PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Supplemental oxygen strategies in infants with bronchopulmonary dysplasia after the Neonatal Intensive Care Unit period: study protocol for a randomised controlled trial (SOS BPD study)
AUTHORS	Balink, Stephanie; Onland, Wes; Vrijlandt, Elianne; Andrinopoulou, Eleni-Rosalina; Bos, Arend; Dijk, Peter; Goossens, Lucas; Hulsmann, Anthon; Nuytemans, Debbie; Reiss, Irwin; Sprij, Arwen; Kroon, André; van Kaam, Anton; Pijnenburg, Marielle; the SOS BPD study group, on behalf of

VERSION 1 – REVIEW

REVIEWER	Shi, Yuan Chongqing Medical University Affiliated Children's Hospital, Neonatology
REVIEW RETURNED	11-Mar-2022

GENERAL COMMENTS	Interesting study. Good design.

REVIEWER	Vali, Payam UC Davis Department of Medicine
REVIEW RETURNED	23-Mar-2022

GENERAL COMMENTS	The optimal oxygen saturation in patients with bronchopulmonary dysplasia is not known. In the submitted study protocol, the authors describe a non-blinded randomized control trial comparing two different SpO2 targets (lower limit of 90% vs. lower limit of 95%) in former < 32 week gestation premature infants diagnosed with moderate to severe BPD at post-menstrual age of 36 weeks. The manuscript is well written includes relevant citations and adheres to the SPIRIT guidelines. I have the following comments/suggestions: - The authors need to take into consideration that the actual difference between the lower and higher SpO2 groups will likely be less than the intended 5%. I suspect that many of the patients that transition to low flow 100% O2 by nasal cannula prior to discharge home (including those who met criteria for severe BPD at 36 weeks postmenstrual age -PMA) will have SpO2 close to 100%. It is not uncommon for patients with a diagnosis of severe BPD to require as little as 1/8 LPM O2 and who maintain SpO2 > 95%. The power calculation that was based on a true difference of 5% between groups, may therefore not be sufficient to show any differences in outcomes in an intention to treat analysis. - The authors state that they had started enrollment in 2020 -have

	they enrolled enough patients to conduct an interim analysis to look at the difference in SpO2 between the groups? How many patients randomized to the low SpO2 group are maintaining SpO2 > 95% on minimal flow? - Can the authors clarify why adjusting/weaning of respiratory support was not standardized, particularly once patients are transitioned to low flow nasal cannula? - Can the authors comment on what weaning/escalating strategies are currently used for patients on low flow nasal cannula when patients do not maintain their assigned SpO2? Is the FIO2 adjusted or are patients receiving 100 O2 and the flow is adjusted? - The authors should consider adding retinopathy of prematurity (ROP) progression as a secondary outcome. There is evidence to suggest that higher SpO2 may prevent progression of ROP. It would be interesting to know if patients assigned to the lower SpO2 limit have higher rates of severe ROP. - Will the authors collect data on the incidence of BPD associated pulmonary hypertension (BPD-PH)? - Can the authors clarify if patients who have a diagnosis of BPD-PH will be included in the randomization? Is there equipoise at the sites in this study to accept SpO2 saturations as low as 90% when PH is present? - Can the authors comment why they have not elected to use one of the more recent BPD definitions (e.g. Higgins RD et al 2018 or Jensen EA et al 2019)? - Owing to the limitations of the current BPD diagnostic criteria, there is great pulmonary disease heterogeneity between severe and moderate cases (which can range from intubated patients on high FIO2 requirements to patients on CPAP on ambient air). How will the authors account for the confounding effect of disease severity on outcomes? - Can the authors clarify at what gestational age randomization will occur?

REVIEWER	Carlo, Waldemar University of Alabama at Birmingham, Pediatrics
REVIEW RETURNED	05-Apr-2022

GENERAL COMMENTS	This is an excellent research idea. The protocol is very well developed and written. I only have a few minor suggestions. General comments This is an important protocol as weak observational data suggest that higher oxygen saturations improve weight gain but the evidence is weak and practice varies. The protocol is very well developed and written. I only have minor suggestions. Methods In the Summary of strengths and limitations, it is stated that data collection on oxygen saturation profiles will be performed twice (in hospital) or once (at home) weekly. In the Methods section it is stated that it will be done daily (or twice daily, not clear) in the

	hospital and weekly at home. Please clarify. In the Methods section; the daily logging of the data is not clear. In Table 2, it is unclear if the severe category includes both invasive and non-invasive support. While this classification is acceptable, the prediction based on this classification varies, which resulted in a newer classification that the investigators may want to consider. Because the block sizes are relatively small and the treatment is open labelled, it would be important for the clinicians not knowing what the block sizes are. Larger block sizes may be possible for the larger centers. While it will be controversial to mask or not the treatment group, I agree with the current plans (even though I am an advocate usually of masking the intervention) given the high emotional aspects of the care and the usual focus on oxygen saturations. Minor comments In the list of participating hospitals' table, principle should be changed to principal.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Yuan Shi, Chongqing Medical University Affiliated Children's Hospital Comments to the Author:
Interesting study. Good design.

We would like to thank Dr. Yuan Shi for the positive comments on our study.

Reviewer: 2
Dr. Payam Vali, UC Davis Department of Medicine Comments to the Author:

Thank you very much for your comments, Dr. Vali.

The authors need to take into consideration that the actual difference between the lower and higher SpO2 groups will likely be less than the intended 5%. I suspect that many of the patients that transition to low flow 100% O2 by nasal cannula prior to discharge home (including those who met criteria for severe BPD at 36 weeks postmenstrual age -PMA) will have SpO2 close to 100%. It is not uncommon for patients with a diagnosis of severe BPD to require as little as 1/8 LPM O2 and who maintain SpO2 > 95%. The power calculation that was based on a true difference of 5% between groups, may therefore not be sufficient to show any differences in outcomes in an intention to treat analysis.

We agree that the actual difference between the high and low SpO2 groups might be less than 5%. We try to avoid this by making the SpO2 profiles. Treating physicians will wean the supplemental oxygen as usual, but based on a lower SpO2 limit as randomized by the study. However, with the SpO2 profiles that we make twice weekly in the hospital or once weekly at home, we check for the actual mean SpO2 in the infants in the trial. If this SpO2 is too much above the limit, we discuss with the treating physicians to wean more vigorously. For example, in a child that has been randomized to the 90% group and has mean saturations of 95%, we will discuss with the treating physician that weaning of oxygen can be more fast. Therefore we are confident that our sample size is adequate.

The authors state that they had started enrollment in 2020 -have they enrolled enough patients to

conduct an interim analysis to look at the difference in SpO2 between the groups? How many patients randomized to the low SpO2 group are maintaining SpO2 > 95% on minimal flow?

We plan an interim-analysis (also for safety reasons) after 50 patients have reached their primary outcome at 6 months. We expect to reach this in 2 months.

Can the authors clarify why adjusting/weaning of respiratory support was not standardized, particularly once patients are transitioned to low flow nasal cannula?

There is no standard protocol in the Netherlands for weaning supplemental oxygen. As 30 centers participate, for feasibility reasons we decided not to intervene in weaning strategies but only compare the 2 lower SpO2 limits for weaning. For centers that did not have a weaning protocol we developed a standard operating procedure how to decrease or increase oxygen supplementation while on CPAP, HFNC or low flow. This SOP is attached as online supplemental file 4 now.

Can the authors comment on what weaning/escalating strategies are currently used for patients on low flow nasal cannula when patients do not maintain their assigned SpO2? Is the FIO2 adjusted or are patients receiving 100 O2 and the flow is adjusted?

We refer to the SOP, in supplemental file 4.

The authors should consider adding retinopathy of prematurity (ROP) progression as a secondary outcome. There is evidence to suggest that higher SpO2 may prevent progression of ROP. It would be interesting to know if patients assigned to the lower SpO2 limit have higher rates of severe ROP.

We agree with the reviewer and have 2 comments here: First, patients with ROP for which the ophthalmologist recommends a patient specific SpO2 target are excluded from the study.
Second, retinopathy of prematurity that has progressed to a stage where (laser coagulation) treatment is necessary, is considered a clinical significant safety outcome if it arises after the start of trial. In the Data Safety Monitoring Board (DSMB) charter it has been indicated as follows: ‘Stopping may be considered at a safety analysis if there is an absolute difference of at least 20% in the aforementioned stage of ROP (with treatment) between the intervention group and the expectative group and a two-sided p-value of less than 0.05 (unblinded analyses) for this difference is obtained. All outcomes will then be evaluated to reach a recommendation on early stopping.’ In the manuscript we added ROP (progression) as secondary outcome (page 14, line 292-3).

Will the authors collect data on the incidence of BPD associated pulmonary hypertension (BPD-PH)?

We will collect data on pulmonary hypertension before 36 weeks PMA (baseline data). As during follow up of patients with BPD there is no regular screening on pulmonary hypertension in the Netherlands, BPD-PH will not be assessed routinely. However, in some centers there is a routine screening for PH and data of this screening (by echocardiography) will be used in a subgroup of infants as secondary outcome (page 14, line 296/297).

Can the authors clarify if patients who have a diagnosis of BPD-PH will be included in the randomization? Is there equipoise at the sites in this study to accept SpO2 saturations as low as 90% when PH is present?

Patients with pulmonary hypertension with medical treatment (such as sildenafil) will be excluded from the study (page 10, line 185-186)

Can the authors comment why they have not elected to use one of the more recent BPD definitions

(e.g. Higgins RD et al 2018 or Jensen EA et al 2019)?

We fully agree that the definition of BPD is under debate. Here we use the definition which is accepted in the Dutch 2021 BPD guideline. (NVK - Richtlijn)

Owing to the limitations of the current BPD diagnostic criteria, there is great pulmonary disease heterogeneity between severe and moderate cases (which can range from intubated patients on high FIO2 requirements to patients on CPAP on ambient air). How will the authors account for the confounding effect of disease severity on outcomes?

We will stratify for disease severity (page 10, line 197).

Can the authors clarify at what gestational age randomization will occur?

Randomization will occur between 36 and 38 weeks postmenstrual age. We added this on page 10, line 191.

Reviewer: 3
Dr. Waldemar Carlo, University of Alabama at Birmingham Comments to the Author:

Thank you very much Dr Carlo for your comments.

In the Summary of strengths and limitations, it is stated that data collection on oxygen saturation profiles will be performed twice (in hospital) or once (at home) weekly. In the Methods section it is stated that it will be done daily (or twice daily, not clear) in the hospital and weekly at home. Please clarify.

In the methods section it is stated that 'During hospitalization, respiratory support and oxygen supplementation will be adjusted based on the assigned lower limit of SpO2, as part of daily clinical care. Twice a week, SpO2 data will be logged from pulse oximeters.' This means that weaning of oxygen is allowed daily as indicated by normal clinical care. However, profiles are only made twice weekly to check if the assigned lower limit of SpO2 is well kept and the medical team will be encouraged to actively wean or increase supplemental oxygen based on the profiles.
Similarly: 'In case participants are discharged on home oxygen, SpO2 data will be logged from a pulse oximeter at home by the parents once weekly.' (page 11, lines 213-222)

In the Methods section; the daily logging of the data is not clear.

The logging of the SpO2 data is as follows:
SpO2 data will be logged from the pulse oximeters and stored on a USB stick. Logging frequency differs from 0.25 to 1 Hertz, depending on the type of pulse oximeter that is used in the respective hospitals. All data downloaded from a pulse oximeter is anonymous, since no patient characteristics are saved on it. Downloaded data will be pseudonomysed with a study and patient specific number by the local researcher who logged the data. Pseudonymised data will then be sent through encrypted file transfer to the researchers. In some hospitals, all clinical data derived from monitoring a patient (for instance oxygen saturation and heart rate), is automatically saved in a central server based storage and can be accessed and downloaded with permission of the hospital or department by the local researcher. If this is the case, we will ask for the oxygen saturation and heart rate data from the digital storage, instead of downloading it from the pulse oximeter, since it saves time and equipment. This data will also be pseudonymised and be sent to the researchers in the same way as when the data was downloaded from the pulse oximeter.
We added 2 sentences on the data logging in order to clarify the process on page 11, lines 217-219.

In Table 2, it is unclear if the severe category includes both invasive and non-invasive support. While this classification is acceptable, the prediction based on this classification varies, which resulted in a newer classification that the investigators may want to consider.

We used the BPD definition as mentioned in the Dutch BPD guideline of 2021, although we agree with the reviewer that this definition is under debate and newer definitions are available. The severe category includes invasive and non-invasive support. We clarified this in the table.

Because the block sizes are relatively small and the treatment is open labelled, it would be important for the clinicians not knowing what the block sizes are. Larger block sizes may be possible for the larger centers.

Most centers will not include more than 3-4 patients during the study. Clinicians are not aware of the block sizes which vary from 4 to 8. Bigger centers such as Erasmus MC will have bigger block sizes than smaller centers.

While it will be controversial to mask or not the treatment group, I agree with the current plans (even though I am an advocate usually of masking the intervention) given the high emotional aspects of the care and the usual focus on oxygen saturations.

We choose to make the study as feasible as possible and as generalizable as possible and are happy that Dr. Carlo agrees with this open study.

Minor comments
In the list of participating hospitals' table, principle should be changed to principal.

Thank you, we changed this typo.

We feel our manuscript improved with the help of the reviewers and hope our manuscript is acceptable now for publication.

VERSION 2 – REVIEW

REVIEWER	Vali, Payam UC Davis Department of Medicine
REVIEW RETURNED	19-May-2022

GENERAL COMMENTS	The authors have satisfactorily addressed my comments/suggestions. Thank you

REVIEWER	Carlo, Waldemar University of Alabama at Birmingham, Pediatrics
REVIEW RETURNED	18-May-2022

GENERAL COMMENTS	The authors have well answered each of the reviewers concerns and edited the manuscript accordingly.