Gonzalez, M.D., Maria Wilinska, M.D., Ph.D., Zhaoqing Yin, M.D., Iwona Sadowska-Krawczenko, M.D., Ph.D., Itziar Serrano-Viñuales, M.D., Barbara Krolak-Olejniak, M.D., Ph.D., Marta M. Ybarra, M.D., Catalina Morales-Betancourt, M.D., Peter Korček, M.D., Ph.D., Marta Teresa-Palacio, M.D., Fabio Mosca, M.D., Anja Hergenhan, M.D., Nilgun Koksall, M.D., Konstantia Tsoni, M.D., Ph.D., Munaf M. Kadri, M.D., Claudia Knöpfli, M.Sc., Elzbieta Rafinska-Wazny, M.D., Mustafa S. Akin, M.D., Tone Nordvik, M.D., Zhang Peng, M.D., Sinem G. Kersin, M.D., Liesbeth Thewissen, M.D., Ph.D., Ana Alarcon, M.D., Ph.D., David Healy, M.D., Berndt Urlesberger, M.D., Münewer Baş, M.D., Jana Baumgartner, M.D., Eleni Skylogianni, M.D., Veronika Karadyova, M.D., Eva Valverde, M.D., Ph.D., Elena Bergon-Sendin, M.D., Ph.D., Jachym Kucera, M.D., Silvia Pisoni, M.D., Le Wang, M.D., Anne Smits, M.D., Ph.D., Rebeca Sanchez-Salmador, M.D., Marie I. Rasmussen, B.M., B.S., Markus H. Olsen, M.D., Aksel K. Jensen, M.Sc., Ph.D., Christian Gluud, M.D., D.M.Sc., Janus C. Jakobsen, M.D., Ph.D., and Gorm Greisen, M.D., D.M.Sc.

The authors' affiliations are as follows: the Departments of Neonatology (M.L.H., G.H.H., M.I.S.R., G.G.) and Intensive Care (S.H.-S.), Copenhagen Trial Unit, Center for Clinical Intervention Research, the Capital Region (M.H.O., C.G., J.C.J.), and the Department of Neuroanesthesiology, Neuroscience Center (M.H.O.), Copenhagen University Hospital-Rigshospitalet, and the Section of Biostatistics, Department of Public Health, University of Copenhagen (A.K.G.J.), Copenhagen, the Neonatal Intensive Care Unit, Aarhus University Hospital, Aarhus (P.A.), the Department of Neonatology, Aalborg University Hospital, Aalborg (L.B.), and the Department of Pediatrics, Odense University Hospital (A.K.), and the Department of Regional Health Research, the Faculty of Health Sciences, University of Southern Denmark (C.G., J.C.J.), Odense — all in Denmark; the Department of Neonatology, La Paz University Hospital (A.P., M.M.Y., E.V., R.S.-S.), the Neonatology Department, 12 de Octubre University Hospital (S.P.-B., C.M.-B., E.B.-S.), the Department of Neonatology, Instituto del Niño y del Adolescente, Hospital Clínico San Carlos-Instituto de Investigación Sanitaria San Carlos (L.A.), Madrid, the Department of Neonatology, Hospital Clínic Barcelona, BCNatal-Barcelona Center for Maternal-Fetal and Neonatal Medicine (M.A.-C., M.T.-P.), and the Department of Neonatology, Hospital Sant Joan de Deu (R.R.F., A.A.), Barcelona, the Neonatal Unit, Marqués de Valdecilla University Hospital, and the Department of Medical and Surgical Sciences, Cantabria University, Santander (I.C.), the Neonatal Intensive Care Unit, Puerta del Mar University Hospital, Cádiz (P.Z.), the Department of Neonatology, Hospital Universitario de Tarragona Juan XXIII, Tarragona (O.O.V.), the Neonatal Unit, University Hospital Virgen de las Nieves, Granada (L.S.L.), the Division of Neonatology, University Hospital Cruces, Biocruces Health Research Institute, Barakaldo (B.L.G.), and the Neonatology Division, Miguel Servet University Hospital, Zaragoza (I.S.-V.) — all in Spain; the Division of Newborn Medicine, Gazi University Hospital (E.E., M. Baş), and the Department of Neonatology, NICU, University of Health Sciences, Ankara City Hospital (S.S.O., M.S.A.), Ankara, the Department of Neonatology, Bursa Uludağ University Faculty of Medicine, Bursa (H.O., N.K.), the Division of Neonatology, Department of Pediatrics, Marmara University Research and Education Hospital, Marmara University, School of Medicine (A.C.M., S.G.K.), and the Department of Neonatology, Kanuni Sultan Suleyman Training and Research Hospital (B.Y., M.C.), Istanbul, and Basaksehir Cam and Sakura City Hospital, Basaksehir (B.Y., M.C.) — all in Turkey; the 2nd Department of Neonatology, Neonatal Biophysical Monitoring and Cardiopulmonary Therapies Research Unit, Poznan University of Medical Sciences, Poznan (T.S.), the Department of Neonatology, Centrum Medyczne Ujastek (B.R.-W., E.R.-W.), and the Department of Neonatology, Jagiellonian University Hospital (R.L.), Krakow, Warsaw University of Medical Sciences (A.B.) and the Neonatology Department, Center of Postgraduate Medical Education (M.W.), Warsaw, the Neonatal Unit, Specialist Hospital No. 2, Bytom (S.M.), the Department of Neonatology, Collegium Medicum in Bydgoszcz Nicolaus Copernicus University in Torun, Bydgoszcz (I.S.-K.), and the Department of Neonatology, Wrocław Medical University, Wrocław (B.K.-O.) — all in Poland; Pediatric Intensive Care and Neonatology, Children's University Hospital of Zurich (C.H.), and the Department of Neonatology, University Hospital Zurich (T.K., C.K.), Zurich, the Intensive Care Unit, Children's Hospital Lucerne, Lucerne (M.S., A.H.), the Clinic of Neonatology, Department of Women, Mother and Child, University Hospital Center, and the University of Lausanne, Lausanne (A.C.T.), and the Division of Neonatology and Pediatric Intensive Care, Children's University Hospital of Geneva, and University of Geneva, Geneva (O.B.) — all in Switzerland; the Department of Development and Regeneration Katholieke Universiteit Leuven, Leuven (G.N., L.T., A.S.), Service de Néonatalogie, Clinique Centre Hospitalier Chrétien Montlégia-Liège-Belgium, Liège (P.M.), the Department of Neonatology, Grand Hôpital de Charleroi, Charleroi (C.L.), NICU, Tivoli Hospital, La Louvière (J. Buyst), and the Department of Neonatology, Algemeen Ziekenhuis St-Jan Bruges, Bruges (L. Cornette) — all in Belgium; the Department of Pediatrics, Division of Newborn Medicine, Mountsinde Medical Center, Montclair, NJ (J. Mintzer); Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (M.F., F.M., S.P.), the Department of Clinical Sciences and Community Health, University of Milan (M.F., F.M.), Milan, Unità Operativa Complessa di Neonatologia, Dipartimento Scienze della Salute della Donna, del Bambino e di Sanità Pubblica, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome (G.V.), the Department of Neonatology, Neonatal Intensive Care Unit and Pediatrics, Filippo Del Ponte Hospital, University of Insubria, Varese (M.A.), and Struttura Complessa Neonatologia, Osp. S.Anna-Città della Salute e della Scienza di Torino, Turin (E.M.) — all in Italy; NICU, Department of Pediatrics, Patras Medical School, Patras (G.D., E.S.), the 1st Department of Neonatology of Aristotle University of Thessaloniki, Ippokrateion General Hospital of Thessaloniki, Thessaloniki (K.S., K.T.), the Neonatal Intensive Care Unit, Alexandra University and State Maternity Hospital,

Athens (E.P.), and the Department of Neonatology and NICU, University Hospital of Heraklion, Heraklion (E.H.) — all in Greece; the Infant Centre and Department of Paediatrics and Child Health, University College Cork, Cork (E.D., D.H.), and the School of Medicine, Department of Paediatrics, Royal College of Surgeons in Ireland (A.E.-K.), National Maternity Hospital (A.C.), Coombe Women and Infant University Hospital (J. Miletin), and Ireland University College Dublin (J. Miletin), Dublin — all in Ireland; the Department of Neonatology, University Hospital Motol (J.T., V.K.), and the Institute for the Care of Mother and Child (J.Š., J. Miletin, P.K., J.K.) and the Third Faculty of Medicine, Charles University (J.Š., P.K.), Prague — all in Czechia; the Department of Neonatology, Children's Hospital of Fudan University, Shanghai (G.C., Z.P., L.W.), the Department of Neonatology, Longgang District Central Hospital, Shenzhen (S.Z.), the Department of Neonatology, Maternal and Child Health Hospital of Zhuang Autonomous Region, Quangxi (X.G.), the Department of Neonatal Intensive Care Unit, Children's Hospital of Zhejiang University School of Medicine, Hangzhou (L.H.), the Department of Neonatology, Hainan Women and Children's Medical Center, Haikou (L.Y.), the Department of Neonatology, Xiamen Children's Hospital, Xiamen (X.X.), and the Department of Neonatology, the People's Hospital of Dehong, Mangshi (Z.Y.) — all in China; the Department of Neonatology, Oslo University Hospital, Oslo (S.F., T.N.); the Department of Neonatal Medicine, Royal Hospital for Children, Glasgow (A.M.H.), and the Neonatology Department, University Hospital Wishaw, Wishaw (K.M.) — both in the United Kingdom; the Department of Pediatrics (G.P., B.U.) and the Research Unit for Neonatal Micro- and Macrocirculation (G.P.), Medical University of Graz, Graz, Austria; the Division of Neonatology and Pediatric Intensive Care Medicine, Center for Pediatrics and Adolescents Medicine, Medical Center—University of Freiburg, and the Faculty of Medicine, University of Freiburg, Freiburg, Germany (H.F., J. Baumgartner); the Department of Neonatology, St. John's Medical College, Bangalore, India (S.N., S.A.R.); the Division of Neonatology, Department of Pediatrics, Loma Linda University Children's Hospital, Loma Linda, CA (A.O.H., M.M.K.); the Division of Neonatology, University of Utah Hospital, Salt Lake City (M. Baserga); the Department of Pediatrics, Division of Newborn Medicine, Washington University School of Medicine, St. Louis (Z.V.); INSERM Unité 1141, University of Paris, Paris (O.B.); and the Division of Pediatrics—Neonatal-Perinatal, UT Southwestern, Dallas (L. Chalak).

REFERENCES

- Blencowe H, Cousens S, Oestergaard MZ, 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.
- Stoll BJ, Hansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics* 2010;126:443-56.
- Adams-Chapman I, Heyne RJ, DeMauro SB, et al. Neurodevelopmental impairment among extremely preterm infants in the Neonatal Research Network. *Pediatrics* 2018;141(5):e20173091.
- Kluckow M. The pathophysiology of low systemic blood flow in the preterm infant. *Front Pediatr* 2018;6:29.
- Greisen G. Autoregulation of cerebral blood flow in newborn babies. *Early Hum Dev* 2005;81:423-8.
- Weisz DE, Yoon E, Dunn M, et al. Duration of and trends in respiratory support among extremely preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2021;106:286-91.
- Greisen G, Trojaborg W. Cerebral blood flow, PaCO₂ changes, and visual evoked potentials in mechanically ventilated, preterm infants. *Acta Paediatr Scand* 1987;76:394-400.
- Greisen G, Vannucci RC. Is periventricular leucomalacia a result of hypoxic-ischaemic injury? Hypocapnia and the preterm brain. *Biol Neonate* 2001;79:194-200.
- Topp M, Uldall P, Greisen G. Cerebral palsy births in eastern Denmark, 1987–90: implications for neonatal care. *Paediatr Perinat Epidemiol* 2001;15:271-7.
- Martini S, Frabboni G, Rucci P, et al. Cardiovascular and cerebrovascular responses to cardio-respiratory events in preterm infants during the transitional period. *J Physiol* 2020;598:4107-19.
- Sortica da Costa C, Cardim D, Molnar Z, et al. Changes in hemodynamics, cerebral oxygenation and cerebrovascular reactivity during the early transitional circulation in preterm infants. *Pediatr Res* 2019;86:247-53.
- Hyttel-Sørensen S, Pellicer A, Alderliesten T, et al. Cerebral near infrared spectroscopy oximetry in extremely preterm infants: phase II randomised clinical trial. *BMJ* 2015;350:g7635.
- Hansen ML, Hyttel-Sørensen S, Jakobsen JC, et al. Cerebral near-infrared spectroscopy monitoring (NIRS) in children and adults: a systematic review with meta-analysis. *Pediatr Res* 2022 February 22 (Epub ahead of print).
- 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.
- Hansen ML, Pellicer A, Gluud C, et al. Cerebral near-infrared spectroscopy monitoring versus treatment as usual for extremely preterm infants: a protocol for the SafeBoosC randomised clinical phase III trial. *Trials* 2019;20:811.
- Hansen ML, Pellicer A, Gluud C, 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* 2019;20:746.
- European Medicines Agency. Guideline for good clinical practice E6 (R2). EMA/CHMP/ICH/135/1995. December 1, 2016 (https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-good-clinical-practice-e6r2-step-5_en.pdf).
- Olsen MH, Hansen ML, Safi S, et al. Central data monitoring in the multicentre randomised SafeBoosC-III trial — a pragmatic approach. *BMC Med Res Methodol* 2021;21:160.
- 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(4):F291-F298.
- Duvall MG, Burns JP. Better late than never? Deferred consent for minimal risk research in the ICU. *Crit Care Med* 2017;45:1571-2.
- Greisen G, Leung T, Wolf M. Has the time come to use near-infrared spectroscopy as a routine clinical tool in preterm infants undergoing intensive care? *Philos Trans A Math Phys Eng Sci* 2011;369:4440-51.
- Pellicer A, Greisen G, Benders 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.
- Kleiser S, Ostojic D, Andresen B, et al. Comparison of tissue oximeters on a liquid phantom with adjustable optical properties: an extension. *Biomed Opt Express* 2017;9:86-101.
- Hansen ML, Rasmussen MI, Rubin S, et al. Pilot test of an online training module on near-infrared spectroscopy monitoring for the randomised clinical trial SafeBoosC-III. *Trials* 2020;21:356.
- International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. *Arch Ophthalmol* 2005;123:991-9.
- Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing

- data in randomised clinical trials — a practical guide with flowcharts. *BMC Med Res Methodol* 2017;17:162.
27. Savović J, Turner RM, Mawdsley D, 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.
28. Gilles F, Gressens P, Dammann O, Leviton A. Hypoxia-ischemia is not an antecedent of most preterm brain damage: the illusion of validity. *Dev Med Child Neurol* 2018;60:120-5.
- Copyright © 2023 Massachusetts Medical Society.

CLINICAL TRIAL REGISTRATION

The *Journal* requires investigators to register their clinical trials in a public trials registry. The members of the International Committee of Medical Journal Editors (ICMJE) will consider most reports of clinical trials for publication only if the trials have been registered. Current information on requirements and appropriate registries is available at www.icmje.org/about-icmje/faqs/.
