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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)

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Bronchopulmonary dysplasia, prematurity, supplemental oxygen, growth, weight, lung function, oxygen saturation

ABSTRACT

Introduction: Supplemental oxygen is the most important treatment for preterm born infants with established bronchopulmonary dysplasia (BPD). However, it is unknown what oxygen saturation levels are optimal to improve outcomes in infants with established BPD from 36 weeks postmenstrual age (PMA) onwards. The aim of this study is to compare the use of a higher oxygen saturation limit (≥ 95%) to a lower oxygen saturation limit (≥ 90%) after 36 weeks PMA in infants diagnosed with moderate or severe BPD.

Methods and analysis: This non-blinded, multicentre, randomised controlled trial will recruit 198 preterm born infants with moderate or severe BPD between 36 and 38 weeks PMA. Infants will be randomised to either a lower oxygen saturation limit of 95% or to a lower limit of 90%; supplemental oxygen and/or respiratory support will be weaned based on the assigned lower oxygen saturation limit. Adherence to the oxygen saturation limit will be assessed by extracting oxygen saturation profiles from pulse oximeters regularly, until respiratory support is stopped. The primary outcome is the weight standard deviation score at six months corrected age. Secondary outcomes include anthropometrics collected at six and twelve months corrected age, re-hospitalizations, respiratory complaints, infant stress, parental quality of life and cost-effectiveness.

Ethics and dissemination: Ethical approval for the trial was obtained from the Medical Ethics Review Committee of the Erasmus University Medical Centre, Rotterdam, the Netherlands (MEC-2018-1515). Local approval for conducting the trial in the participating hospitals has been, or will be obtained from the local institutional review boards. Informed consent will be obtained from the parents or legal guardians of all study participants.

Trial registration: Dutch Trial Registry (www.trialregister.nl): NL7149 / NTR7347; registered on July 10, 2018.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first randomised controlled trial that aims to identify the optimal lower limit of oxygen saturation for infants with moderate or severe bronchopulmonary dysplasia to improve growth and respiratory health.
- Adherence to the assigned limit for weaning supplemental oxygen will be increased by collecting oxygen saturation profiles twice (in hospital) or once (at home) weekly.
- Limitations of this study are that the study is not blinded and that protocols amongst the participating centres to wean oxygen or respiratory support are not standardized.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is the most common complication of extreme preterm birth. The pathogenesis of BPD is complex and multifactorial: pre- and postnatal risk factors such as intrauterine growth restriction, pregnancy-related hypertensive disorders, mechanical ventilation and infections all may impact on the immature, developing lungs of extremely preterm infants.(1) As a consequence, there is an arrest in lung development characterized by a decreased number of alveoli, which are larger and simplified, combined with small airway injury and abnormal development of the pulmonary vasculature.(2) Despite advances in perinatal and neonatal care, the incidence of BPD remains high, affecting almost half of infants born <28 weeks' gestation who survived to 36 weeks' postmenstrual age (PMA).(3) Infants with BPD may experience poor respiratory health and impaired lung function throughout childhood, even persisting into adulthood.(4, 5) Particularly the first years of life are characterized by prolonged use of supplemental oxygen, frequent respiratory symptoms and an increased risk of hospitalization.(6, 7) Having a child with BPD also poses an important burden on family life and is associated with a decreased quality of life of caregivers.(8)

Supplemental oxygen is the most important treatment for preterm infants with established BPD. It reduces respiratory symptoms, reduces or prevents pulmonary hypertension and has possible beneficial effects on growth and neurodevelopment.(9) However, no study has ever examined the optimal oxygen saturation (SpO_2) target in children with established BPD, while both too little and too much oxygen may lead to serious adverse events.(10) Few guidelines include recommendations for SpO_2 levels in infants with BPD. The European Respiratory Society guideline on long term management of children with BPD suggests the use of a lower limit of SpO_2 of 90% when using supplemental oxygen.(11) The American

Thoracic Society Guideline on home oxygen therapy suggests a level of 93% as minimum threshold.(12) However, the level of evidence supporting these recommendations is low. This has led to substantial practice variation in the applied SpO_2 limits in infants with BPD still receiving respiratory support and/or supplemental oxygen after 36 weeks PMA.

In contrast to the limited evidence available *after* 36 weeks PMA, optimal SpO_2 targets have been extensively studied in preterm infants *before* the age of 36 weeks PMA. The Supplemental Therapeutic Oxygen for Prethreshold Retinopathy Of Prematurity (STOP-ROP) trial, the Benefits Of Oxygen Saturation Targeting (BOOST) trial and the Neonatal Oxygen Prospective Meta-analysis (NeOProM) Collaboration (including 5 randomised controlled trials) all compared different SpO_2 targets in preterm infants before 36 weeks PMA.(13-15) All trials studied slightly different SpO_2 target ranges (Table 1).

Table 1. SpO_2 target ranges in different trials (13-15)

Trial	Lower SpO_2 range	Higher SpO_2 range
STOP-ROP trial	89 – 94%	96 – 99%
BOOST trial	91 – 94%	95 – 98%
NeOProM Collaboration	85 – 89%	91 – 95%

SpO_2 = oxygen saturation

The STOP-ROP trial found no differences in progression of retinopathy of prematurity, but targeting a higher SpO_2 did lead to a higher incidence of respiratory morbidity (pneumonia or exacerbations of chronic lung disease).(13) However, this study was not designed, nor powered for respiratory outcomes. The BOOST trial found no differences between the two groups on growth or neurodevelopment at 12 months corrected age, but infants in the higher

SpO_2 range had an increased length of oxygen therapy and required home oxygen more often.(14) The meta-analysis of the NeOProM Collaboration showed that targeting a higher SpO_2 range decreased the incidence of death and necrotizing enterocolitis, but the incidence of retinopathy of prematurity requiring treatment was higher in the higher saturation group. The use of supplemental oxygen at 36 weeks PMA was higher in the group with a higher SpO_2 target range, due to the study protocol.(16) The incidence of blindness, severe hearing loss and cerebral palsy was similar across the groups.(15)

Based on the outcomes of these studies, the American Academy of Pediatrics concluded that the optimal SpO_2 range for extremely low birth weight infants remains unknown, but that an SpO_2 range of 90 to 95% may be safer than 85 to 89%.(17)

It is important to acknowledge that there are several reasons why the results of these oxygen targeting studies before 36 weeks PMA may not be extrapolated to infants with established BPD who have reached near term age. Firstly, the lungs have reached a new stage of development as alveolar growth starts from approximately 36 weeks of gestation.(18) In addition, there is a transition from lung development to lung growth in infancy and childhood, as lung volume will increase about 23 times between birth and adulthood in healthy subjects.(18) Secondly, it has been suggested that vulnerability to oxidative stress is less pronounced at 36 weeks PMA compared to the first weeks of life as antioxidant systems have matured. Thirdly, also the pulmonary vascular system undergoes important differentiation during the different stages of lung development.(19) The optimal SpO_2 range to prevent pulmonary vascular disease may be different from the range to improve pulmonary vascular disease. Therefore, infants with established BPD after 36 weeks PMA may require another approach to oxygen treatment than infants with developing BPD before 36 weeks PMA.

In summary, there is a lack of evidence on the optimal SpO_2 levels in infants with established BPD from 36 weeks PMA onwards to optimize respiratory health. Therefore, the aim of this study is to compare a higher SpO_2 (i.e. 95% lower limit) to a lower SpO_2 (i.e. 90% lower limit) in infants with moderate or severe BPD from 36 weeks PMA and onwards. Our hypothesis is that a higher SpO_2 target in infants with established moderate or severe BPD, improves weight gain and lung growth.

OBJECTIVES

The primary objective is to investigate whether a higher SpO_2 (i.e. 95% lower limit) leads to a higher weight at 6 months corrected age, as a surrogate for lung growth. Secondary objectives are to determine if a higher SpO_2 translates into higher weight and height at 12 months corrected age, less healthcare consumption, less infant stress, better quality of life for parents or caregivers and more favourable cost-effectiveness.

METHODS AND ANALYSIS

Study design and setting

The SOS BPD study is an open, randomised controlled trial and will be conducted in the Netherlands in approximately (but not limited to) 30 hospitals. In the Netherlands, the care for extremely preterm born infants is concentrated in 9 hospital clusters. Each cluster consists of one or two level 3 Neonatal Intensive Care Units (NICU) and several post-intensive care/high care (post-IC/HC) units in surrounding level 2 centres. The participating hospitals include 10 NICU centres and 20 post-IC/HC units. A list of recruiting sites is provided in online supplemental file 1. The SOS BPD study is conducted within the Neonatology Network Netherlands (N3) organization.(20)

The protocol for this trial is reported based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Checklist(21) (online supplemental file 2: SPIRIT Checklist).

Study population

Infants with moderate or severe BPD, born before 32 weeks of gestation, who still receive respiratory support at 36 weeks PMA are eligible for inclusion. BPD is defined as the use of supplemental oxygen (i.e. >21% oxygen) for ≥28 days since birth.(22) Depending on the level of respiratory support at 36 weeks PMA, BPD severity is classified as mild, moderate or severe (Table 2). An oxygen reduction test will be used to assess severity if indicated.(23)

Table 2. BPD diagnostic criteria for infants born <32 weeks PMA. Severity is classified at 36 weeks PMA.(22)

Definition of BPD	**Severity classification**		
	Mild	**Moderate**	**Severe**
Treatment with supplemental oxygen for ≥28 days	Breathing room air or nasal cannula with ≤1L flow, FiO_2 21%	Supplemental oxygen >21%, but <30%	Supplemental oxygen ≥30%, or (non-)invasive positive pressure ventilation, including HFNC

BPD = bronchopulmonary dysplasia, FiO_2 = fraction of inspired oxygen; HFNC = High Flow Nasal Cannula; L = liter; PMA = postmenstrual age

Written informed consent will be obtained from parents or legal guardians by the local PI of the hospital where the participant is admitted between 36 to 38 weeks PMA (online supplemental file 3: English version of the patient information and informed consent document). Exclusion criteria are significant congenital heart disease (not being patent ductus arteriosus, small atrial septal defect, ventricular septal defect), pulmonary hypertension with medical treatment, retinopathy of prematurity for which the ophthalmologist recommends a patient specific SpO_2 target, severe acquired upper airway abnormalities, such as subglottic stenosis and interstitial lung diseases.

Randomisation

Participants will be randomised 1:1 to one of two parallel treatment arms: weaning of supplemental oxygen and respiratory support based on an SpO_2 lower limit of 95% or weaning based on a lower limit of 90%.

For the randomisation procedure, an electronic data capture system that uses a computer-generated randomisation list (Castor EDC) will be used.(24) We will use block randomisation, with a variable block size (4 – 8). Allocation will be stratified by NICU centre (10 centres) and BPD severity (moderate or severe). In case of multiple birth, the firstborn infant will be randomised according to standard procedures. Siblings will be manually assigned to the same treatment arm as the firstborn infant.

Enrolment, registration and electronic randomisation in Castor EDC will be carried out by the local PI of the hospital where the participant is included.

This is a non-blinded study, since it is not feasible to blind treating physicians and parents for SpO_2 values as measured with pulse oximetry in the hospital or at home.

Study procedures

After randomisation, participants are assigned to one of the 2 treatment arms. A lower limit of 95% was chosen for the first group, as the median SpO_2 in preterm infants without BPD is > 95% (25) and SpO_2 >94% reduces the incidence of pulmonary hypertension.(9) Also, with a lower limit of 95% there is a clear contrast between the 2 groups. A lower limit of 90% was chosen for the second group, since this lower limit is advised in the BPD guideline of the European Respiratory Society and SpO_2 values < 90% have been associated with adverse outcomes.(11, 17)

During hospitalization, respiratory support and oxygen supplementation will be adjusted based on the assigned lower limit of SpO_2, as part of daily clinical care. Twice a week, SpO_2 data will be logged from pulse oximeters. Logging frequency differs from 0.25 to 1 Hertz, depending on the type of pulse oximeter that was used in the respective hospitals. Pseudonymised SpO_2 data will be sent to the research team using encrypted file transfer. Based on the recorded SpO_2 data and group assignment, the medical team will receive advice to actively wean or increase supplemental oxygen.

In case participants are discharged on home oxygen, SpO_2 data will be logged from a pulse oximeter at home by the parents once weekly and will be sent to the research team through encrypted file transfer. Feedback and advice to adjust supplemental oxygen will be given to the parents and treating physician.

SpO_2 profiles will be obtained until one week after discontinuation of respiratory support.

If an infant is readmitted to hospital while still on supplemental oxygen, the assigned SpO_2 lower limit will be kept. If infants are readmitted after they were weaned from supplemental oxygen for at least two weeks, the lower SpO_2 limit will be set according to the local hospital policy.

In order to follow routine clinical care as much as possible, physicians will wean supplemental oxygen according to their local hospital protocol. If no such protocol is

available, a study specific standard operating procedure will give recommendations on weaning supplemental oxygen.

In order to improve feasibility and generalizability, the use of diuretics, inhaled or oral corticosteroids, other medications, fluid restriction and feedings will be according to national guidelines or local policies. Data on these parameters will be collected during the study.

Interpretation of SpO_2 profiles

If the time spent below the assigned lower limit of SpO_2 is ≥10% of the recorded time (equivalent to <90% of the time spent above the lower limit), the treating team is advised to increase supplemental oxygen and/or respiratory support. When the SpO_2 is below the assigned lower limit for ≤10% of the time (equivalent to >90% of the time spent above the lower limit), the treating team is advised to wean supplemental oxygen and/or respiratory support.

The British Thoracic Society Guideline for home oxygen in children suggests that the lower limit target SpO2 should be met for at least 95% of a stable recording period.(9) However, this does not take into account that a 24-hour SpO_2 profile is prone to artefacts due to periods of feeding, physical activity and external manipulation of the saturation probe. Furthermore, Terrill et al. studied normative oximetry data in extreme preterm infants at term equivalent age and reported mean saturations of 96.1% (95.4–96.8%) with 7.56% (5.1–10.0%) of the measuring time spent below an SpO_2 of 90%.(26, 27) Therefore, we chose this limit of 10% below the assigned SpO_2 to adjust oxygen supplementation.

Temporary deviation of the protocol is possible if this is deemed necessary for medical reasons according to the treating physician. Reasons for these protocol deviations have to be reported to the research team.

Follow-up

The study duration will be 12 months, with two follow-up visits at 6 and 12 months corrected age. These follow-up visits follow the national neonatal follow-up program; no extra study visits are required.(28) Data that will be obtained during study visits are weight, height, head circumference, caloric intake, use of medication, respiratory complaints, number of health care visits and hospitalizations.

In a subgroup of patients, additional investigations including chest CT scan (assessed with PRAGMA-BPD scores),(29) multiple breath washout tests (Lung Clearance Index), polysomnography (baseline SpO_2, oxygen desaturation index, apnea-hypopnea index) and/or an echocardiogram will be performed, as part of routine care in some hospitals during follow-up at six months corrected age.

Parents will receive monthly online questionnaires that address the health situation of their child in the past month and also contain questions used for cost-effectiveness analyses. In addition, parents will be asked to fill in the Dutch version of the Care-Related Quality of Life instrument (CarerQoL-7D). The CarerQoL is designed to measure and value the impact of providing informal care on caregivers.(30)

At the start of the study and at the corrected age of 6 and 12 months, parents will also be asked to fill in the Dutch version of the Infant Behavior Questionnaire – Revised (IBQ-R) Very Short Form.(31) The IBQ-R is designed to measure the temperament of infants between 3 and 12 months.

Outcomes

The primary outcome of the study is weight standard deviation score (SDS) at 6 months corrected age as a surrogate for lung growth. Increased weight and weight gain during

infancy are associated with better lung function and structure.(32, 33) Appropriate growth is also an important measure of general well-being in infancy, whilst growth delay is associated with an increased risk of future respiratory and cardiovascular disease and impaired intellectual outcomes.(34, 35) Growth failure is very common in infants with BPD. The exact underlying mechanisms are unknown, but increased respiratory demands and periods of intermittent hypoxia probably play an important role.(27) Secondary outcomes are weight SDS at 12 months corrected age, height and head circumference SDS at 6 and 12 months corrected age, rate of re-hospitalisations, respiratory symptoms (including wheezing, dyspnea, exercise induced symptoms), unscheduled health care visits, infant temperament (IBQ-r), quality of life of caregivers (CarerQoL) and cost-effectiveness.

In a subgroup of infants, additional secondary outcomes are lung function (lung clearance index), lung structure as assessed with chest CT scan, and pulmonary hypertension and/or right ventricular systolic function as assessed with echocardiography at the corrected age of 6 months. These examinations are part of the standard of care protocol in some of the outpatient follow-up programs in the Netherlands.

Data collection and management

For data management Castor EDC will be used: a password protected, electronic database. Baseline characteristics including gestational age, birth weight, gender, pregnancy complications such as pre-eclampsia, past illnesses and retinopathy of prematurity will be recorded in the database at inclusion by the local research team. SpO_2 data will be entered into the database by the central research team. Data from follow-up visits will be entered by the research team of the responsible NICU, as outpatient follow-up takes place in those centres. In case of missing data, every attempt will be undertaken to retrieve the data by contacting the respective hospitals.

Collected data will be pseudonymised and coded with a unique number, complying with the European General Data Protection Regulation. The key to link participants with their data will only be accessible to the local PI of the centre of inclusion and PI of the associated NICU. Data will be stored securely and will be saved for 15 years according to national legislation. Only central study investigators will have access to all collected data.

Patient and public involvement

Parents of children with BPD and several patient associations (Lung Foundation Netherlands, European Lung Foundation and the Neonatal Parents Organization (Care4Neo)) were involved in the development of the trial. In addition, parents of preterm born infants are part of the Advisory Board of the trial. They provide their experience in improving patient information material, publications and presentations for layman and will help with implementation after finalization of the study.

Sample size estimation

A simulation study with four scenarios was performed to estimate the sample size needed with weight SDS at 6 months corrected age as primary outcome. We assumed a mixed effects model with a random intercept to account for the correlation between the patients from the same hospital. We assumed 10 clusters (10 NICU centres with post IC/HC departments in the surrounding regional hospitals) with each cluster having 16 (±3) or 18 (±3) patients. The mean weight at 6 months for the group with a lower saturation limit of 90% was assumed -1.15 SD (data from BPD cohort Erasmus MC, Rotterdam, the Netherlands, data on file). The mean weight at 6 months for the group with a lower saturation limit of 95% was assumed -0.65 SD, since a 0.5 SDS higher weight was considered clinically relevant. The variation in weight due to differences between individuals was assumed 1.18 SD, while the variation in

weight due to differences between hospitals was assumed 0.10 and 0.20 SD. The scenario with the highest power (0.83) and greatest variation of weight between the various hospital clusters (0.20 SD) was chosen. This scenario leads to a sample size of 180 patients. Accounting for a drop-out rate of 10%, we aim to include 198 infants.

Statistical analysis

Analyses will be performed on an intention-to-treat (ITT) basis. The ITT population will include all randomised infants, regardless of protocol deviations.

Comparison between the two groups for the primary endpoint will be made using a mixed effect model with a random intercept to account for the correlation between patients from the same hospital cluster. All secondary parameters will be assessed by linear mixed effect models for continuous outcomes or logistic mixed effect models for binary outcomes. BPD severity and weight at inclusion are considered relevant variables for the outcome weight SDS at 6 months. For the secondary analysis, these variables will be included in the mixed model analysis as fixed effects. Significance levels will be 0.05.

Missing values in the baseline covariates, if >10%, will be assumed to be missing at random and multiple imputations will be used. We do expect less than 10% missing data for the primary endpoint, weight SDS.

All analyses will be completed with the statistical software package R (www.rproject.org), and SPSS/PC Statistics 21.0 (SPSS Inc., Chicago, IL, USA).

Cost-effectiveness analysis

A trial-based economic evaluation will be used as a cost-effectiveness analysis performed from a societal perspective as well as from a healthcare perspective. The initial time horizon is one year. Costs will be calculated based on patient-level data on resource use inside and

outside the healthcare sector during the first year of life of the infant. If an oxygen weaning strategy leads to better health outcomes at higher costs, incremental cost-effectiveness ratios will be calculated. Depending on which treatment is more effective, these ratios will express the additional costs per unit of health gain or the savings per unit of health forgone.

Although it is very plausible that health effects and differences in costs persist or occur later in life, currently available data and literature do not allow a meaningful extrapolation after the study period. Nevertheless, the children will be followed until the age of 8 year, outside of the scope of this initial study, according to national follow-up guidelines for preterm born children. This will make it possible to track costs and effects in the longer term.

ETHICS AND DISSEMINATION

Ethical consideration

Ethical approval for the trial has been obtained from the Medical Ethics Review Committee of the Erasmus University Medical Center, Rotterdam, the Netherlands (MEC-2018-1515). Local approval for conducting the trial in the participating hospitals has been, or will be obtained from the local institutional review boards. Written informed consent will be obtained from the parents or legal guardians of all study participants, adhering the Good Clinical Practice guideline.(36)

Protocol modifications will be communicated to all relevant parties.

Safety reporting and auditing

All serious adverse events (SAE) will be reported to the approving ethics committee in accordance with national guidelines. SAEs will be collected and recorded from informed consent signature to two weeks after stopping supplemental oxygen. After this period until the last follow-up visit at 12 months corrected age, only intensive care admissions for

complicated respiratory tract infections and death will be considered SAEs and will be reported as such.

All participating sites will be audited by an independent study monitor. For frequency and procedures, see online supplemental file 4.

Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) is installed. Although this study does not add extra risks to the safety of the patients, the DSMB is installed because of the vulnerability of the population and complicated logistics of a multicentre trial. The DSMB will monitor the safety, validity and credibility of the trial in order to protect the patients, but not futility. In principle, the trial will not be stopped early for a beneficial effect on the primary outcome. Safety analyses will be performed when approximately 25%, 50% and 75% of patients have reached the end of the follow-up (12 months corrected age). The safety data analysis will include retinopathy of prematurity and serious adverse events. The DSMB is independent from the sponsor; the committee members have declared no competing interests.

Dissemination

Results of the trial will be published in open-access journals. After ending of the trial and publication of results, the data collection of this trial will be available for sharing under conditions, through a secured, online portal (DANS).(37)

Trial status

Patient inclusion was started in January 2020, but was temporarily paused due to regulations during the Corona virus pandemic (COVID-19). Inclusion restarted in August 2020.

Statements

Contributors: MP, AvK, WO, DN, EV, PD, AB, AK, IR and SB constitute the trial steering committee. MP, AvK, WO, DN, EV, PD, AB, AK and IR designed the trial and will provide clinical expertise in the conduct of the trial; MP is the Chief Investigator and has overall leadership of the trial; DN is partly responsible for logistical coordination of the trial; SB is responsible for overall coordination of the trial and management of the clinical data. AH and AS constitute the Advisory Board and provide clinical expertise in the conduct of the trial. LG is responsible for cost-effectiveness analyses. EA is the trial statistician. The SOS BPD study group consists of all local investigators in the participating hospitals who are responsible for patient recruitment and data collection.

SB wrote the first draft version of the manuscript; all authors, including the study group, reviewed draft versions and approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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531

List of participating hospitals in the SOS BPD trial

All sites, participating in the SOS BPD trial, at the time of submission of the trial protocol:

Hospital	Location	Local principle investigator
Albert Schweitzer Hospital	Dordrecht	M. de Jong
Amphia Hospital	Breda	A.R. Hulsmann
Amsterdam University Medical Centers – Locations AMC and VuMC	Amsterdam	A.H. van Kaam, W. Onland
Deventer Hospital	Deventer	A.C.M. Dassel
Elisabeth-Tweesteden Hospital	Tilburg	J.C.R. van Hoften
Erasmus MC – Sophia Children's Hospital	Rotterdam	M.W.H. Pijnenburg, A.A. Kroon
Flevo Hospital	Almere	C.E. Counsilman
Franciscus Gasthuis & Vlietland	Rotterdam	A. Kamerbeek
Groene Hart Hospital	Gouda	J.S. von Lindern
Haga Hospital	Den Haag	A.M. de Grauw
Isala Women and Children's Hospital	Zwolle	E.E.M. Mulder
Leiden University Medical Center	Leiden	R.N.G.B. Tan
Maasstad Hospital	Rotterdam	M.G.A. Baartmans
Maastricht University Medical Center	Maastricht	E. Villamor
Martini Hospital	Groningen	H.D. Buiter
Maxima Medical Center	Veldhoven	H.J. Niemarkt
Meander Medical Center	Amersfoort	C.A. Dalen Meurs
Medical Center Leeuwarden	Leeuwarden	M.A.G. van Scherpenzeel - de Vries
Medisch Spectrum Twente	Enschede	L.G.M. van Rooij
Noordwest Hospitalgroup	Alkmaar	G.J. Blok
OLVG	Amsterdam	A.A.M.W. van Kempen
Radboud University Medical Center	Nijmegen	W.P. de Boode
Reinier de Graaf Gasthuis	Delft	L.H. van der Meer
Rijnstate Hospital	Arnhem	C.H. ten Hove
Spaarne Gasthuis	Haarlem	I.A.M. Schiering
St. Antonius Hospital	Nieuwegein	J.L.A.M. van Hillegersberg
University Medical Center Groningen	Groningen	P.H. Dijk
Viecuri Medical Center	Venlo	J.H.L. van Hoorn
Zuyderland Medical Center	Heerlen	R.M.J. Moonen

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	1 – 24
Funding	4	Sources and types of financial, material, and other support	23, 24
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 23
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	23, 24
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	23

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5 - 8
	6b	Explanation for choice of comparators	11
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9 – 10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11 – 12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11 – 12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13 – 14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11 – 13

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15 – 16
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N / A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13 – 15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14 – 15

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14 – 15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16 – 17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16 – 17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17 – 18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18, supplemental file 4
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10, supplemental file 3
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Supplemental file 3
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplemental file 3
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Trial subject information for participation in medical-scientific trials

Additional oxygen for BPD

"Supplemental oxygen in children with bronchopulmonary dysplasia (BPD) following the neonatal intensive care period: the SOS BPD study"

Introduction

Dear Sir/Madam,

You are receiving this letter because your child has bronchopulmonary dysplasia (BPD) and requires supplemental oxygen. We kindly request that you allow your child to take part in a medical-scientific trial. Participation is on a voluntary basis. To take part, you will have to give us consent in writing.
Before you decide whether or not to take part in the trial, we will explain what exactly the trial entails. Please read this information through carefully and ask the researcher for further explanation if you have any questions. Alternatively, you can ask the independent expert, specified at the bottom of this letter, for additional information. You may also discuss it with your partner, friends or family.
Further information about participating in trials can be found on the website of the Rijksoverheid: www.rijksoverheid.nl/mensenonderzoek.

1. General information

This trial has been set up by paediatricians from the Sophia Children's Hospital (Rotterdam), the Emma Children's Hospital (Amsterdam) and the Beatrix Children's Hospital (Groningen) and is being conducted by paediatricians in different hospitals across the country.
This trial requires 198 children from the Netherlands who have BPD. The Erasmus MC medical ethics review committee has approved this trial. General information about reviewing trials can be found in the 'Medical-scientific trials' brochure.

2. Aim of the trial

The aim of this trial is to find out what the best lower saturation limit ('the oxygen content in the blood') is to withdraw supplemental oxygen from children with BPD. In this trial, we are comparing a lower limit of 90% with a lower limit of 95%. Or, is it better to keep the saturation higher or the same as 95% or is 90% just as good?

3. Background to the trial

Supplemental oxygen is the main treatment for children with BPD. However, it has never been investigated what a safe lower saturation limit is in children with BPD after the first few weeks of life, from week 36 of the pregnancy onwards. Both too much and too little oxygen can have serious consequences. Too little oxygen can lead to poorer increase in weight and thereby also poorer lung development and more lung complaints. Too little oxygen can also lead to a higher risk of cot death and be detrimental to development. Too much oxygen is also harmful to the lungs and brain, especially in premature children. Most hospitals observe a lower saturation limit of 90%; however, international guidelines advise 93-95%. But the higher the lower saturation limit should be, the longer children are given additional oxygen and the more frequently they will go home with it.

4. What participation entails

If you wish to allow your child to take part in the trial, we will follow your child's progress up to 1 year after the due date of the pregnancy.

When is your child able to participate?

Your child may take part in the trial from the moment that the pregnancy would have reached 36 weeks onwards. At that time, your child should still require supplemental oxygen, otherwise he or she will not be able to take part. The children participating in the trial are randomly distributed between 2 groups: in one group, we withdraw the supplemental oxygen at a lower limit of 90%; in the other group, at a lower limit of 95%. Fate decides in what group your child ends up; you and the physicians and researchers don't have any influence over this.

Visits and measurements

The trial will take 1 year to complete. During that year, you will visit the hospital twice, when your child is 6 and 12 months of age respectively. These are the standard visits that always take place after (extreme) prematurity, even if you aren't taking part in the trial. The visit will take around 1 hour. During each visit, we will weigh and measure your child and ask about lung complaints, hospital admissions and doctors' visits. Part of the standard treatment in some hospitals includes: a lung function test (by wearing a mask on the face), a CT scan, a sleep study and/or an ultrasound of the heart. The physician treating your child will tell you whether this happens in your hospital too. If your child takes part in the SOS BPD trial, the visit to the outpatients' clinic won't be any different or longer than it usually would be. We will, however, collect the data from the visits for the trial.

In addition to the standard outpatient visits, we will also ask you to answer a number of questions 3 times before the trial by means of a questionnaire sent to you via the internet. This will happen at the beginning of the study, when your child is 6 months old and when your child is 12 months old. The questionnaire will take around 20 minutes to complete.

You will also receive a monthly e-mail asking whether your child has been ill, has been given any medication or has been admitted to hospital recently. You will also have the opportunity to make notes on a secure page on the trial website.

As long as your child is receiving supplemental oxygen, we will ask your physician or yourself (if your child is going home with oxygen) to actively withdraw the oxygen. Oxygen is usually withdrawn in consultation between you and the physician treating your child. For the trial, we will ask you or the physician treating your child to download the saturations from the saturation meter twice a week (or once a week if your child is at home with oxygen) and to e-mail the readings to the researchers. This will be explained to you if you decide to take part in the trial. If the downloaded data reveal that your child is exceeding the lower limit of 90 or 95% too frequently, we will ask the doctor or you to withdraw the oxygen faster. It may also become apparent that your child is falling under the lower limit just that bit too frequently, in which case we will ask you or your doctor to turn the oxygen level up.

Different to the usual care

The visits at 6 and 12 months are standard visits. At this age, all premature children are monitored in the neonatal centre, so these do not constitute additional visits. The questionnaires and the monthly e-mails are additional, however. What's more, the adjustments to your child's oxygen are also different: this happens using the data from the saturation meter which we will ask you to download.

5. What is expected of you?

Participation in the trial means:

- That we will ask you and your doctor to observe the agreed saturation limit
- That we will ask you to keep a note of any admissions, doctors' visits and complaints in an online diary
- That in some hospitals, an additional test will be conducted: a lung function test which involves wearing a mask on the face.

6. Potential detrimental effects

This trial is being conducted because we don't know what's best for children with BPD: a lower limit of 90% or of 95%. Most hospitals currently maintain a lower limit of 90%. The benefit of this is that children are able to stop taking oxygen more quickly and don't go home with oxygen as frequently. The disadvantage could be that children and their lungs don't grow as well. Too low a volume of oxygen could also affect development. The advantage of a lower limit of 95% is that we expect children to grow better and therefore develop more healthy lung tissue. The disadvantage is that children are given additional oxygen for longer and will go home with it more frequently. Too much oxygen can also be harmful to the lungs.

7. Potential advantages and disadvantages

It is important that you weigh up the potential advantages and disadvantages carefully before deciding to take part. A higher lower limit for the oxygen may cause growth/lung growth to improve, but this isn't guaranteed.

Disadvantages of participating in the trial are: potential detrimental effects on the trial measurements.

Participation in the trial also means:

- the child may have to use oxygen at home for longer
- that you will have agreements (in relation to the lower oxygen limit, in particular) that you will have to observe.

It is important that you weigh up the potential advantages and disadvantages carefully before deciding to take part.

8. Your child's resistance

Your child could be resistant (refuse to cooperate) during the trial, in which case, the researcher would have to stop the trial straight away. It is difficult to describe exactly what resistance is. Before the start of the trial, we will discuss with you what is understood by resistance. The researcher will abide by the Code of Conduct for the Resistance of Under-Aged Patients.

9. If you do not wish to participate in or wish to stop the trial

It is up to you whether your child takes part in the trial. Participation is entirely voluntary in nature.
If you do not want your child to take part, your child will be treated for BPD in the usual manner. That means that the doctor treating your child will decide the lower saturation limit with you.

If you do decide to participate, you can change your mind at any time and stop, even during the trial. Once again, your child will be treated the usual way without having to state your reasons for doing so. However, you will need to report this to the researcher straight away. The data that has been collected up to that moment will be used for the trial.

If there is new information about the trial that is important for you, please allow the researcher to tell you. You will then be asked whether you wish to continue to take part.

10. End of the trial

Your child's participation in the trial will stop once:

- all visits are over
- you yourself decide to stop
- the researcher or your child's doctor thinks it's better if your child stops

- the authorities or the assessing medical ethics review committee decides to stop the trial.

The entire trial is over once all participants have finished.
After processing all the data, the researcher will notify you of the main results of the trial. Because the entire trial takes three-and-a-half years to complete, it can take a while before you can expect the results.

11. Use and retention of your child's data

For this trial, it is necessary to collect and use medical and personal data relating to your child. This is necessary to answer the questions asked in this trial and to publish the results.

Confidentiality of your child's data

To protect your child's privacy, each trial subject is given a code which is stated on the data. The name and other personal data that could be used to identify your child are omitted. The researcher is the only person who knows your child's code. The key for the code remains with the researcher. Even in reports about the trial, only that code is used.

Access to the data

Some people may view your child's medical and personal data to verify whether the trial has been conducted properly and reliably. General information about this can be found in the 'Medical-scientific trials' brochure.

People who are able to view your data are: the research team, the safety committee monitoring the trial, an auditor who has been brought in by the researchers of the trial and the Dutch Health Care Inspectorate. They will keep your data confidential. When you sign the consent form, you are consenting to the collection, retention and viewing of your medical and personal data.

Data retention period

The researcher will retain your child's data for a period of 15 years in accordance with the statutory retention period.

Withdrawing consent

You can withdraw your consent to the use of personal data again at any time. This applies both to this trial and to its retention and use for any future trials. Trial data collected up to the moment you withdraw your consent will then still be used in the research.

Further information about your rights when processing data

For general information about your rights when processing your personal data, you may consult the Dutch Data Protection Authority's website (www.autoriteitpersoonsgegevens.nl).

If you have any questions about your rights, please contact the data controller responsible for the processing of your personal data, See enclosure A for contact details.

If you have any questions or complaints about the processing of your personal data, we advise contacting the trial location in the first instance. You may also contact the Data Protection Officer at the Erasmus MC or the Dutch Data Protection Authority.

Registration of the clinical trial

This trial also appears in a list of medical-scientific trials, namely the trial register (www.trialregister.nl; trial code 7347). This website doesn't contain any information that can be traced back to your child. However, the website may show a summary of the results. General information about registering trials can be found in the 'Medical-scientific trials' brochure.

12. Insurance for trial subjects

Appropriate insurance will be taken out for everyone who decides to enter this trial. The insurance covers damage caused by the trial. It does not cover all damage. **Enclosure B** contains further information about the insurance, including who you can report damage to.

13. Notifying the GP and/or treating specialist

We always send your child's GP and/or treating paediatrician a letter to tell them that your child is taking part in the trial. This is for your child's own safety. If you do not agree to this, your child will not be able to take part in this trial. The GP or paediatrician will also receive a letter concerning the 6 and 12-month visits. This is also the norm even if your child is not taking part in the trial.

14. No payment for participating

The additional tests and treatment for the trial won't cost you anything. You will not receive payment for taking part in this trial.

15. Any questions?

If you have any questions, please contact the trial team. For independent advice about taking part in this trial, please contact the independent doctor, Dr P.J.F.M. Merkus. He knows a great deal about this trial, but doesn't have anything to do with the trial.
In the event of complaints, please contact the complaints officer at your hospital. All information can be found in **Enclosure A**: Contact details.

16. Signing of consent form

Once you have had sufficient thinking time, you will be asked to decide about your child's participation in this trial. If you decide to take part and give consent, please confirm this in writing using the enclosed informed consent form. By giving written consent, you confirm that you have understood the information and agree to take part in the clinical trial.
The signatures page will be retained by the doctor treating your child. You will receive a copy of this consent form.

Thank you for taking the time to read this letter.

Enclosures to this information

A. Contact details

B. Information about insurance

C. Consent form

Enclosure A: contact details for *name hospital*

Researcher at *name hospital*:

Local principle investigator.

Telephone number: *xxxxx*. E-mail: *xxxxxx*

Coordinating researcher:

Ms S.J.A. Balink, research physician at Erasmus MC - Sophia Children's Hospital.

Telephone number: +31 (0)6 500 33994. E-mail: sosbpd@erasmusmc.nl.

Independent doctor:

Dr P.J.F.M. Merkus, paediatric pulmonologist, Amalia Children's Hospital, Radboud UMC Nijmegen. Telephone number: +31 (0)24 361 4430. E-mail: Peter.Merkus@radboudumc.nl

Complaints:

Hospital format

Data Protection Officer:

Hospital format

SOS BPD

Enclosure B: information about insurance

Erasmus MC has taken out insurance for everyone taking part in this trial. The insurance covers damage caused as a result of taking part in the trial. This applies to damage caused during the trial or within four years of the end of the trial. Claims must be submitted to the insurer within this four-year period.

This insurance policy does not cover all damage. You will find a brief outline of the exceptions below.
The full version of these provisions are included in the Compulsory Insurance for Medical Research Involving Human Subjects Decree, which can be consulted at www.ccmo.nl, the website of the Central Committee on Research Involving Human Subjects (go to 'Bibliotheek' and select 'Wet- en regelgeving').

In case of damage, submit your claim directly to the insurer.

The insurer for this clinical trial is:	
Name:	CNA Insurance Company Limited
Address:	Polarisavenue 140, 2134 JX Hoofddorp
Telephone number:	+31 (0)23 303 6004
E-mail:	Esther.vanherk@cnaeurope.com
Policy number:	10.220.695
Contact person:	Ms Esther Van Herk

The insurance offers coverage of €650,000 per trial subject and €5,000,000 for the entire trial and €7,500,000 per year for all trials conducted by the Erasmus MC.

The following damage is **not** covered by the insurance policy:

- damage caused by a risk of which you were informed in the written information. This does not apply if the materialisation of the risk is more severe than foreseen or if materialisation of the risk was highly unlikely.
- damage to your health that would also have materialised if you had not entered the clinical trial;
- damage as a result of failure to follow directions or instructions or failure to follow these in full;
- damage to your descendants caused by an adverse effect of the trial on you or your descendants;
- damage caused by an existing treatment method in the case of research into existing treatment methods.

SOS BPD

Enclosure C: Consent form for parents or guardians

Additional oxygen for BPD

I have been asked to give my consent to my child's participation in this medical-scientific trial:

Name of child: Date of birth: __ / __ / __

- I have read the information letter for parents/guardians. I was also able to ask questions. My questions have been answered satisfactorily. I had enough time to decide whether or not to enter my child in the trial.
- I know that participation is voluntary. I also know that I may decide to withdraw my child from the trial at any time, without having to state any reasons for doing so.
- I give my consent to the GP/paediatrician treating my child being informed that my child is taking part in this trial.
- I give my consent to the requesting of information from the paediatrician treating my child concerning my child's hospital admissions.
- I am aware that some people are able to view my child's data. The people in question are specified in this information letter.
- I give my consent to the use of the data in the manner and for the purposes stated in the information letter.
- I give my consent to my child's data being retained at the trial location for a period of 15 years after this trial has finished.
- I give my consent to the use of my e-mail address, only for this trial.
- I □ **do***
  □ **do not**
  give my consent to my child being contacted again about a follow-up trial once this trial has ended.

- I agree to my child taking part in this clinical trial.

Name of parent/guardian 1: ……

Signature: Date: __ / __ / __

E-mail address: ……..

Name of parent/guardian 2: ……

Signature: Date: __ / __ / __

E-mail address: ……....

I hereby declare that I have notified in full the above-mentioned person/persons about the named trial.

If any information were to emerge during the trial that could affect the parent's or guardian's consent, I shall notify him/her in due time.

Clinical researcher's name (or his/her representative):

Signature: Date: __ / __ / __

Additional information has been provided by:

Name:

Position:

Signature Date: __ / __ / __

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* Place a cross next to that which is applicable.

Supplemental file 4: Audit frequency and procedures

Monitoring frequency

Visit no.	Selected Sites	Planning*
Initiation Visit	All	Before enrolment of the first subject, but after Ethics Committee and Board of Deans approval has been obtained.
First Monitoring Visit A	All participating sites	After 2 - 3 randomised subjects, irrespective of (e)CRF completion.
First Monitoring Visit B	All 10 NICUs	Only if not including subjects so when Visit A has not been performed. After 5 - 6 randomised subjects have completed the 6 month visit, irrespective of (e)CRF completion.
Remote Visit	All sites	Contact via telephone or email approximately 12 weeks after the First Monitoring Visit A or B
Second Monitoring Visit	5 high recruiting sites	After all subjects have been randomised, the 5 sites who have randomised the most subjects
Remote Visit	All 5 high recruiting sites	Contact via telephone or email approximately 12 weeks after the Second Monitoring Visit
Remote Close Out	All sites	After database lock
TMF check in combinations with check on 6 months FU data if possible	Sponsor site	In 2019 and 2022

*The frequency may be changed based on the total enrolment period, the inclusion rate, quality issues and/ or site performance, but only after consultation with the Coordinating PI.

Monitoring procedures

The follow items will be discussed/ verified by the Clinical Research Associate (CRA) during the different visits.

First Monitoring Visit

- Who is/ are the contact person(s) at site

- Is the entire investigators' study staff adequately informed about the study e.g. randomisation procedure, sample collection, procedures in case of protocol deviations/ serious breaches, SAE notification procedures etc.
- Is the entire investigators' study staff WMO/GCP trained and authorized (site signature and delegation log)
- Has the study staff sufficient time to perform the study?
- How and by whom is the subject informed about the study?
- By whom is consent obtained and is it properly documented?
- Who will examine the subject every visit?
- Who performs the screening, baseline and other visits/ how is this arranged?
- Which source documents are available?
- Source Data Review
- Source Data Verification
- Where is the source data stored?
- Who will maintain the subject identification code list/ screening log/ enrolment log?
- Who is completing the (e)CRF?
- When/ how/ where and by who are questionnaires filled in?
- Which facilities are used (any changes)?
- Which equipment is used (any changes)?
- Have any Serious Adverse Events (SAEs) occurred?
- Reporting of SAE's
- Are there any known protocol deviations and/ or serious breaches of ICH-GCP and/ or protocol?
- Is the Trial Master File/ Investigator Site File up to date (AMC SOP CTR 006/ ICH-GCP guideline 8.1 – 8.3)?
- What is the expected recruitment rate?
- Competitive studies running?
- Informed consent process, use of Patient Information Form and Informed Consent form
- In- and exclusion criteria

Remote Visits

- Discuss progress of follow-up of action items
- Is the enrolment overview up to date (amount screened subjects, amount of screen failures/withdrawn subjects, amount of randomised/enrolled subjects, amount of active subjects, amount of subjects in follow-up and amount of subjects that have completed the trial)?.
- Are there any changes in the investigators' study staff (trained and authorized)?
- Are there any changes in facilities or equipment?
- Have any SAEs been reported since previous on-site monitor visit?
- Are there any known protocol deviations and/or serious breaches of ICH-GCP and/or protocol?

Ongoing Monitoring Visits

- Is the entire investigators' study staff adequately informed about the study?

- Is the entire investigators' study staff WMO/GCP trained and authorized (site signature and delegation log)
- Are there any changes in the investigators' study staff (trained and authorized)?
- Are there any changes in facilities or equipment?
- Is the investigational medicinal product accountability properly documented?
- Have any SAEs occurred?
- Are there any known protocol deviations and/or serious breaches of ICH-GCP and/or protocol?
- Is the Trial Master File/ Investigator Site File up to date (AMC SOP CTR 006/ICH-GCP guideline 8.1 – 8.3)?
- Are there any new amendments in place?

BMJ Open

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)

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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)

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Bronchopulmonary dysplasia, prematurity, supplemental oxygen, growth, weight, lung function, oxygen saturation

ABSTRACT

Introduction: Supplemental oxygen is the most important treatment for preterm born infants with established bronchopulmonary dysplasia (BPD). However, it is unknown what oxygen saturation levels are optimal to improve outcomes in infants with established BPD from 36 weeks postmenstrual age (PMA) onwards. The aim of this study is to compare the use of a higher oxygen saturation limit (≥ 95%) to a lower oxygen saturation limit (≥ 90%) after 36 weeks PMA in infants diagnosed with moderate or severe BPD.

Methods and analysis: This non-blinded, multicentre, randomised controlled trial will recruit 198 preterm born infants with moderate or severe BPD between 36 and 38 weeks PMA. Infants will be randomised to either a lower oxygen saturation limit of 95% or to a lower limit of 90%; supplemental oxygen and/or respiratory support will be weaned based on the assigned lower oxygen saturation limit. Adherence to the oxygen saturation limit will be assessed by extracting oxygen saturation profiles from pulse oximeters regularly, until respiratory support is stopped. The primary outcome is the weight standard deviation score at six months corrected age. Secondary outcomes include anthropometrics collected at six and twelve months corrected age, re-hospitalizations, respiratory complaints, infant stress, parental quality of life and cost-effectiveness.

Ethics and dissemination: Ethical approval for the trial was obtained from the Medical Ethics Review Committee of the Erasmus University Medical Centre, Rotterdam, the Netherlands (MEC-2018-1515). Local approval for conducting the trial in the participating hospitals has been, or will be obtained from the local institutional review boards. Informed consent will be obtained from the parents or legal guardians of all study participants.

Trial registration: Dutch Trial Registry (www.trialregister.nl): NL7149 / NTR7347; registered on July 10, 2018.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first randomised controlled trial that aims to identify the optimal lower limit of oxygen saturation for infants with moderate or severe bronchopulmonary dysplasia to improve growth and respiratory health.
- Adherence to the assigned limit for weaning supplemental oxygen will be increased by collecting oxygen saturation profiles twice (in hospital) or once (at home) weekly.
- Limitations of this study are that the study is not blinded and that protocols amongst the participating centres to wean oxygen or respiratory support are not standardized.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is the most common complication of extreme preterm birth. The pathogenesis of BPD is complex and multifactorial: pre- and postnatal risk factors such as intrauterine growth restriction, pregnancy-related hypertensive disorders, mechanical ventilation and infections all may impact on the immature, developing lungs of extremely preterm infants.(1) As a consequence, there is an arrest in lung development characterized by a decreased number of alveoli, which are larger and simplified, combined with small airway injury and abnormal development of the pulmonary vasculature.(2) Despite advances in perinatal and neonatal care, the incidence of BPD remains high, affecting almost half of infants born <28 weeks' gestation who survived to 36 weeks' postmenstrual age (PMA).(3) Infants with BPD may experience poor respiratory health and impaired lung function throughout childhood, even persisting into adulthood.(4, 5) Particularly the first years of life are characterized by prolonged use of supplemental oxygen, frequent respiratory symptoms and an increased risk of hospitalization.(6, 7) Having a child with BPD also poses an important burden on family life and is associated with a decreased quality of life of caregivers.(8)

Supplemental oxygen is the most important treatment for preterm infants with established BPD. It reduces respiratory symptoms, reduces or prevents pulmonary hypertension and has possible beneficial effects on growth and neurodevelopment.(9) However, no study has ever examined the optimal oxygen saturation (SpO_2) target in children with established BPD, while both too little and too much oxygen may lead to serious adverse events.(10) Few guidelines include recommendations for SpO_2 levels in infants with BPD. The European Respiratory Society guideline on long term management of children with BPD suggests the use of a lower limit of SpO_2 of 90% when using supplemental oxygen.(11) The American

Thoracic Society Guideline on home oxygen therapy suggests a level of 93% as minimum threshold.(12) However, the level of evidence supporting these recommendations is low. This has led to substantial practice variation in the applied SpO_2 limits in infants with BPD still receiving respiratory support and/or supplemental oxygen after 36 weeks PMA.

In contrast to the limited evidence available *after* 36 weeks PMA, optimal SpO_2 targets have been extensively studied in preterm infants *before* the age of 36 weeks PMA. The Supplemental Therapeutic Oxygen for Prethreshold Retinopathy Of Prematurity (STOP-ROP) trial, the Benefits Of Oxygen Saturation Targeting (BOOST) trial and the Neonatal Oxygen Prospective Meta-analysis (NeOProM) Collaboration (including 5 randomised controlled trials) all compared different SpO_2 targets in preterm infants before 36 weeks PMA.(13-15) All trials studied slightly different SpO_2 target ranges (Table 1).

Table 1. SpO_2 target ranges in different trials (13-15)

Trial	Lower SpO_2 range	Higher SpO_2 range
STOP-ROP trial	89 – 94%	96 – 99%
BOOST trial	91 – 94%	95 – 98%
NeOProM Collaboration	85 – 89%	91 – 95%

SpO_2 = oxygen saturation

The STOP-ROP trial found no differences in progression of retinopathy of prematurity, but targeting a higher SpO_2 did lead to a higher incidence of respiratory morbidity (pneumonia or exacerbations of chronic lung disease).(13) However, this study was not designed, nor powered for respiratory outcomes. The BOOST trial found no differences between the two groups on growth or neurodevelopment at 12 months corrected age, but infants in the higher

SpO_2 range had an increased length of oxygen therapy and required home oxygen more often.(14) The meta-analysis of the NeOProM Collaboration showed that targeting a higher SpO_2 range decreased the incidence of death and necrotizing enterocolitis, but the incidence of retinopathy of prematurity requiring treatment was higher in the higher saturation group. The use of supplemental oxygen at 36 weeks PMA was higher in the group with a higher SpO_2 target range, due to the study protocol.(16) The incidence of blindness, severe hearing loss and cerebral palsy was similar across the groups.(15)

Based on the outcomes of these studies, the American Academy of Pediatrics concluded that the optimal SpO_2 range for extremely low birth weight infants remains unknown, but that an SpO_2 range of 90 to 95% may be safer than 85 to 89%.(17)

It is important to acknowledge that there are several reasons why the results of these oxygen targeting studies before 36 weeks PMA may not be extrapolated to infants with established BPD who have reached near term age. Firstly, the lungs have reached a new stage of development as alveolar growth starts from approximately 36 weeks of gestation.(18) In addition, there is a transition from lung development to lung growth in infancy and childhood, as lung volume will increase about 23 times between birth and adulthood in healthy subjects.(18) Secondly, it has been suggested that vulnerability to oxidative stress is less pronounced at 36 weeks PMA compared to the first weeks of life as antioxidant systems have matured. Thirdly, also the pulmonary vascular system undergoes important differentiation during the different stages of lung development.(19) The optimal SpO_2 range to prevent pulmonary vascular disease may be different from the range to improve pulmonary vascular disease. Therefore, infants with established BPD after 36 weeks PMA may require another approach to oxygen treatment than infants with developing BPD before 36 weeks PMA.

In summary, there is a lack of evidence on the optimal SpO_2 levels in infants with established BPD from 36 weeks PMA onwards to optimize respiratory health. Therefore, the aim of this study is to compare a higher SpO_2 (i.e. 95% lower limit) to a lower SpO_2 (i.e. 90% lower limit) in infants with moderate or severe BPD from 36 weeks PMA and onwards. Our hypothesis is that a higher SpO_2 target in infants with established moderate or severe BPD, improves weight gain and lung growth.

OBJECTIVES

The primary objective is to investigate whether a higher SpO_2 (i.e. 95% lower limit) leads to a higher weight at 6 months corrected age, as a surrogate for lung growth. Secondary objectives are to determine if a higher SpO_2 translates into higher weight and height at 12 months corrected age, less healthcare consumption, less infant stress, better quality of life for parents or caregivers and more favourable cost-effectiveness.

METHODS AND ANALYSIS

Study design and setting

The SOS BPD study is an open, randomised controlled trial and will be conducted in the Netherlands in approximately (but not limited to) 30 hospitals. In the Netherlands, the care for extremely preterm born infants is concentrated in 9 hospital clusters. Each cluster consists of one or two level 3 Neonatal Intensive Care Units (NICU) and several post-intensive care/high care (post-IC/HC) units in surrounding level 2 centres. The participating hospitals include 10 NICU centres and 20 post-IC/HC units. A list of recruiting sites is provided in online supplemental file 1. The SOS BPD study is conducted within the Neonatology Network Netherlands (N3) organization.(20)

The protocol for this trial is reported based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Checklist(21) (online supplemental file 2: SPIRIT Checklist).

Study population

Infants with moderate or severe BPD, born before 32 weeks of gestation, who still receive respiratory support at 36 weeks PMA are eligible for inclusion. BPD is defined as the use of supplemental oxygen (i.e. >21% oxygen) for ≥28 days since birth.(22) Depending on the level of respiratory support at 36 weeks PMA, BPD severity is classified as mild, moderate or severe (Table 2). An oxygen reduction test will be used to assess severity if indicated.(23)

Table 2. BPD diagnostic criteria for infants born <32 weeks PMA. Severity is classified at 36 weeks PMA.(22)

Definition of BPD	**Severity classification**		
	Mild	**Moderate**	**Severe**
Treatment with supplemental oxygen for ≥28 days	Breathing room air or nasal cannula with ≤1L flow, FiO_2 21%	Supplemental oxygen >21%, but <30%	Supplemental oxygen ≥30%, or invasive or noninvasive positive pressure ventilation, including HFNC

BPD = bronchopulmonary dysplasia, FiO_2 = fraction of inspired oxygen; HFNC = High Flow Nasal Cannula; L = liter; PMA = postmenstrual age

Written informed consent will be obtained from parents or legal guardians by the local PI of the hospital where the participant is admitted between 36 to 38 weeks PMA (online supplemental file 3: English version of the patient information and informed consent document). Exclusion criteria are significant congenital heart disease (not being patent ductus arteriosus, small atrial septal defect, ventricular septal defect), pulmonary hypertension with medical treatment, retinopathy of prematurity for which the ophthalmologist recommends a patient specific SpO_2 target, severe acquired upper airway abnormalities, such as subglottic stenosis and interstitial lung diseases.

Randomisation

Participants will be randomised 1:1 between 36 and 38 weeks postmenstrual age, to one of two parallel treatment arms: weaning of supplemental oxygen and respiratory support based on an SpO_2 lower limit of 95% or weaning based on a lower limit of 90%.

For the randomisation procedure, an electronic data capture system that uses a computer-generated randomisation list (Castor EDC) will be used.(24) We will use block randomisation, with a variable block size (4 – 8). Allocation will be stratified by NICU centre (10 centres) and BPD severity (moderate or severe). In case of multiple birth, the firstborn infant will be randomised according to standard procedures. Siblings will be manually assigned to the same treatment arm as the firstborn infant.

Enrolment, registration and electronic randomisation in Castor EDC will be carried out by the local PI of the hospital where the participant is included.

This is a non-blinded study, since it is not feasible to blind treating physicians and parents for SpO_2 values as measured with pulse oximetry in the hospital or at home.

Study procedures

After randomisation, participants are assigned to one of the 2 treatment arms. A lower limit of 95% was chosen for the first group, as the median SpO_2 in preterm infants without BPD is > 95% (25) and SpO_2 >94% reduces the incidence of pulmonary hypertension.(9) Also, with a lower limit of 95% there is a clear contrast between the 2 groups. A lower limit of 90% was chosen for the second group, since this lower limit is advised in the BPD guideline of the European Respiratory Society and SpO_2 values < 90% have been associated with adverse outcomes.(11, 17)

During hospitalization, respiratory support and oxygen supplementation will be adjusted based on the assigned lower limit of SpO_2, as part of daily clinical care. Twice a week, SpO_2 data will be logged from 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 was 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 SpO_2 data will be sent to the research team using encrypted file transfer. Based on the recorded SpO_2 data and group assignment, the medical team will receive advice to actively wean or increase supplemental oxygen.

In case participants are discharged on home oxygen, SpO_2 data will be logged from a pulse oximeter at home by the parents once weekly and will be sent to the research team through encrypted file transfer. Feedback and advice to adjust supplemental oxygen will be given to the parents and treating physician.

SpO_2 profiles will be obtained until one week after discontinuation of respiratory support.

If an infant is readmitted to hospital while still on supplemental oxygen, the assigned SpO_2 lower limit will be kept. If infants are readmitted after they were weaned from supplemental

oxygen for at least two weeks, the lower SpO_2 limit will be set according to the local hospital policy.

In order to follow routine clinical care as much as possible, physicians will wean supplemental oxygen according to their local hospital protocol. If no such protocol is available, a study specific standard operating procedure will give recommendations on weaning supplemental oxygen (online supplemental file 4).

In order to improve feasibility and generalizability, the use of diuretics, inhaled or oral corticosteroids, other medications, fluid restriction and feedings will be according to national guidelines or local policies. Data on these parameters will be collected during the study.

Interpretation of SpO_2 profiles

If the time spent below the assigned lower limit of SpO_2 is ≥10% of the recorded time (equivalent to <90% of the time spent above the lower limit), the treating team is advised to increase supplemental oxygen and/or respiratory support. When the SpO_2 is below the assigned lower limit for ≤10% of the time (equivalent to >90% of the time spent above the lower limit), the treating team is advised to wean supplemental oxygen and/or respiratory support.

The British Thoracic Society Guideline for home oxygen in children suggests that the lower limit target SpO2 should be met for at least 95% of a stable recording period.(9) However, this does not take into account that a 24-hour SpO_2 profile is prone to artefacts due to periods of feeding, physical activity and external manipulation of the saturation probe. Furthermore, Terrill et al. studied normative oximetry data in extreme preterm infants at term equivalent age and reported mean saturations of 96.1% (95.4–96.8%) with 7.56% (5.1–10.0%) of the measuring time spent below an SpO_2 of 90%.(26, 27) Therefore, we chose this limit of 10% below the assigned SpO_2 to adjust oxygen supplementation.

Temporary deviation of the protocol is possible if this is deemed necessary for medical reasons according to the treating physician. Reasons for these protocol deviations have to be reported to the research team.

Follow-up

The study duration will be 12 months, with two follow-up visits at 6 and 12 months corrected age. These follow-up visits follow the national neonatal follow-up program; no extra study visits are required.(28) Data that will be obtained during study visits are weight, height, head circumference, caloric intake, use of medication, respiratory complaints, number of health care visits and hospitalizations.

In a subgroup of patients, additional investigations including chest CT scan (assessed with PRAGMA-BPD scores),(29) multiple breath washout tests (Lung Clearance Index), polysomnography (baseline SpO_2, oxygen desaturation index, apnea-hypopnea index) and/or an echocardiogram will be performed, as part of routine care in some hospitals during follow-up at six months corrected age.

Parents will receive monthly online questionnaires that address the health situation of their child in the past month and also contain questions used for cost-effectiveness analyses. In addition, parents will be asked to fill in the Dutch version of the Care-Related Quality of Life instrument (CarerQoL-7D). The CarerQoL is designed to measure and value the impact of providing informal care on caregivers.(30)

At the start of the study and at the corrected age of 6 and 12 months, parents will also be asked to fill in the Dutch version of the Infant Behavior Questionnaire – Revised (IBQ-R) Very Short Form.(31) The IBQ-R is designed to measure the temperament of infants between 3 and 12 months.

Outcomes

The primary outcome of the study is weight standard deviation score (SDS) at 6 months corrected age as a surrogate for lung growth. Increased weight and weight gain during infancy are associated with better lung function and structure.(32, 33) Appropriate growth is also an important measure of general well-being in infancy, whilst growth delay is associated with an increased risk of future respiratory and cardiovascular disease and impaired intellectual outcomes.(34, 35) Growth failure is very common in infants with BPD. The exact underlying mechanisms are unknown, but increased respiratory demands and periods of intermittent hypoxia probably play an important role.(27) Secondary outcomes are weight SDS at 12 months corrected age, height and head circumference SDS at 6 and 12 months corrected age, rate of re-hospitalisations, respiratory symptoms (including wheezing, dyspnea, exercise induced symptoms), unscheduled health care visits, (progression of) retinopathy of prematurity (ROP), infant temperament (IBQ-r), quality of life of caregivers (CarerQoL) and cost-effectiveness.

In a subgroup of infants, additional secondary outcomes are lung function (lung clearance index), lung structure as assessed with chest CT scan, and pulmonary hypertension and/or right ventricular systolic function as assessed with echocardiography at the corrected age of 6 months. These examinations are part of the standard of care protocol in some of the outpatient follow-up programs in the Netherlands.

Data collection and management

For data management Castor EDC will be used: a password protected, electronic database. Baseline characteristics including gestational age, birth weight, gender, pregnancy complications such as pre-eclampsia, past illnesses and retinopathy of prematurity will be

recorded in the database at inclusion by the local research team. SpO_2 data will be entered into the database by the central research team. Data from follow-up visits will be entered by the research team of the responsible NICU, as outpatient follow-up takes place in those centres. In case of missing data, every attempt will be undertaken to retrieve the data by contacting the respective hospitals.

Collected data will be pseudonymised and coded with a unique number, complying with the European General Data Protection Regulation. The key to link participants with their data will only be accessible to the local PI of the centre of inclusion and PI of the associated NICU. Data will be stored securely and will be saved for 15 years according to national legislation. Only central study investigators will have access to all collected data.

Patient and public involvement

Parents of children with BPD and several patient associations (Lung Foundation Netherlands, European Lung Foundation and the Neonatal Parents Organization (Care4Neo)) were involved in the development of the trial. In addition, parents of preterm born infants are part of the Advisory Board of the trial. They provide their experience in improving patient information material, publications and presentations for layman and will help with implementation after finalization of the study.

Sample size estimation

A simulation study with four scenarios was performed to estimate the sample size needed with weight SDS at 6 months corrected age as primary outcome. We assumed a mixed effects model with a random intercept to account for the correlation between the patients from the same hospital. We assumed 10 clusters (10 NICU centres with post IC/HC departments in the

surrounding regional hospitals) with each cluster having 16 (±3) or 18 (±3) patients. The mean weight at 6 months for the group with a lower saturation limit of 90% was assumed -1.15 SD (data from BPD cohort Erasmus MC, Rotterdam, the Netherlands, data on file). The mean weight at 6 months for the group with a lower saturation limit of 95% was assumed -0.65 SD, since a 0.5 SDS higher weight was considered clinically relevant. The variation in weight due to differences between individuals was assumed 1.18 SD, while the variation in weight due to differences between hospitals was assumed 0.10 and 0.20 SD. The scenario with the highest power (0.83) and greatest variation of weight between the various hospital clusters (0.20 SD) was chosen. This scenario leads to a sample size of 180 patients. Accounting for a drop-out rate of 10%, we aim to include 198 infants.

Statistical analysis

Analyses will be performed on an intention-to-treat (ITT) basis. The ITT population will include all randomised infants, regardless of protocol deviations.

Comparison between the two groups for the primary endpoint will be made using a mixed effect model with a random intercept to account for the correlation between patients from the same hospital cluster. All secondary parameters will be assessed by linear mixed effect models for continuous outcomes or logistic mixed effect models for binary outcomes. BPD severity and weight at inclusion are considered relevant variables for the outcome weight SDS at 6 months. For the secondary analysis, these variables will be included in the mixed model analysis as fixed effects. Significance levels will be 0.05.

Missing values in the baseline covariates, if >10%, will be assumed to be missing at random and multiple imputations will be used. We do expect less than 10% missing data for the primary endpoint, weight SDS.

All analyses will be completed with the statistical software package R (www.rproject.org),

and SPSS/PC Statistics 21.0 (SPSS Inc., Chicago, IL, USA).

Cost-effectiveness analysis

A trial-based economic evaluation will be used as a cost-effectiveness analysis performed from a societal perspective as well as from a healthcare perspective. The initial time horizon is one year. Costs will be calculated based on patient-level data on resource use inside and outside the healthcare sector during the first year of life of the infant. If an oxygen weaning strategy leads to better health outcomes at higher costs, incremental cost-effectiveness ratios will be calculated. Depending on which treatment is more effective, these ratios will express the additional costs per unit of health gain or the savings per unit of health forgone.

Although it is very plausible that health effects and differences in costs persist or occur later in life, currently available data and literature do not allow a meaningful extrapolation after the study period. Nevertheless, the children will be followed until the age of 8 year, outside of the scope of this initial study, according to national follow-up guidelines for preterm born children. This will make it possible to track costs and effects in the longer term.

ETHICS AND DISSEMINATION

Ethical consideration

Ethical approval for the trial has been obtained from the Medical Ethics Review Committee of the Erasmus University Medical Center, Rotterdam, the Netherlands (MEC-2018-1515). Local approval for conducting the trial in the participating hospitals has been, or will be obtained from the local institutional review boards. Written informed consent will be obtained from the parents or legal guardians of all study participants, adhering the Good Clinical Practice guideline.(36)

Protocol modifications will be communicated to all relevant parties.

Safety reporting and auditing

All serious adverse events (SAE) will be reported to the approving ethics committee in accordance with national guidelines. SAEs will be collected and recorded from informed consent signature to two weeks after stopping supplemental oxygen. After this period until the last follow-up visit at 12 months corrected age, only intensive care admissions for complicated respiratory tract infections and death will be considered SAEs and will be reported as such.

All participating sites will be audited by an independent study monitor. For frequency and procedures, see online supplemental file 5.

Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) is installed. Although this study does not add extra risks to the safety of the patients, the DSMB is installed because of the vulnerability of the population and complicated logistics of a multicentre trial. The DSMB will monitor the safety, validity and credibility of the trial in order to protect the patients, but not futility. In principle, the trial will not be stopped early for a beneficial effect on the primary outcome. Safety analyses will be performed when approximately 25%, 50% and 75% of patients have reached the end of the follow-up (12 months corrected age). The safety data analysis will include retinopathy of prematurity and serious adverse events. The DSMB is independent from the sponsor; the committee members have declared no competing interests.

Dissemination

Results of the trial will be published in open-access journals. After ending of the trial and publication of results, the data collection of this trial will be available for sharing under conditions, through a secured, online portal (DANS).(37)

Trial status

Patient inclusion was started in January 2020, but was temporarily paused due to regulations during the Corona virus pandemic (COVID-19). Inclusion restarted in August 2020.

Statements

Contributors: MP, AvK, WO, DN, EV, PD, AB, AK, IR and SB constitute the trial steering committee. MP, AvK, WO, DN, EV, PD, AB, AK and IR designed the trial and will provide clinical expertise in the conduct of the trial; MP is the Chief Investigator and has overall leadership of the trial; DN is partly responsible for logistical coordination of the trial; SB is responsible for overall coordination of the trial and management of the clinical data. AH and AS constitute the Advisory Board and provide clinical expertise in the conduct of the trial. LG is responsible for cost-effectiveness analyses. EA is the trial statistician. The SOS BPD study group consists of all local investigators in the participating hospitals who are responsible for patient recruitment and data collection.

SB wrote the first draft version of the manuscript; all authors, including the study group, reviewed draft versions and approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Collaborators: the SOS BPD study group: M.G.A. Baartmans, G.J. Blok, W.P. de Boode, H.D. Buiter, C.E. Counsilman, C.A. Dalen Meurs, A.C.M. Dassel, A.M. de Grauw, M.E.N. van den Heuvel, J.L.A.M. van Hillegersberg, J.C.R. van Hoften, J.H.L. van Hoorn, C.H. ten Hove, M. de Jong, A. Kamerbeek, A.A.M.W. van Kempen, J.S. von Lindern, L.H. van der

Meer, R.M.J. Moonen, E.E.M. Mulder, H.J. Niemarkt, L.G.M. van Rooij, M.A.G. van Scherpenzeel-de Vries, I.A.M. Schiering, R.N.G.B. Tan, E. Villamor.

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Competing interests: none declared

Patient consent for publication: Not required

Provenance and peer review: Not commissioned; externally reviewed for funding and ethical approval prior to submission.

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List of participating hospitals in the SOS BPD trial

All sites, participating in the SOS BPD trial, at the time of submission of the trial protocol:

Hospital	**Location**	**Local principalle investigator**
Albert Schweitzer Hospital	Dordrecht	M. de Jong
Amphia Hospital	Breda	A.R. Hulsmann
Amsterdam University Medical Centers – Locations AMC and VuMC	Amsterdam	A.H. van Kaam, W. Onland
Deventer Hospital	Deventer	A.C.M. Dassel
Elisabeth-Tweesteden Hospital	Tilburg	J.C.R. van Hoften
Erasmus MC – Sophia Children's Hospital	Rotterdam	M.W.H. Pijnenburg, A.A. Kroon
Flevo Hospital	Almere	C.E. Counsilman
Franciscus Gasthuis & Vlietland	Rotterdam	A. Kamerbeek
Groene Hart Hospital	Gouda	J.S. von Lindern
Haga Hospital	Den Haag	A.M. de Grauw
Isala Women and Children's Hospital	Zwolle	E.E.M. Mulder
Leiden University Medical Center	Leiden	R.N.G.B. Tan
Maasstad Hospital	Rotterdam	M.G.A. Baartmans
Maastricht University Medical Center	Maastricht	E. Villamor
Martini Hospital	Groningen	H.D. Buiter
Maxima Medical Center	Veldhoven	H.J. Niemarkt
Meander Medical Center	Amersfoort	C.A. Dalen Meurs
Medical Center Leeuwarden	Leeuwarden	M.A.G. van Scherpenzeel - de Vries
Medisch Spectrum Twente	Enschede	L.G.M. van Rooij
Noordwest Hospitalgroup	Alkmaar	G.J. Blok
OLVG	Amsterdam	A.A.M.W. van Kempen
Radboud University Medical Center	Nijmegen	W.P. de Boode
Reinier de Graaf Gasthuis	Delft	L.H. van der Meer
Rijnstate Hospital	Arnhem	C.H. ten Hove
Spaarne Gasthuis	Haarlem	I.A.M. Schiering
St. Antonius Hospital	Nieuwegein	J.L.A.M. van Hillegersberg
University Medical Center Groningen	Groningen	P.H. Dijk
Viecuri Medical Center	Venlo	J.H.L. van Hoorn
Zuyderland Medical Center	Heerlen	R.M.J. Moonen

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	1 – 24
Funding	4	Sources and types of financial, material, and other support	23, 24
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 23
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	23, 24
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	23

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5 - 8
	6b	Explanation for choice of comparators	11
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9 – 10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11 – 12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11 – 12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13 – 14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11 – 13

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15 – 16
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N / A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13 – 15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14 – 15

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14 – 15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16 – 17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16 – 17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17 – 18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18, supplemental file 4
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10, supplemental file 3
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Supplemental file 3
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplemental file 3
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Trial subject information for participation in medical-scientific trials

Additional oxygen for BPD

"Supplemental oxygen in children with bronchopulmonary dysplasia (BPD) following the neonatal intensive care period: the SOS BPD study"

Introduction

Dear Sir/Madam,

You are receiving this letter because your child has bronchopulmonary dysplasia (BPD) and requires supplemental oxygen. We kindly request that you allow your child to take part in a medical-scientific trial. Participation is on a voluntary basis. To take part, you will have to give us consent in writing.
Before you decide whether or not to take part in the trial, we will explain what exactly the trial entails. Please read this information through carefully and ask the researcher for further explanation if you have any questions. Alternatively, you can ask the independent expert, specified at the bottom of this letter, for additional information. You may also discuss it with your partner, friends or family.
Further information about participating in trials can be found on the website of the Rijksoverheid: www.rijksoverheid.nl/mensenonderzoek.

1. General information

This trial has been set up by paediatricians from the Sophia Children's Hospital (Rotterdam), the Emma Children's Hospital (Amsterdam) and the Beatrix Children's Hospital (Groningen) and is being conducted by paediatricians in different hospitals across the country.
This trial requires 198 children from the Netherlands who have BPD. The Erasmus MC medical ethics review committee has approved this trial. General information about reviewing trials can be found in the 'Medical-scientific trials' brochure.

2. Aim of the trial

The aim of this trial is to find out what the best lower saturation limit ('the oxygen content in the blood') is to withdraw supplemental oxygen from children with BPD. In this trial, we are comparing a lower limit of 90% with a lower limit of 95%. Or, is it better to keep the saturation higher or the same as 95% or is 90% just as good?

3. Background to the trial

Supplemental oxygen is the main treatment for children with BPD. However, it has never been investigated what a safe lower saturation limit is in children with BPD after the first few weeks of life, from week 36 of the pregnancy onwards. Both too much and too little oxygen can have serious consequences. Too little oxygen can lead to poorer increase in weight and thereby also poorer lung development and more lung complaints. Too little oxygen can also lead to a higher risk of cot death and be detrimental to development. Too much oxygen is also harmful to the lungs and brain, especially in premature children. Most hospitals observe a lower saturation limit of 90%; however, international guidelines advise 93-95%. But the higher the lower saturation limit should be, the longer children are given additional oxygen and the more frequently they will go home with it.

4. What participation entails

If you wish to allow your child to take part in the trial, we will follow your child's progress up to 1 year after the due date of the pregnancy.

When is your child able to participate?

Your child may take part in the trial from the moment that the pregnancy would have reached 36 weeks onwards. At that time, your child should still require supplemental oxygen, otherwise he or she will not be able to take part. The children participating in the trial are randomly distributed between 2 groups: in one group, we withdraw the supplemental oxygen at a lower limit of 90%; in the other group, at a lower limit of 95%. Fate decides in what group your child ends up; you and the physicians and researchers don't have any influence over this.

Visits and measurements

The trial will take 1 year to complete. During that year, you will visit the hospital twice, when your child is 6 and 12 months of age respectively. These are the standard visits that always take place after (extreme) prematurity, even if you aren't taking part in the trial. The visit will take around 1 hour. During each visit, we will weigh and measure your child and ask about lung complaints, hospital admissions and doctors' visits. Part of the standard treatment in some hospitals includes: a lung function test (by wearing a mask on the face), a CT scan, a sleep study and/or an ultrasound of the heart. The physician treating your child will tell you whether this happens in your hospital too. If your child takes part in the SOS BPD trial, the visit to the outpatients' clinic won't be any different or longer than it usually would be. We will, however, collect the data from the visits for the trial.

In addition to the standard outpatient visits, we will also ask you to answer a number of questions 3 times before the trial by means of a questionnaire sent to you via the internet. This will happen at the beginning of the study, when your child is 6 months old and when your child is 12 months old. The questionnaire will take around 20 minutes to complete.

You will also receive a monthly e-mail asking whether your child has been ill, has been given any medication or has been admitted to hospital recently. You will also have the opportunity to make notes on a secure page on the trial website.

As long as your child is receiving supplemental oxygen, we will ask your physician or yourself (if your child is going home with oxygen) to actively withdraw the oxygen. Oxygen is usually withdrawn in consultation between you and the physician treating your child. For the trial, we will ask you or the physician treating your child to download the saturations from the saturation meter twice a week (or once a week if your child is at home with oxygen) and to e-mail the readings to the researchers. This will be explained to you if you decide to take part in the trial. If the downloaded data reveal that your child is exceeding the lower limit of 90 or 95% too frequently, we will ask the doctor or you to withdraw the oxygen faster. It may also become apparent that your child is falling under the lower limit just that bit too frequently, in which case we will ask you or your doctor to turn the oxygen level up.

Different to the usual care

The visits at 6 and 12 months are standard visits. At this age, all premature children are monitored in the neonatal centre, so these do not constitute additional visits. The questionnaires and the monthly e-mails are additional, however. What's more, the adjustments to your child's oxygen are also different: this happens using the data from the saturation meter which we will ask you to download.

5. What is expected of you?

Participation in the trial means:

- That we will ask you and your doctor to observe the agreed saturation limit
- That we will ask you to keep a note of any admissions, doctors' visits and complaints in an online diary
- That in some hospitals, an additional test will be conducted: a lung function test which involves wearing a mask on the face.

6. Potential detrimental effects

This trial is being conducted because we don't know what's best for children with BPD: a lower limit of 90% or of 95%. Most hospitals currently maintain a lower limit of 90%. The benefit of this is that children are able to stop taking oxygen more quickly and don't go home with oxygen as frequently. The disadvantage could be that children and their lungs don't grow as well. Too low a volume of oxygen could also affect development. The advantage of a lower limit of 95% is that we expect children to grow better and therefore develop more healthy lung tissue. The disadvantage is that children are given additional oxygen for longer and will go home with it more frequently. Too much oxygen can also be harmful to the lungs.

7. Potential advantages and disadvantages

It is important that you weigh up the potential advantages and disadvantages carefully before deciding to take part. A higher lower limit for the oxygen may cause growth/lung growth to improve, but this isn't guaranteed.

Disadvantages of participating in the trial are: potential detrimental effects on the trial measurements.

Participation in the trial also means:

- the child may have to use oxygen at home for longer
- that you will have agreements (in relation to the lower oxygen limit, in particular) that you will have to observe.

It is important that you weigh up the potential advantages and disadvantages carefully before deciding to take part.

8. Your child's resistance

Your child could be resistant (refuse to cooperate) during the trial, in which case, the researcher would have to stop the trial straight away. It is difficult to describe exactly what resistance is. Before the start of the trial, we will discuss with you what is understood by resistance. The researcher will abide by the Code of Conduct for the Resistance of Under-Aged Patients.

9. If you do not wish to participate in or wish to stop the trial

It is up to you whether your child takes part in the trial. Participation is entirely voluntary in nature.
If you do not want your child to take part, your child will be treated for BPD in the usual manner. That means that the doctor treating your child will decide the lower saturation limit with you.

If you do decide to participate, you can change your mind at any time and stop, even during the trial. Once again, your child will be treated the usual way without having to state your reasons for doing so. However, you will need to report this to the researcher straight away. The data that has been collected up to that moment will be used for the trial.

If there is new information about the trial that is important for you, please allow the researcher to tell you. You will then be asked whether you wish to continue to take part.

10. End of the trial

Your child's participation in the trial will stop once:

- all visits are over
- you yourself decide to stop
- the researcher or your child's doctor thinks it's better if your child stops

- the authorities or the assessing medical ethics review committee decides to stop the trial.

The entire trial is over once all participants have finished.
After processing all the data, the researcher will notify you of the main results of the trial. Because the entire trial takes three-and-a-half years to complete, it can take a while before you can expect the results.

11. Use and retention of your child's data

For this trial, it is necessary to collect and use medical and personal data relating to your child. This is necessary to answer the questions asked in this trial and to publish the results.

Confidentiality of your child's data

To protect your child's privacy, each trial subject is given a code which is stated on the data. The name and other personal data that could be used to identify your child are omitted. The researcher is the only person who knows your child's code. The key for the code remains with the researcher. Even in reports about the trial, only that code is used.

Access to the data

Some people may view your child's medical and personal data to verify whether the trial has been conducted properly and reliably. General information about this can be found in the 'Medical-scientific trials' brochure.

People who are able to view your data are: the research team, the safety committee monitoring the trial, an auditor who has been brought in by the researchers of the trial and the Dutch Health Care Inspectorate. They will keep your data confidential. When you sign the consent form, you are consenting to the collection, retention and viewing of your medical and personal data.

Data retention period

The researcher will retain your child's data for a period of 15 years in accordance with the statutory retention period.

Withdrawing consent

You can withdraw your consent to the use of personal data again at any time. This applies both to this trial and to its retention and use for any future trials. Trial data collected up to the moment you withdraw your consent will then still be used in the research.

Further information about your rights when processing data

For general information about your rights when processing your personal data, you may consult the Dutch Data Protection Authority's website (www.autoriteitpersoonsgegevens.nl).

If you have any questions about your rights, please contact the data controller responsible for the processing of your personal data, See enclosure A for contact details.

If you have any questions or complaints about the processing of your personal data, we advise contacting the trial location in the first instance. You may also contact the Data Protection Officer at the Erasmus MC or the Dutch Data Protection Authority.

Registration of the clinical trial

This trial also appears in a list of medical-scientific trials, namely the trial register (www.trialregister.nl; trial code 7347). This website doesn't contain any information that can be traced back to your child. However, the website may show a summary of the results. General information about registering trials can be found in the 'Medical-scientific trials' brochure.

12. Insurance for trial subjects

Appropriate insurance will be taken out for everyone who decides to enter this trial. The insurance covers damage caused by the trial. It does not cover all damage. **Enclosure B** contains further information about the insurance, including who you can report damage to.

13. Notifying the GP and/or treating specialist

We always send your child's GP and/or treating paediatrician a letter to tell them that your child is taking part in the trial. This is for your child's own safety. If you do not agree to this, your child will not be able to take part in this trial. The GP or paediatrician will also receive a letter concerning the 6 and 12-month visits. This is also the norm even if your child is not taking part in the trial.

14. No payment for participating

The additional tests and treatment for the trial won't cost you anything. You will not receive payment for taking part in this trial.

15. Any questions?

If you have any questions, please contact the trial team. For independent advice about taking part in this trial, please contact the independent doctor, Dr P.J.F.M. Merkus. He knows a great deal about this trial, but doesn't have anything to do with the trial.
In the event of complaints, please contact the complaints officer at your hospital. All information can be found in **Enclosure A**: Contact details.

16. Signing of consent form

Once you have had sufficient thinking time, you will be asked to decide about your child's participation in this trial. If you decide to take part and give consent, please confirm this in writing using the enclosed informed consent form. By giving written consent, you confirm that you have understood the information and agree to take part in the clinical trial.
The signatures page will be retained by the doctor treating your child. You will receive a copy of this consent form.

Thank you for taking the time to read this letter.

Enclosures to this information

A. Contact details

B. Information about insurance

C. Consent form

Enclosure A: contact details for *name hospital*

Researcher at *name hospital*:

Local principle investigator.

Telephone number: *xxxxx*. E-mail: *xxxxxx*

Coordinating researcher:

Ms S.J.A. Balink, research physician at Erasmus MC - Sophia Children's Hospital.

Telephone number: +31 (0)6 500 33994. E-mail: sosbpd@erasmusmc.nl.

Independent doctor:

Dr P.J.F.M. Merkus, paediatric pulmonologist, Amalia Children's Hospital, Radboud UMC Nijmegen. Telephone number: +31 (0)24 361 4430. E-mail: Peter.Merkus@radboudumc.nl

Complaints:

Hospital format

Data Protection Officer:

Hospital format

Enclosure B: information about insurance

Erasmus MC has taken out insurance for everyone taking part in this trial. The insurance covers damage caused as a result of taking part in the trial. This applies to damage caused during the trial or within four years of the end of the trial. Claims must be submitted to the insurer within this four-year period.

This insurance policy does not cover all damage. You will find a brief outline of the exceptions below.
The full version of these provisions are included in the Compulsory Insurance for Medical Research Involving Human Subjects Decree, which can be consulted at www.ccmo.nl, the website of the Central Committee on Research Involving Human Subjects (go to 'Bibliotheek' and select 'Wet- en regelgeving').

In case of damage, submit your claim directly to the insurer.

The insurer for this clinical trial is:	
Name:	CNA Insurance Company Limited
Address:	Polarisavenue 140, 2134 JX Hoofddorp
Telephone number:	+31 (0)23 303 6004
E-mail:	Esther.vanherk@cnaeurope.com
Policy number:	10.220.695
Contact person:	Ms Esther Van Herk

The insurance offers coverage of €650,000 per trial subject and €5,000,000 for the entire trial and €7,500,000 per year for all trials conducted by the Erasmus MC.

The following damage is **not** covered by the insurance policy:

- damage caused by a risk of which you were informed in the written information. This does not apply if the materialisation of the risk is more severe than foreseen or if materialisation of the risk was highly unlikely.
- damage to your health that would also have materialised if you had not entered the clinical trial;
- damage as a result of failure to follow directions or instructions or failure to follow these in full;
- damage to your descendants caused by an adverse effect of the trial on you or your descendants;
- damage caused by an existing treatment method in the case of research into existing treatment methods.

SOS BPD

Enclosure C: Consent form for parents or guardians

Additional oxygen for BPD

I have been asked to give my consent to my child's participation in this medical-scientific trial:

Name of child: Date of birth: __ / __ / __

- I have read the information letter for parents/guardians. I was also able to ask questions. My questions have been answered satisfactorily. I had enough time to decide whether or not to enter my child in the trial.
- I know that participation is voluntary. I also know that I may decide to withdraw my child from the trial at any time, without having to state any reasons for doing so.
- I give my consent to the GP/paediatrician treating my child being informed that my child is taking part in this trial.
- I give my consent to the requesting of information from the paediatrician treating my child concerning my child's hospital admissions.
- I am aware that some people are able to view my child's data. The people in question are specified in this information letter.
- I give my consent to the use of the data in the manner and for the purposes stated in the information letter.
- I give my consent to my child's data being retained at the trial location for a period of 15 years after this trial has finished.
- I give my consent to the use of my e-mail address, only for this trial.
- I □ **do*** □ **do not** give my consent to my child being contacted again about a follow-up trial once this trial has ended.

- I agree to my child taking part in this clinical trial.

Name of parent/guardian 1: ……

Signature: Date: __ / __ / __

E-mail address: ……..

Name of parent/guardian 2: ……

Signature: Date: __ / __ / __

E-mail address: ……....

I hereby declare that I have notified in full the above-mentioned person/persons about the named trial.

If any information were to emerge during the trial that could affect the parent's or guardian's consent, I shall notify him/her in due time.

Clinical researcher's name (or his/her representative):

Signature: Date: __ / __ / __

Additional information has been provided by:

Name:

Position:

Signature Date: __ / __ / __

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* Place a cross next to that which is applicable.

Supplemental material file 4

Weaning of supplemental oxygen and respiratory support

Continuous positive airway pressure (CPAP)

The available methods of weaning CPAP are:
1. Withdrawal of CPAP (to room air or nasal cannula/low flow with oxygen)
2. Gradually reduce time on CPAP, i.e. alternating hours without CPAP with hours on CPAP
3. Gradually reduce pressure on CPAP, for example from 6 cm H2O to 5, to 4 cm H2O.

A systematic review [1] shows that none of these methods leads to better outcomes. Gradual reduction may be preferable.
The optimal FiO2 from which weaning can be performed with CPAP has not been defined. Successful weaning is unlikely in children who need >40% oxygen [2].

Step 1	Weaning from CPAP based on local protocol.
Step 2	If there is no local protocol to wean from CPAP, then the following is advised: - If FiO2 > 30%, first decrease FiO2 in steps of 5%, maximal 1 step per 12 hours. - If increase in desaturations, then increase FiO2 until child is stable at/above saturation limit. - If FiO2 is stable during 24 hours and ≤ 30%, then proceed to step 3
Step 3	Gradually decrease the pressure of the CPAP to 3-4 cm H2O and then discontinue. - Decrease per step by 1 cm H2O - A maximum of 1 step per 24 hours is advised After discontinuation of CPAP, there is no additional support required unless there is an increased work of breathing. You can then start with low flow.

Heated Humidified High Flow Nasal Cannula (HHHFNC)

There is no evidence on how to taper off HHHFNC [3]. The following recommendations are based on expert opinion [4]:

- Wean first FiO2, then flow rate. Weaning is more likely to be successful in children who get less than 30% FiO2.-
- Wean 1 L/min every 12 hours, guided by the child's work of breathing
- Consider discontinuing at flow rates between 2-4 L/min (lowest amount of flow is device
- dependent). There is no evidence (yet) about the benefits of HHHFNC on flow rates less than 3 L/min.

Step 1	Weaning from HHHFNC based on local protocol.
Step 2	If there is no local protocol to wean from HHHFNC, then the following is advised: - First decrease FiO2 to < 30%. - Decrease flow with 1 L/min, maximal 2 steps per 24 hours. Consider steps of 0.5 L/min if increased work of breathing. - Wean to 2 L/min and 30% FiO2, then stop HHHFNC. Low flow supplemnatl oxygen may be considered.

Low flow supplemental oxygen (< 2 L/min)

There are no guidelines or RCTs known regarding the reduction of low flow support in newborns. Some societies do make a cautious recommendation about discontinuation of support, including the British Thoracic Society and the Thoracic Society of Australia and New Zealand [5-8].
With regard to the cessation of oxygen support, it is stated that hypoxia is likely most common during feedings and sleeping. That is why it is recommended first to discontinue O2 support during waking episodes and expand from there during sleep.

Step 1	Weaning from low flow based on local protocol.
Step 2	If there is no local protocol to wean from low flow O2, then the following is advised: - reduce with 0.5 L/min per step till 1 L/min. - If flow 1 L/min, consider to switch to nasal prongs with 100% FiO2. - If flow ≤ 1 L/min, decrease with 0.1 L/min per step to minimal flow of 0.1 L/min.
Step 3	If on 0.1 L/min 100% O2 further steps are: - Stop low flow during awake periods for a max of 3 hours. - Increase time without supplemental oxygen when awake - Stop low flow during the day (including sleep periods during the day) - Stop low flow

Increasing supplemental oxygen and respiratory support

If the saturation profile shows that the child is below the SpO2 target 10% of the time or more, then respiratory support should be intensified.
Also if parents or treating physicians observe frequent desaturations outside a measurement period (saturation profile), then the support should be intensified.

Step 1		Go back to the last step before weaning
Step 2		If insufficient effect, next steps are dependent on the type of respiratory support.
	CPAP	- Increase FiO2 with steps of 5% to max of 40% until a stable situation is reached - If FiO2 > 40 is needed, increase pressure with 1 cm H2O
	HHHFNC	- Increase FiO2 with steps of 5% to max of 40% until a stable situation is reached - If FiO2 > 40 is needed, increase flow with 1 L/min
	Low flow 1-2 L/min, variable FiO2	- Increase FiO2 with steps of 5% to max of 40% until a stable situation is reached - If FiO2 > 40 is needed, increase flow with 0.5 L/min
	Low flow 0.1-1 L/min FiO2 100%	- Increase flow with 0.1 L/min until a stable situation is reached

References

1. Amatya S, Rastogi D, Bhutada A, Rastogi S: Weaning of nasal CPAP in preterm infants: who, when and how? a systematic review of the literature. World J Pediatr 2015, 11(1):7-13.
2. Abdel-Hady H, Shouman B, Nasef N: Weaning preterm infants from continuous positive airway pressure: evidence for best practice. World J Pediatr 2015, 11(3):212- 218.
3. Farley RC, Hough JL, Jardine LA: Strategies for the discontinuation of humidified high flow nasal cannula (HHFNC) in preterm infants. Cochrane Database Syst Rev 2015(6):CD011079.
4. Roehr CC, Yoder BA, Davis PG, Ives K: Evidence Support and Guidelines for Using Heated, Humidified, High-Flow Nasal Cannulae in Neonatology: Oxford Nasal High-Flow Therapy Meeting, 2015. Clin Perinatol 2016, 43(4):693-705.
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6. Adde FV, Alvarez AE, Barbisan BN, Guimaraes BR: Recommendations for long-term home oxygen therapy in children and adolescents. J Pediatr (Rio J) 2013, 89(1):6-17.
7. Primhak R: Oxygen titration strategies in chronic neonatal lung disease. Paediatr Respir Rev 2010, 11(3):154-157.
8. Thoracic Society of A, New Z, Fitzgerald DA, Massie RJ, Nixon GM, Jaffe A, Wilson A, Landau LI, Twiss J, Smith G et al: Infants with chronic neonatal lung disease: recommendations for the use of home oxygen therapy. Med J Aust 2008, 189(10):578-582

Supplemental file 5: Audit frequency and procedures

Monitoring frequency

Visit no.	Selected Sites	Planning*
Initiation Visit	All	Before enrolment of the first subject, but after Ethics Committee and Board of Deans approval has been obtained.
First Monitoring Visit A	All participating sites	After 2 - 3 randomised subjects, irrespective of (e)CRF completion.
First Monitoring Visit B	All 10 NICUs	Only if not including subjects so when Visit A has not been performed. After 5 - 6 randomised subjects have completed the 6 month visit, irrespective of (e)CRF completion.
Remote Visit	All sites	Contact via telephone or email approximately 12 weeks after the First Monitoring Visit A or B
Second Monitoring Visit	5 high recruiting sites	After all subjects have been randomised, the 5 sites who have randomised the most subjects
Remote Visit	All 5 high recruiting sites	Contact via telephone or email approximately 12 weeks after the Second Monitoring Visit
Remote Close Out	All sites	After database lock
TMF check in combinations with check on 6 months FU data if possible	Sponsor site	In 2019 and 2022

*The frequency may be changed based on the total enrolment period, the inclusion rate, quality issues and/ or site performance, but only after consultation with the Coordinating PI.

Monitoring procedures

The follow items will be discussed/ verified by the Clinical Research Associate (CRA) during the different visits.

First Monitoring Visit

- Who is/ are the contact person(s) at site

- Is the entire investigators' study staff adequately informed about the study e.g. randomisation procedure, sample collection, procedures in case of protocol deviations/ serious breaches, SAE notification procedures etc.
- Is the entire investigators' study staff WMO/GCP trained and authorized (site signature and delegation log)
- Has the study staff sufficient time to perform the study?
- How and by whom is the subject informed about the study?
- By whom is consent obtained and is it properly documented?
- Who will examine the subject every visit?
- Who performs the screening, baseline and other visits/ how is this arranged?
- Which source documents are available?
- Source Data Review
- Source Data Verification
- Where is the source data stored?
- Who will maintain the subject identification code list/ screening log/ enrolment log?
- Who is completing the (e)CRF?
- When/ how/ where and by who are questionnaires filled in?
- Which facilities are used (any changes)?
- Which equipment is used (any changes)?
- Have any Serious Adverse Events (SAEs) occurred?
- Reporting of SAE's
- Are there any known protocol deviations and/ or serious breaches of ICH-GCP and/ or protocol?
- Is the Trial Master File/ Investigator Site File up to date (AMC SOP CTR 006/ ICH-GCP guideline 8.1 – 8.3)?
- What is the expected recruitment rate?
- Competitive studies running?
- Informed consent process, use of Patient Information Form and Informed Consent form
- In- and exclusion criteria

Remote Visits

- Discuss progress of follow-up of action items
- Is the enrolment overview up to date (amount screened subjects, amount of screen failures/withdrawn subjects, amount of randomised/enrolled subjects, amount of active subjects, amount of subjects in follow-up and amount of subjects that have completed the trial)?.
- Are there any changes in the investigators' study staff (trained and authorized)?
- Are there any changes in facilities or equipment?
- Have any SAEs been reported since previous on-site monitor visit?
- Are there any known protocol deviations and/or serious breaches of ICH-GCP and/or protocol?

Ongoing Monitoring Visits

- Is the entire investigators' study staff adequately informed about the study?

- Is the entire investigators' study staff WMO/GCP trained and authorized (site signature and delegation log)
- Are there any changes in the investigators' study staff (trained and authorized)?
- Are there any changes in facilities or equipment?
- Is the investigational medicinal product accountability properly documented?
- Have any SAEs occurred?
- Are there any known protocol deviations and/or serious breaches of ICH-GCP and/or protocol?
- Is the Trial Master File/ Investigator Site File up to date (AMC SOP CTR 006/ICH-GCP guideline 8.1 – 8.3)?
- Are there any new amendments in place?