

## Consensus on Science with Treatment Recommendations (COSTR) October 24, 2024

**Near Infrared Spectroscopy during Respiratory Support at Birth**

*This CoSTR is a final version prepared by ILCOR and is labelled “draft” to allow for public comments and to comply with copyright rules of journals. The ‘draft label’ will be removed from this website once a summary article has been published in a scientific journal.*

## Conflict of Interest Declaration

The ILCOR Continuous Evidence Evaluation process is guided by a rigorous ILCOR Conflict of Interest policy. The following Task Force members and other authors were recused from the discussion as they declared a conflict of interest: None

The following Task Force members and other authors declared an intellectual conflict of interest, and this was acknowledged and managed by the Task Force Chairs and Conflict of Interest committees:

Georg Schmölzer has written several papers on near-infrared spectroscopy in the delivery room, including the two studies analyzed in this review {Pichler 2023 e072313, Pichler 2016 73} and he was excluded from decisions about these studies.

This author acknowledged his potential intellectual conflicts of interest and participated in the Task Force discussion of the consensus on science and treatment recommendations.

## CoSTR Citation

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**Methodological Preamble and Link to Published Systematic Review**

Preterm birth may have lifelong consequences for neurodevelopmental outcomes such as cerebral palsy and learning difficulties with resulting social and health economic implications. Initial oxygenation is a determinant of morbidity and mortality in premature infants. There is evidence that suggests that although preterm infants may reach early target peripheral oxygen saturations (SpO2), regional cerebral oxygen saturation (crSO2) measured with near-infrared spectroscopy (NIRS) may be low. A low crSO2 may be a risk factor for intraventricular hemorrhage {Baik 2015 F422}.

The question whether monitoring of crSO2 with a dedicated treatment guideline in addition to standard care improves outcomes when compared to standard care alone has not been reviewed by the International Liaison Committee on Resuscitation (ILCOR) previously. Severe intraventricular hemorrhage (Papile grade III or IV) and/or periventricular leukomalacia may impact the outcome survival without neurodevelopmental impairment, all defined as critical outcomes {Strand 2020 328}. If the intervention reduces severe intraventricular hemorrhage and/or periventricular leukomalacia in preterm infants, this would be of anticipated substantial benefit to the target population.

Up to five percent of newborn infants require positive pressure respiratory support {Skare 2016 25}, with a higher incidence in preterm infants and those receiving continuous positive airway pressure (CPAP). As the use of NIRS may help optimizing the delivery of respiratory support (CPAP and/or intermittent positive pressure ventilation (IPPV)) to avoid both cerebral hypoxia and hyperoxia {Pichler 2017 29}, the ILCOR Neonatal Life Support (NLS) Task Force (TF) considered that the effectiveness of monitoring crSO2 with NIRS and a dedicated treatment guideline in addition to standard care should be evaluated. The topic was prioritized by the NLS TF for consideration after the publication of a recent multicenter randomized controlled trial {Pichler 2023 e072313}.

A systematic review and knowledge synthesis may impact existing ILCOR recommendations for respiratory support at birth and identify knowledge gaps to be addressed in future research.

In this context, a search for evidence for monitoring crSO2 with NIRS and a dedicated treatment guideline in addition to standard care at birth was performed. The population of interest included term infants, in addition to preterm infants. The continuous evidence evaluation process for the creation of Consensus of Science and Treatment Recommendations (CoSTR) started with a systematic review (PROSPERO 2024 CRD42024511496) conducted by Vix Monnelly, Firdose Nakwa, Justin B Josephsen, Georg M Schmölzerand Anne Lee Solevåg. Evidence from neonatal literature was sought and considered by the NLS TF and clinical content experts. These data were taken into account when formulating the Treatment Recommendations.

## Systematic Review

Monnelly V, Nakwa F, Josephsen JB, Schmölzer GM, Solevåg AL, Rabi Y, Wyckoff MH, Weiner GM, Liley HG; on behalf of the International Liaison Committee on Resuscitation Neonatal Life Support Task Force. Near Infrared Spectroscopy during Respiratory Support at Birth: A Systematic Review. To be submitted

## PICOST

**Population:** Newborn infants receiving CPAP and/or IPPV (any interface) during stabilization/resuscitation at birth

**Intervention:** Monitoring of crSO2 with a dedicated treatment guideline in addition to clinical assessment, pulse oximetry and/or electrocardiogram (ECG)

**Comparison:** Clinical assessment, pulse oximetry and/or ECG only

**Outcomes:**

*Primary outcome:* Survival without neurodevelopmental impairment (Critical)

*Secondary outcomes:*

* Survival (Critical)
* Neurodevelopmental impairment (Critical)
* Response to resuscitation:
	+ crSO2 <10th or >90th percentile (Important – Task Force defined),
	+ Maximum FiO2 used (Important – Task Force defined)
	+ Total oxygen exposure (Important – Task Force defined)
	+ In infants < 34 weeks
		- Severe intraventricular hemorrhage (Papile grade III or IV) {Papile 1978 529} (Critical)
		- Periventricular leukomalacia (Critical)

Outcomes ratings using the GRADE classifications of critical or important were decided according to a consensus for international neonatal resuscitation guidelines {Strand 2020 328}, unless otherwise specified. Outcomes were converted into main outcomes and additional outcomes for submission to PROSPERO (CRD42024511496).

Potential subgroups were defined *a priori*: methods of NIRS (brand, manufacturer); CPAP versus IPPV; Cord management strategy, i.e., immediate/delayed cord clamping or cord milking; Sex, Gestational age (weeks): <280/7; 280/7 -336/7; and 340/7 or more

## Study Design: Randomized controlled trials (RCTs) and nonrandomized studies (non-RCTs, interrupted time series, controlled before-and-after studies, and cohort studies) were eligible for inclusion. Case series, case reports, animal studies and unpublished studies (conference abstracts, trial protocols) were excluded.

## Timeframe: All years and all languages were included provided there was an English abstract. The literature was first searched on February 16th 2024, and updated November 6 2024. No additional studies were identified in the updated search.

**Definitions:**

* NIRS - A real time, non-invasive method for estimating cerebral oxygen supply and consumption using reflectance spectroscopy to detect changes in oxygenation status of hemoglobin in the cerebral circulation. Results are influenced by cardiac output, acid-base status, oxygen saturation levels in the proximal aorta and regional perfusion in the brain.
* crSO2 – Measurement, using standardized placement of cerebral oximeter probes on the scalp, of the saturation of hemoglobin in an area of the brain (usually frontal cortex).
* CPAP – Continuous delivery of air or a mixture of oxygen and air by positive pressure into the lungs. Delivered through a non-invasive interface.
* IPPV – Intermittent delivery of air or a mixture of oxygen and air by positive pressure into the lungs. Delivered through a non-invasive interface or endotracheal tube.
* Periventricular leukomalacia: Transient flares or white matter injury adjacent to the cerebral ventricles diagnosed by any imaging exam at any time before hospital discharge.
* Resuscitation (newborn): Interventions provided for the restoration /preservation of life by the establishment and/or maintenance of airway, breathing and circulation, and related emergency care, including such measures when used to promote transition from intrauterine to extrauterine life.
* A dedicated treatment guideline: In the case of pulse oximetry oxygen saturation within the normal range, but crSO2 <10th or >90th percentile {Pichler 2013 1558}, the fraction of inspired oxygen is titrated to reach target crSO2.

**PROSPERO registration:** 2024 CRD42024511496

**Risk of Bias:**

We used the GRADE approach {Guyatt 2008 924} to determine the certainty of evidence for each outcome deemed critical or important with the relevant risk of bias instrument: Cochrane risk of bias tool 2 for RCTs. {Sterne 2019 l4898}

**Consensus on Science**

A search of Medline, Embase, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials identified 515 references. After removal of one duplicate, titles and abstracts were screened and full text review was conducted for 13 papers. Two RCTs {Pichler 2023 e072313, Pichler 2016 73} with a similar intervention, but only some of the same outcomes were included.

{Pichler 2016 73} included 60 infants <34 weeks (pilot study) and {Pichler 2023 e072313} included 607 preterm infants <32 weeks (phase 3 RCT). Briefly, the intervention was using crSO2 values to provide respiratory support or to adjust FiO2 provided that SpO2 was between the 10th and 90th percentile {Pichler 2013 1558}. In the control group, respiratory support and FiO2 was guided by SpO2 only.

For the critical outcome of **survival, clinical benefit or harm could not be excluded** (Relative risk (RR) 1.02, 95% CI 0.99 to 1.05), **low certainty evidence** from 667 infants included in 2 RCTs {Pichler 2023 e072313, Pichler 2016 73}. The certainty of evidence was downgraded for very serious imprecision due to optimal information size not being met.

For the critical outcome of **severe intraventricular hemorrhage, clinical benefit or harm could not be excluded** (RR 0.76, 95% CI 0.38 to 1.54), **very low certainty evidence** from 667 infants included in 2 RCTs {Pichler 2023 e072313, Pichler 2016 73}. The certainty of evidence was downgraded for risk of bias and very serious imprecision.

For the critical outcome of **periventricular leukomalacia, clinical benefit or harm could not be excluded** (RR 1.93, 95% CI 0.66 to 5.70), **very low certainty evidence** from667 infants included in 2 RCTs infants {Pichler 2023 e072313, Pichler 2016 73}. The certainty of evidence was downgraded for risk of bias and very serious imprecision.

For the important outcome of **regional cerebral tissue oxygen saturation <10th percentile {Pichler 2013 1558}clinical benefit or harm could not be excluded** (RR 1.00, 95% CI 0.78 to 1.29), **very low certainty evidence** from 60 infants included in one RCT {Pichler 2016 73}. The certainty of evidence was downgraded for risk of bias and very serious imprecision.

The important outcome **maximum FiO2** (one RCT involving 607 infants {Pichler 2023 e072313}, was “slightly higher”, 0.48 (0.45-0.50) vs. 0.44 (0.42-0.46) in the intervention vs. control group. The highest FiO2 was used at 5 min in both groups with a corresponding SpO2 of 77.6 (76.1-79.2) and 78.3 (76.7-79.8), respectively. Thus, **clinical benefit or harm** from monitoring of crSO2 with a dedicated treatment guideline in addition to clinical assessment, pulse oximetry and/or ECGcompared to clinical assessment, pulse oximetry and/or ECG only **could not be excluded.**

Table 1 (attachment)

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No data were found for the critical outcomes survival without neurodevelopmental impairment and neurodevelopmental impairment; and no data were found for the important outcomes crSO2 saturation >90th percentile {Pichler 2013 1558} and total oxygen exposure.

Thus, based on the available evidence, clinical benefit or harm associated with delivery room monitoring of crSO2 with a dedicated treatment guideline in addition to clinical assessment, pulse oximetry and/or ECG over clinical assessment, pulse oximetry and/or ECG only could not be excluded. This includes the critical outcomes severe intraventricular hemorrhage (Papile grade III or IV) and periventricular leukomalacia. However, due to the low sample sizes and imprecision of the results, the desirable effects are presently uncertain.

No data were found on pre-specified subgroups: methods of NIRS (both studies used the same method for monitoring of crSO2), CPAP versus IPPV; Cord management strategy, i.e., immediate/delayed cord clamping or cord milking; Sex, Gestational age (weeks): <280/7; 280/7 -336/7; and 340/7 or more. One RCT involving 607 infants {Pichler 2023 e072313} stratified outcomes by gestational age <28 weeks or $\geq $28 weeks. There was no difference in survival or severe intraventricular hemorrhage leukomalacia between the intervention and control in these subgroups

Table 2 (attachment)

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**Treatment Recommendations**

In newborn infants receiving CPAP and/or IPPV immediately after birth, there is insufficient evidence to recommend for or against use of delivery room monitoring of crSO2 with a dedicated treatment guideline in addition to (and in comparison with) clinical assessment and pulse oximetry with or without ECG (very low certainty evidence). However, concerns about clinical effectiveness, resources, equity, acceptability and feasibility led the Task Force to make the following recommendation:

In the absence of evidence of benefit or harm, delivery room monitoring of cerebral oxygen saturation with a dedicated treatment guideline should only be considered where resources permit and ideally in the context of a structured research trial or to close knowledge gaps.

## Justification and Evidence to Decision Framework Highlights

In making this recommendation, the Neonatal Life Support Task Force acknowledges the following:

No specific device cost or training cost were reported in the trials. However, the cost of purchasing and implementing new devices is significant. In addition, there are several human factor issues that should be addressed if monitoring of crSO2 is being implemented in clinical practice.

The lack of clinical benefit and the lack of cost-effectiveness data, contributed to the recommendation statement.

Purchasing NIRS equipment and training of personnel in its use and interpretation are expected to increase costs and require personnel resources. Implementing monitoring of crSO2 with a dedicated treatment guideline into routine clinical practice is expected to require significant training and cost. Human factor issues also need to be addressed should monitoring of crSO2 with a dedicated treatment guideline be more widespread (see Research priorities section below). Additional monitoring equipment might distract healthcare professionals from focusing on the infant.

We place value on not allocating human and financial resources to an intervention yet to be proven to be associated with a benefit for critical or important outcomes.

Units that implement monitoring of crSO2 in the delivery room should consider monitoring and evaluating acceptability amongst staff, as well as resource requirements including a potential need for more people attending deliveries, as well as training requirements.

## Knowledge Gaps

Research priorities should include human factors, opportunities to reduce inequity, and cost-benefit analysis.

Potential research questions are listed below:

* What are the training requirements to achieve and maintain competency in interpretation of crSO2 monitoring during neonatal resuscitation?
* What is the cost effectiveness for monitoring of crSO2 during neonatal resuscitation?
* Monitoring crSO2 alone versus monitoring crSO2 with a dedicated treatment guideline should also potentially be explored.
* What, if any are the important components of a treatment guideline (e.g., technical aspects including sensor placement and interventions in response to results).
* No studies addressed the critical outcomes survival without neurodevelopmental impairment and neurodevelopmental impairment.

Future studies should address these outcomes. Sufficiently powered trials to investigate a difference in the critical outcomes severe intraventricular hemorrhage and periventricular leukomalacia should also be considered.

## References

Baik N, Urlesberger B, Schwaberger B, Schmolzer GM, Avian A, Pichler G. Cerebral haemorrhage in preterm neonates: does cerebral regional oxygen saturation during the immediate transition matter? Archives of disease in childhood Fetal and neonatal edition. 2015;100(5)F422-7.

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj. 2008;336(7650)924-6.

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(4)529-34.

Pichler G, Binder C, Avian A, Beckenbach E, Schmolzer GM, Urlesberger B. Reference ranges for regional cerebral tissue oxygen saturation and fractional oxygen extraction in neonates during immediate transition after birth. J Pediatr. 2013;163(6)1558-63.

Pichler G, Goeral K, Hammerl M, Perme T, Dempsey EM, Springer L, et al. Cerebral regional tissue Oxygen Saturation to Guide Oxygen Delivery in preterm neonates during immediate transition after birth (COSGOD III): multicentre randomised phase 3 clinical trial. BMJ. 2023;380e072313.

Pichler G, Schmolzer GM, Urlesberger B. Cerebral Tissue Oxygenation during Immediate Neonatal Transition and Resuscitation. Front Pediatr. 2017;529.

Pichler G, Urlesberger B, Baik N, Schwaberger B, Binder-Heschl C, Avian A, et al. Cerebral Oxygen Saturation to Guide Oxygen Delivery in Preterm Neonates for the Immediate Transition after Birth: A 2-Center Randomized Controlled Pilot Feasibility Trial. J Pediatr. 2016;17073-8 e1-4.

Skare C, Boldingh AM, Nakstad B, Calisch TE, Niles DE, Nadkarni VM, et al. Ventilation fraction during the first 30s of neonatal resuscitation. Resuscitation. 2016;10725-30.

Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366l4898.

Strand ML, Simon WM, Wyllie J, Wyckoff MH, Weiner G. Consensus outcome rating for international neonatal resuscitation guidelines. Archives of disease in childhood Fetal and neonatal edition. 2020;105(3)328-330.