RESEARCH PROTOCOL

SOS BPD study

(February 2021, version 4)

PROTOCOL TITLE

'Supplemental oxygen strategies in children with Bronchopulmonary dysplasia (BPD) after the neonatal intensive care unit: the SOS BPD study.'

Protocol ID	**SOS BPD**
Short title	**The SOS BPD study.**
EudraCT number	**Not applicable**
Version	**4**
Date	**01-02-2021**
Coordinating investigator/project leader	Dr. M.W.H. Pijnenburg Erasmus MC – Sophia, Room SP3456 Wytemaweg 80 3015 CN Rotterdam m.pijnenburg@erasmusmc.nl 010 7036263/ 7020
Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder)	**Erasmus MC – Sophia Children's Hospital, Rotterdam** Dr. M.W.H. Pijnenburg Prof. I. Reiss Dr. A.A. Kroon **AMC - Emma Children's Hospital and VU medical center, Amsterdam** Prof. Dr. A.H. van Kaam Dr. W. Onland **UMCG – Beatrix Children's Hospital, Groningen** Dr E.J.L.E.Vrijlandt Dr. P.H. Dijk Prof. A.F. Bos **LUMC – Leiden**

	R. Tan **UMCU – Utrecht** K. Rademaker **Radboud UMC – Nijmegen** P.R. Matthijsse **MUMC – Maastricht** B. Kramer **Maxima Medisch Centrum – Veldhoven** H. Niemarkt **Isala - Zwolle** H.L. van Straaten
Sponsor (in Dutch: verrichter/opdrachtgever)	Prof. Dr. E. H. H.M. Rings, head dept. Paediatrics Erasmus MC - Sophia Wytemaweg 80 3015 CN Rotterdam e.rings@erasmusmc.nl T 010 7036226
Subsidising party	1.Longfonds Contact: Bas Holverda Postbus 627 3800 AP Amersfoort 2.ZonMW Doelmatigheid

	Contact: Anneke Middeldorp Postbus 93 245 2509 AE Den Haag
Independent expert (s)	Dr. P.J.F.M. Merkus Radboud UMC Geert Grooteplein Zuid 10 6525 GA Nijmegen Peter.merkus@radboudumc.nl T 024 361 111
Laboratory sites	Not applicable
Pharmacy	Not applicable

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Sponsor or legal representative: **Head of Department:** Prof. Dr. E. H. H.M. Rings, Head of dept. Paediatrics, Erasmus MC, Sophia Children's Hospital		19/2/21
[Coordinating Investigator/Project leader/Principal Investigator]: Dr. M.W.H. Pijnenburg, head dept. Paediatric Respiratory Medicine and Allergology, Erasmus MC, Sophia Children's Hospital		19/2/21

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
BPD	**Bronchopulmonary dysplasia**
CarerQOL	**Caregivers quality of life questionnaire**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CPAP	**Continuous Positive Airway Pressure**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
GCP	**Good Clinical Practice**
HFNC	**High Flow Nasal Cannulae**
IBQ-R	**Infant Behaviour Questionnaire-Revised**
IC	**Informed Consent**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
NICU	**Neonatal Intensive Care Unit**
PMA	**Postmenstrual age**
(S)AE	**(Serious) Adverse Event**
SD(S)	**Standard deviation score**
SpO2	**Oxygen saturation measured by pulse oximetry**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Every year in the Netherlands, 500 preterm born children develop bronchopulmonary dysplasia (BPD), a chronic lung disease with life-long sequelae. (1) The main treatment of BPD is supplemental oxygen. 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. International guidelines, based on expert opinion only, recommend a lower limit ranging between 93 and 95%, while limits of 90% are considered usual care in most Dutch neonatal units and regional hospitals. (2) We hypothesize that a lower limit of 95% when compared to 90% leads to better lung growth assessed indirectly by body weight at 6 months corrected age.

Objective: The primary objective of this study is to investigate if targeting a higher SpO_2 (i.e. 95% lower limit) leads to superior growth of normal lung tissue (assessed indirectly by body weight) at 6 months corrected age as compared to targeting a lower SpO_2 (90% lower limit) in children with moderate-severe BPD from 36 weeks PMA and onwards.

Study design: Randomised controlled open multi-centre study with two arms: 1. Lower SpO_2 limit of 95%; 2. Lower SpO_2 limit of 90%. Follow up will be one year with three visits. SpO_2 curves will be audited from pulse oximeters and feedback will be given to the physicians and/or parents. They will be stimulated to actively wean the children from supplemental oxygen based on these curves and study group.

Study population: Children born < 32 weeks of gestational age with moderate or severe BPD, will be included between 36 and 38 weeks of PMA. BPD will be defined as oxygen need for ≥ 28 days from birth until 36 weeks of PMA. BPD severity will be assessed at 36 weeks PMA. Children who, at that time, need ≥ 30% supplemental oxygen or depend on nasal continuous positive airway pressure (nCPAP), high flow nasal cannula oxygen (HFNC) or mechanical ventilation are classified as having severe BPD. If children need >21% oxygen but < 30% they are classified as having moderate BPD. If needed, an oxygen reduction test will be performed to assess BPD severity. (3)

Intervention: weaning of supplemental oxygen based on a lower SpO_2 limit of 95% as compared to 90% (usual care).

Main study parameters/endpoints: The primary outcome is body weight at 6 months corrected age, as a surrogate for lung growth. Secondary outcomes are weight and height at 12 months corrected age, hospital re-admissions, parental quality of life, infant stress, length of hospital stay, duration of oxygen supplementation and unscheduled health care visits. Lung function and CT scores will be measured in a subgroup of patients. A cost-effectiveness analysis will be performed alongside this trial.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The burden and risks associated with participation in the study are limited. There are no extra visits to the hospital as the 2 visits follow the routine follow-up of patients born extremely preterm. At every visit weight, height and head circumference are measured, which is routine care. In a subgroup of patients lung function tests and/or a free breathing CT scan of the chest will be performed, only if these tests are routine care in the specific hospitals. The parents will be asked to fill in 2 questionnaires (CarerQOL and IBQ-R) at inclusion, 6 and 12 months. Parents will have the possibility to record data on respiratory complaints, admissions, and absence from work in an online monthly diary.
The risks of the study are negligible as the lower limit of 90% is considered usual care. Also, in a study in *younger* children from 32 weeks PMA onwards there was no difference in endpoints (growth, neurodevelopmental outcome) between a lower (91-94%) and a higher (95-98%) SpO_2 target. (4) Our study includes children with an established diagnosis of BPD, from 36 weeks PMA onwards, which is the period that alveolarization starts, which implies that SpO_2 limits may be different in this group. Potential benefit of the study is that weaning of oxygen is performed in a controlled and well-monitored way with frequent feedback to treating physicians and/or parents. A disadvantage of the study may be that children in the high SpO_2 group will be longer on oxygen, whether in the hospital or at home. In the study by Askie et al length of hospital stay was not different for the high versus low SpO_2 group. (4)

1. INTRODUCTION AND RATIONALE

Extreme preterm birth leads to an arrest in lung and pulmonary vascular development which may result in bronchopulmonary dysplasia (BPD). (5) BPD is a chronic lung disease that leads not only to life-long respiratory issues, but also to adverse cardiovascular and neurodevelopmental outcomes. (6) Moreover, the impact on parents of taking care of a child with BPD can be significant with increased stress, low sleep quality and depressive symptoms, all having an impact on their quality of life. (7) In the Netherlands, BPD affects approximately 500 infants each year, of whom two thirds have the moderate to severe form of the disease, which means that they are still oxygen-dependent at 36 weeks postmenstrual age (PMA). (1)

The main treatment for BPD is supplemental oxygen. Several randomised controlled trials have assessed a liberal versus a restricted use of supplemental oxygen in extreme preterm infants in the first weeks of life on major outcomes such as death, development of BPD or retinopathy of prematurity, and neurodevelopment. (8, 9) However, no study has ever examined the optimal oxygen saturation (SpO_2) target that should be obtained by supplemental oxygen in children with established BPD after 36 weeks PMA. This target may be different from the established SpO_2 targets in the first weeks of life, as at 36 weeks PMA vulnerability to oxidative stress (and e.g. development of retinopathy of prematurity) has most probably decreased. Moreover, alveolar growth only starts from approximately 34 weeks of gestation, announcing a new era in lung growth.

Due to the lack of studies, the Dutch BPD guideline refrains from any recommendations on SpO_2 targets in children with established BPD. (10) This has resulted in wide practice variability between hospitals in lower SpO_2 targets, with most hospitals accepting a lower SpO_2 limit of 90%. However, this limit may be too low, because, according to a number of observational studies, supplemental oxygen may decrease respiratory symptoms, prevent pulmonary hypertension, be beneficial for neurodevelopment and improve weight gain if BPD is present. (11-14) Importantly, in children with BPD, body weight during infancy has been positively associated with the amount of normal lung tissue as assessed with CT scans, and better lung growth is related to increased lung function in later life. (15, 16) Furthermore, poor weight gain is associated with increased vulnerability to infections and supplementary oxygen may reduce the risk for nosocomial infections and consequently for re-hospitalisation. (17, 18) On the other hand, hyperoxia (e.g. too much oxygen) may result in increased levels of reactive oxygen species and subsequent oxidative damage. (19) This may negatively influence lung development but also the development of other organs such as the eyes and

the brain. (20) In short, too little oxygen may have detrimental effects on preterm children with BPD, while too much oxygen should also be avoided, and it is unknown where this balance lies between too little and too much oxygen.

What will this study add

This study will determine the optimal lower SpO_2 target in children with moderate- severe BPD, i.e. children who are oxygen-dependent at 36 weeks PMA. The results of this study will be implemented in updated guidelines.

Study population

This study can only be performed in preterm infants with established moderate or severe BPD at 36 weeks PMA. BPD is a disease of infancy, which may have life-long consequences.

2. OBJECTIVES

Primary Objective

1. The primary objective of this study is to investigate if targeting a higher SpO_2 (i.e. 95% lower limit) leads to superior growth of normal lung tissue (assessed indirectly by body weight) at 6 months corrected age as compared to targeting a lower SpO_2 (90% lower limit) in children with moderate-severe BPD from 36 weeks PMA and onwards.

Secondary objectives:

2. To determine if targeting a higher SpO_2 (i.e. 95% lower limit) translates into better body weight and height at 12 months corrected age, less health care consumption and better quality of life of the parents or caregivers.

3. To determine if a strategy aiming at a lower limit of SpO_2 of ≥ 95% is cost-effective.

Secondary objectives in a subgroup of children:

4. To determine if a strategy aiming at a lower limit of SpO_2 of ≥ 95% translates into better lung function (lower lung clearance index) and/or better lung structure as assessed with CT scans.

5. To determine if a strategy aiming at a lower limit of SpO_2 of ≥ 95% translates into less pulmonary hypertension and/or better right ventricle systolic function.

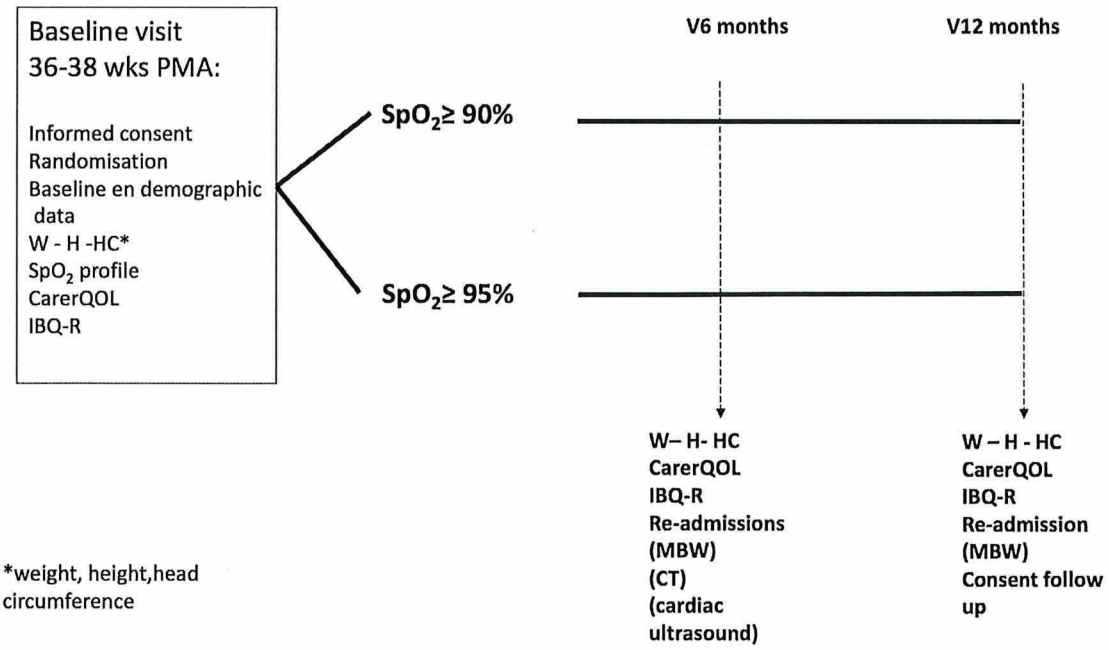
3. STUDY DESIGN

This is a multi-centre randomised controlled, open study in children with moderate-severe BPD from 36 weeks PMA onwards with two parallel arms:

1. weaning of supplemental oxygen based on SpO_2 lower limit ≥ 95%
2. weaning of supplemental oxygen based on SpO_2 lower limit ≥ 90%.

This is a non-blinded study because we considered it not feasible to blind parents and treating physicians for SpO_2, as supplemental oxygen will be weaned based on SpO_2.
Study duration for each patient will be one year with three visits: at inclusion and at 6 and 12 months corrected age.
Setting of the study: patients will be included between 36 and 38 weeks PMA, when they are still admitted on the NICU or post-IC-high care units. Follow up will be alongside neonatal follow up pathways at outpatient clinics.

Study design:



4. STUDY POPULATION

4.1 Population

Children born < 32 weeks of gestational age, with moderate or severe BPD, will be included between 36 and 38 weeks of PMA. BPD will be defined as oxygen need for ≥ 28 days from birth until 36 weeks of PMA. BPD severity will be assessed at 36 weeks PMA. Children who, at that time, need ≥ 30% supplemental oxygen or depend on nasal continuous positive airway pressure (nCPAP), high flow nasal cannula (HFNC) oxygen (≥2 L/ min) or mechanical ventilation are classified as having severe BPD. If children need >21% oxygen but < 30% an oxygen reduction test will be performed to assess BPD severity. (3) Only children with moderate BPD according to the oxygen reduction test can be included.

The protocol allows for twins and triplets to be included if meeting the inclusion criteria. For logistical reasons all infants from one family will be assigned to the same treatment arm.

Children will be assessed for eligibility by the treating physician in the NICU where the child was born, as all children born < 32 weeks of gestational age are treated in a NICU. Between 35 and 36 weeks PMA, the local investigator of the NICU will contact the treating physician of the hospital where the child is admitted (whether this is NICU or post-IC high care unit) to determine if the child is still eligible for the study (e.g. moderate or severe BPD and still in need of supplemental oxygen). If so, the treating physician will be asked to explain the study to the parents and will provide them with parent information on the study.

<u>Feasibility of recruitment</u>

In the Netherlands in 2015 170.510 children were born. (21) Around 1540 of them were born < 32 weeks of gestation AND were still alive after 28 days. The incidence of BPD in children born < 32 weeks in the Netherlands is not known. Recent international data from Western Europe show a mean incidence of moderate-severe BPD at 36 weeks PMA of 22% in this group. (22) This gives an estimated number of eligible children of 339 per year in the Netherlands.

We aim to include 198 neonates over a period of 2.5 years of recruitment based on an expected response rate of 30% and allowing a drop-out rate of 10%. Every NICU will aim to include 0.3-2 children per month from their centre. The heads of all NICUs expressed their (written and signed) willingness to participate in the study.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Born <32 weeks gestation
- Diagnosis of moderate or severe BPD according to national guidelines
- Written informed consent by parents and/or caregivers

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Significant congenital heart disease (not being persisting ductus arteriosus, small atrial septal defect, ventricular septal defect)
- pulmonary hypertension treated with sildenafil or bosentan
- retinopathy of prematurity for which the ophthalmologist recommended a patient specific SpO_2 target
- congenital malformations of the lung or airways
- severe acquired upper airway abnormalities like subglottic stenosis necessitating endotracheal intubation
- interstitial lung diseases

4.4 Sample size calculation

There have been no studies addressing our research question in children from the age of 36 weeks PMA.

A simulation study with 4 scenarios was performed to calculate how many patients are needed in order to obtain a significant differences between the 2 groups after 6 months. Our outcome is weight standard deviation score at 6 months corrected age. We assumed a mixed effect model with a random intercept to account for the correlation between the patients that come from the same hospital. We assume 10 hospital-clusters (10 NICU centres with appurtenant post IC/HC departments in the surrounding regional hospitals) with each hospital-cluster having 16 (±3) or 18 (±3) number of patients. The mean weight at 6 months for group 0 was assumed -1.15 SD and the mean weight at 6 months for group 1 was assume -0.65 SD since a higher weight of 0.5 SDS 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 0.1 and 0.2 SD.

	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Power	0.72	0.82	0.73	0.83
Variation of weight (hospital)	0.10	0.10	0.20	0.20
Total patients	160	180	160	180

For the actual study sample size, we will use scenario 4. This scenario has the highest power and it assumes the greatest variation of weight between different hospital clusters. This leads to a sample size for our study of 180 patients. Accounting for a drop-out rate of 10%, we aim to include 198 neonates.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

We will investigate an active supplemental oxygen weaning strategy based on a lower limit of SpO_2 of 95% as compared to 90%. In the intervention group supplemental oxygen will be weaned on a lower limit of SpO_2 of 95% (lower alarm limit will be set on 94%). This limit has been chosen for several reasons. First, the median SpO_2 in well term infants and in convalescent preterm born infants is 98% and 95-97% respectively. (23) International guidelines meanwhile recommend to keep SpO_2 >93% and, setting a lower limit of 95% vs 90% will make overlap between the intervention and usual care group (the controls) as small as possible. (2, 24) As the current standard care target is 90%, in the control group, supplemental oxygen will be weaned on a lower limit of SpO_2 of 90% (lower alarm limit will be set on 89%). (25-27)

As long as the child is on supplemental oxygen, SpO_2 curves will be obtained and audited from hospital pulse oximeters by the research team twice weekly and feedback will be given to the treating team. They will be stimulated to actively wean the children from supplemental oxygen if SpO_2 is above the lower limit according to the treatment arm for > 90% of the time. In children who will be discharged home on oxygen, the research team will obtain weekly SpO_2 curves from home pulse oximeters. Feedback will be given to the caregivers in close collaboration with the treating physician and they will be instructed to decrease supplemental oxygen if SpO_2 is above the lower limit according to the treatment arm for > 90% of the time.

There is no evidence on a cut-off point for the amount of time that is accepted for an infant to saturate above or below an established limit. 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.(2) However, this does not take into account that a 24 hour saturation profile made with pulse oximetry in an infant is prone to artefacts, since periods of feeding, activity and sleeping are all registered. Furthermore, Terrill et al. studied normative oximetry data in extreme preterm infants at term equivalent age. They found mean saturations of 96.1% (95.4–96.8%) with 7.56% (5.1–10.0%) of the measuring time spent below an oxygen saturation of 90%.(28, 29).

For this reason, the time spent below the lower limit will be accepted to a maximum of 10%: when the oxygen saturation is below the assigned SpO_2 lower limit for ≥10% of the recorded time (equivalent to <90% of the time spent above the lower limit), the treating team is stimulated to increase supplemental oxygen. When the oxygen saturation 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 will be advised to wean supplemental oxygen.

SpO_2 data can be logged in different ways:

1. Logged from the pulse oximeters and stored on a USB stick. All data downloaded from a pulse oximeter is anonymous, since no patient characteristics are saved on it. The USB stick will not be secured with BitLocker, since a pulse oximeter does not recognize BitLocker and will not log it's data on the USB device. Since only anonymous data are logged, this will not be a problem. Downloaded data will be pseudonymised with a study and patient specific number by the local researcher who logged the data. Pseudonymised data will then be sent through encrypted file transfer to the researchers.
2. In some hospitals, all clinical data derived from monitoring a patient (for instance oxygen saturation and heart rate), is automatically saved in a central server based storage and can be accessed and downloaded with permission of the hospital or department by the local researcher. If this is the case, the necessary data can be downloaded from the hospital server, instead of logging it onto a USB device. This data will also be pseudonymised and be sent to the researchers in the same way as when the data was downloaded from the pulse oximeter.

A standard operating procedure will give recommendations on weaning supplemental oxygen; this SOP will follow daily practice as closely as possible. In children on low flow oxygen, most children will have 100% oxygen and lowering flows of oxygen is the only way to wean, at least in the home situation. In this group of patients, we will recommend to start weaning by lowering flows of oxygen with 0.1 L/min/period. Once the oxygen requirement reaches 0.1 L/min, discontinuation should be considered. One week after stopping supplemental oxygen a control SpO_2 profile will be obtained and audited. If this profile shows SpO_2 > target for > 90% of the time no more SpO_2 profiles will be obtained.

If a child is readmitted to hospital while still on supplemental oxygen the lower SpO2 limit

to which the child was randomized will be kept. If children are readmitted after they stopped supplemental oxygen for at least 2 weeks, the lower SpO2 limit will be up to the treating physician during admission.

All NICU centres post-IC/HC centres participate in the study. Rarely, a study participant will be transferred to a hospital that does not participate in the study (non-(post)IC/HC centre) for medical reasons. Oxygen saturation profiles cannot be made in that hospital. This will be accepted and will be noted as a protocol deviation; the time without saturation profiles will be noted as well. The participant will not be excluded from the study, since data has already been collected until then and exclusion is not ethical.

If thereafter the study participant is discharged home with supplemental oxygen from the non-participating hospital, saturation profiles can be resumed and be obtained from home pulse oximeters. The feedback and adjustment of respiratory treatment of the participant then falls under the joint responsibility of the (participating) NICU centre and the regional hospital.

Analysis will be on an intention-to-treat basis.

In the usual care group (the control group) treatment is similar to the intervention group except for supplemental oxygen being weaned on a lower limit of SpO2 of 90% (lower alarm limit will be set on 89%).

5.2 Use of co-intervention

All other interventions during the study such as feedings, fluid restriction, diuretics and inhaled or oral corticosteroids will be according to national guidelines or local policies if guidelines are not available, in order to improve feasibility and generalizability of the results of the trial. Feedings and medication will be recorded weekly as long as children receive supplemental oxygen, and during study visits.

5.3 Escape medication

Deviation of the protocol is possible if according to the treating physician this is deemed necessary for urgent medical reasons. Deviations of the protocol will be discouraged if SpO_2 profiles show that SpO_2 is above the target SpO_2 for > 95% of the time. Protocol deviations should be reported to the research team with the reasons for deviation from the

protocol. Deviation from the protocol because of failure to thrive is not allowed, as growth is our primary endpoint. Analysis will be on an intention-to-treat basis.

6. INVESTIGATIONAL PRODUCT

Not applicable.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The primary endpoint of this study is weight standard deviation score (SDS) at 6 months corrected age. We choose weight as primary outcome for the following reasons:

1. Increased weight and weight gain during infancy are associated with better lung function and structure (30, 31); as such, growth is a surrogate for lung growth.
2. Growth delay is associated with an increased risk of future respiratory and cardio-metabolic disease and impaired intellectual outcomes. (32, 33)
3. Growth is an important measure of general well-being in infancy.
4. Growth was the primary outcome in the BOOST trial giving some precedence to our proposed approach. (4)

8.1.2 Secondary study parameters/endpoints (if applicable)

Secondary outcomes are rates of re-hospitalisations, quality of life of the caregivers (Dutch version of the CarerQOL questionnaire) (34) and infant stress (Infant Behaviour Questionnaire – Revised, IBQ-R) (35), length SDS and head circumference SDS at 6 months corrected age and weight SDS, length SDS, head circumference SDS at 12 months corrected age. Length of hospital stay and length of oxygen supplementation will be obtained from medical records. Also, respiratory symptoms and unscheduled health care visits to the emergency department, general practitioner or paediatrician will be secondary outcomes at all visits. Parents will also be asked to bring the growth chart ('groeiboekje') from the child consultation clinic to obtain basic growth data at earlier time points.

8.1.3 Other study parameters (if applicable)

We will collect the following maternal characteristics: age, ethnic origin, highest completed level of education, parental smoking, mode of delivery, antenatal corticosteroids, chorioamnionitis, hypertension, pre-eclampsia and multiple pregnancy. We will also present the following baseline characteristics of patients: gestational age, sex, birth weight, Apgar score at 5 minutes, surfactant therapy, patent ductus arteriosus, age at randomisation, BPD severity, time on mechanical ventilation and ventilation mode, and other major neonatal morbidities. Actual treatment at time of randomisation such as the settings of ventilatory support and/or oxygen supplementation, and medications will be recorded. All variables will be

presented as summary statistics according to allocation arm.

8.2 Randomisation, blinding and treatment allocation

Eligible patients will be randomly allocated in a 1:1 ratio to the low (90%) or high (95%) SpO2 limit. Block randomisation will be used. All patients born in the same NICU will be clustered in 1 block; participants will be allocated to one of the treatment arms within these blocks such that an equal number are assigned to each treatment. Stratification for BPD severity will be performed. Each participant will be randomly assigned to a treatment arm using a fully GCP-compliant random number generator function, which will be centrally controlled and web-based, using a dedicated, password-protected, SSL-encrypted website (ELEA).
The protocol allows for twins and triplets to be included if meeting the inclusion criteria. For logistical reasons all infants from one family will be assigned to the same treatment arm.

8.3 Study procedures

SpO_2 profiles

As long as the child is admitted and on supplemental oxygen, SpO_2 curves will be uploaded by the local treating physician or nurse from hospital pulse oximeters and audited by the research team twice weekly. Data will be logged from the pulse oximeters by Raspberry Pi computers and stored on a USB stick, which will be secured with Bitlocker. Pseudonymised data will then be sent through encrypted file transfer to the researchers. Feedback will be given to the treating team and parents by the research team. They will be stimulated to actively wean the children from supplemental oxygen if SpO_2 is above the target for > 95% of the time. (2)

In children who will be discharged home on oxygen, the research team will obtain weekly SpO_2 curves from home pulse oximeters. If children are discharged without a pulse oximeter, which is the standard procedure in some hospitals, the research team will provide a pulse oximeter. The research team will give feedback to the caregivers directly or to the treating physician who will inform the caregivers, depending on the preference of parents and/or treating physician. Caregivers will be instructed to decrease supplemental oxygen if SpO_2 is above the target for > 95% of the time. In any case, the treating physician will be updated on changes in supplemental oxygen.

After stopping supplemental oxygen, a SpO_2 profile will be obtained after 1 week. If this profile shows SpO_2 values above the target for > 95% of the time no more SpO_2 profiles will be obtained.

If a child is readmitted to hospital while still on supplemental oxygen the lower SpO_2 limit to which the child was randomized will be kept. If children are readmitted after they stopped supplemental oxygen for at least 2 weeks, the lower SpO_2 limit will be up to the treating physician during admission.

If a child is discharged home and experiences any medical problems, the parents should contact the treating physician. Changes in oxygen supplementation will be reported to the research team.

In case of medical problems caregivers will contact their treating physician to discuss the treatment. The treating physician contacts the research team if needed (e.g. if changes in supplemental oxygen are considered).

All SpO_2 profiles are research measurements.

CarerQOL-7D

The Care-related Quality of Life instrument (CarerQol) is designed to measure and value the impact of providing informal care on carers. (34)It combines a subjective burden measure that provides a comprehensive description of the caregiving situation (CarerQol-7D) with a valuation of informal care in terms of well-being (CarerQol-VAS) (www.imta.nl). The Dutch version of the CarerQol will be used in this study, which is a 7 question and 1 page questionnaire which includes a Visual Analogue Scale. This CarerQol will be assessed during all visits and online monthly.

Weight, height, head circumference

At every visit weight, height and head circumference are measured. This is according to standard care.

IBQ-R

The Infant Behavior Questionnaire – Revised (IBQ-R), very short form, Dutch version is an instrument assessing 36 items on 3 broad scales of infant temperament. (36) The questionnaire assesses 6 domains: activity level, soothability, fear, distress to limitations, smiling and laughter and duration of orienting. The items on the IBQ-R ask parents to rate the frequency of specific temperament-related behaviors observed over the past week.

The IBQ-R is a research tool and will be assessed at all visits (0,6 and 12 months).

Multiple Breath Washout (MBW)

If available in the local NICU/ high care centre, lung clearance index (LCI) and functional residual capacity (FRC) will be measured with SF6 as a tracer gas (Exhalyzer, Ecomedics, Switzerland) as routine clinical care at 6 months and/or 12 months corrected age. In short, the measurement will be performed in supine position. A facemask is placed over the nose and mouth of the child. SF6, an inert gas, will be washed in until an equilibrium is established between in- and expiratory gas of a concentration of 4%. Then the washing out starts and will be finished if the concentration of SF6 is 2.5% of the concentration after wash in. From this procedure LCI and FRC can be derived.

Chest CT scan

In addition, if available as routine care in the local NICU/ high care centre, patients will be offered a free breathing volumetric chest CT scan without sedation at 6 months corrected age according to the local routine care protocol. (31). CT scans are scored by an experienced thoracic radiologist using the quantitative Perth-Rotterdam Annotated Grid Morphometric Analysis (PRAGMA)-BPD scoring method. (37) This scoring system identifies lung tissue with a normal appearance, hypoattenuation, hyperattenuation and bronchial wall thickening and expresses their volume in ml and as percentage of total lung volume. In addition, the severity of architectural distortion of the lung, meaning an abnormal displacement of bronchi, vessels, fissures and/or septa caused by diffuse or localized lung disease, will be scored.

Cardiac Ultrasound

If available as routine care, children will be screened for pulmonary hypertension by cardiac ultrasound at 6 months corrected age. For this echocardiogram, we will use an EPIC 7C (Philips Medical Systems, Best, the Netherlands) or Vivid E9 (GE Healthcare, Wauwatosa, WI, USA) ultrasound system. Apical 4-chamber, parasternal long-axis and short-axis views will be acquired and stored. M-mode, 2D, color Doppler and pulsed wave Doppler images will be acquired to collect data on tricuspid regurgitant jet, pulmonic valve insufficiency, pulmonary acceleration time, right and left ventricular (RV and LV) dimensions and mass, shortening fraction of the LV, and fractional area change (FAC) of the RV. All measurements will be performed off-line using Xcellera (version R4.1, Philips, Best, The Netherlands).

Costs

In between visits, a monthly electronic tailor-made diary will be provided to the parents to obtain data on hospital re-admissions, oxygen supplementation, unscheduled visits to health care providers, medication, absence from work and attendance of day care between the study visits. These data will be used for the cost-effectiveness analysis.

Informed consent for follow up studies

At the last clinic visit we will ask written informed consent for follow up studies.

Table

	Visit 0 months	Visit 6 months	Visit 12 months
Weight, height, head circumference	x	x	x
CarerQOL-7D*	x	x	x
IBQ-R	x	x	x
Multiple breath washout**		x	x
Chest CT scan**		x	
Cardiac ultrasound**		x	

*also measured monthly in an online diary, together with data on admissions and absence of work

** not mandatory, if available as routine care

8.4 Withdrawal of individual subjects

Parents or caregivers can withdraw their child from the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

If the treating physician and/or parents are non-compliant to the study protocol and do not comply to the advice of the research team on oxygen supplementation on at least 3 consecutive times, the patient will be withdrawn from the study.

8.4.1 Specific criteria for withdrawal (if applicable)

Not applicable

8.5 Replacement of individual subjects after withdrawal

Patients withdrawn from the study before reaching the primary endpoint at 6 months corrected age but after they finished supplemental oxygen, will not be replaced.

Patients who are withdrawn before supplemental oxygen is stopped will be replaced.

8.6 Follow-up of subjects withdrawn from treatment

Patients will be followed during the routine clinical neonatology follow up for preterm infants.

8.7 Premature termination of the study

An independent Data Safety Monitoring Board (DSMB) will monitor the study on safety aspects and can recommend termination of the study if safety endpoints as specified in the DSMB charter are met.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the trial procedure or the experimental intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

The health risks associated with participation in the study are negligible and no adverse health effects are expected. The occurrence of AE's however, is inherent to (extreme) premature birth (for instance: laboratory abnormalities, sepsis, feeding intolerance) and are expected as a part of normal daily clinical practice and context. For this reason, AE's will be recorded in the patient files as part of standard clinical care, but will not be reported to the sponsor and METC.

AE's that will be monitored and reported to the sponsor and METC according to current guidelines, as long as the children are still dependent of supplemental oxygen, are:

- Increase in retinopathy of prematurity (ROP stadium, or new ROP after 36 weeks
- Deterioration in respiratory state

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;

- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

SAE's will be collected and recorded from informed consent signature to two weeks after stopping supplemental oxygen (after this period the study intervention ends and SpO2 lower limit will no longer be dependent of study regulations but of usual care). After this period until the last follow-up visit at 12 months corrected age, ICU admissions for complicated respiratory tract infections will be considered SAE's and will be reported as such.

An elective hospital admission (e.g. hernia inguinalis repair, vaccination) will not be considered as a serious adverse event. This also applies to hospital admissions for uncomplicated respiratory tract infections (not involving admission to the ICU department) and uncomplicated gastro-intestinal tract infections. These hospital admissions will be listed and will be reported in the annual report to the METC.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable.

9.3 Annual safety report

Not applicable.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

9.5 Data Safety Monitoring Board (DSMB)

Although this study does not add extra risks to the safety of the patients, we propose to compose an external DSMB because of the vulnerability of the population and the complicated logistics of the study. The DSMB will monitor the safety, validity and credibility of the trial in order to protect the patients and will provide the trial's Steering Committee with recommendations regarding continuation or cessation of the trial. The composition, tasks, responsibilities and working procedures of the DSMB are described in the DSMB charter. The DSMB will meet to discuss the findings of the interim analyses. These will be conducted when the data of 25%, 50% and 75% of the inclusions have been gathered. The DSMB will assess safety, not futility. In principle, the trial will not be stopped early for beneficial effect on the primary outcome. During the closed DSMB meetings, the data manager will be stand-by to reveal any additional data if the DSMB thinks this is necessary. The advice(s) of the DSMB will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

The DSMB will be composed of 3 individuals:

- Prof. A.H. Maitland- van der Zee, pharmacist/researcher, department of Respiratory Diseases, AMC Amsterdam
- Prof.dr. S. Bambang Oetomo, pediatrician/neonatologist, Chief Medical Officer at Bambi Medical
-
- Prof.dr.ir. René Eijkemans, biostatisticus, UMC Utrecht
- Dr. D. Cianci, biostatisticus UMC Utrecht

The Steering Committee will propose a detailed mandate and review this with the DSMB. Identification and circulation of external evidence (e.g. from other trials or systematic

reviews) is not the responsibility of the members of the DSMB. It is the responsibility of the coordinating principal investigator to provide any such information to the DSMB.

10. STATISTICAL ANALYSIS

Analyses will be performed on an intention-to-treat (ITT) basis. The ITT population includes all randomised infants, regardless of protocol deviations, and includes patients with a signed informed consent for the study who have been randomised.
Descriptive statistics will be used to describe the characteristics of the study population. Means and standard deviations will be reported (normal continuous distributed data) or medians and interquartile range (skewed continuous variables). Categorical data will be presented as percentages.
In case of missing data, every attempt will be undertaken to retrieve the data by contacting NICUs and general hospitals where the child has been admitted and by contacting the child consultation clinic (with permission of the caregivers). Missing data, 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.
Significance level will be 0.05.
All analyses will be completed with the statistical software package R (free download from www.rproject.org), and SPSS/PC Statistics 21.0 (SPSS Inc., Chicago, IL, USA).

10.1 Primary study parameter(s)

The primary endpoint is weight SDS at 6 months corrected age. Comparison between the two groups for this primary endpoint will be made using a mixed effect model with a random intercept to account for the correlation between the patients that come from the same hospital cluster.

10.2 Secondary study parameter(s)

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. These variables will be included in the mixed model analysis as fixed effects.

Secondary outcomes are:

- Rates of re-hospitalisations: the rates of re-hospitalisations between the 2 groups will be assessed.
- Quality of life of the caregivers (Dutch version of the CarerQOL questionnaire) (34) Changes in the total score of the CarerQOL between baseline and 6 months and between baseline and 12 months will be assessed.

- Infant stress (Infant Behaviour Questionnaire – Revised, IBQ-R) (35): changes in the total score of the IBQ-R between baseline and 6 months and between baseline and 12 months will be assessed.
- Weight SDS, Length SDS, Head circumference SDS at 12 months corrected age, length SDS and head circumference SDS at 6 months corrected age: comparison between the two groups for these endpoints will be made.
- Length of hospital stay, length of oxygen supplementation: comparison between the two groups will be made.
- Unscheduled health care visits to the emergency department, general practitioner or paediatrician: comparison between the 2 groups will be assessed.

10.3 Other study parameters

Not applicable.

10.4 Interim analysis (if applicable)

Although this is a low risk study, a DSMB will be established to advice on continuing or stopping of the study. The DSMB should receive and review the progress and accruing data of this trial and provide advice on the conduct of the trial to the Trial Steering Committee (TSC). Specifically, the DSMB should judge interim reports of the trial's progress, including updated figures on recruitment, SAE's, data quality, and main outcomes and safety data. The DSMB should inform the Chair of the Trial Steering Committee if, in their view there are concerns on:

(i) safety concerns related to the high SpO_2 arm, in particular if the incidence of retinopathy of prematurity in the high SpO_2 group is increased compared to the control group.

(ii) the rate of serious adverse events

(iii) Logistics, patient inclusion and study violations:

- monitor recruitment figures and losses to follow-up;
- decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or for some participant subgroups suggest additional data analyses;
- advise on protocol modifications suggested by investigators or sponsors (e.g., to inclusion criteria, trial endpoints, or sample size adjustment);
- monitor compliance with previous DMC recommendations;
- consider the ethical implications of any recommendations made by the DMC;

- assess the impact and relevance of external evidence

The DSMB will not assess futility.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (version 9, 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

11.2 Recruitment and consent

Since all participants are born preterm, all patients in this study will be born in or transferred to 1 of the 10 hospitals with a neonatal intensive care unit (NICU). The local coordinator of the NICU will make a list of eligible children and will check if children have moderate or severe BPD at 36 weeks PMA. If the child is at that time point still admitted to the NICU, the local NICU coordinator will discuss the study and ask for written informed consent. If the child has been transferred to a local hospital by 36 weeks PMA, the local coordinator will check with the treating physician at the local hospital, if the child is eligible. If so, the treating physician will discuss the study and ask for consent.
Parents will have at least 24 hours to consider their decision.
If the parents consent with the study, the research team will be informed and will contact the local hospital and the parents. The child will be randomised and the local physician and parents will be instructed.

11.3 Objection by minors or incapacitated subjects (if applicable)

We will act according to the code of conduct of objection by minors from the Netherlands Association for Paediatric Medicine: Code of conduct relating to expressions of objection by minors participating in medical research - Netherlands Association for Paediatric Medicine

Code of conduct

1. Individual children respond differently to diagnostic and treatment procedures and to participation in medical research. Various factors help to determine the nature of the response: the way the child is prepared for what is going to happen, the parent-child relationship, the doctor-patient relationship, the child-friendliness of the environment in which the procedure takes place and so on. One child will not be unduly disturbed by having an injection (even if he or she winces or makes some other display of pain), while another will find the experience distressing. Although responses vary considerably from child to child, there is a general correlation between the degree of

'invasiveness' of a procedure and the strength of the response. In some cases, fear regarding participation or a particular procedure will prompt a child to object. Patient and understanding explanation and reassurance will generally be sufficient to enable the research or the procedure to proceed without problems. Where a newborn child or infant is concerned, it is much harder to ascertain whether objection has been expressed. As a general rule, however, it is reasonable to suggest that a child may be deemed to object if its behaviour clearly differs in nature or degree from that normally displayed by the child when confronted with situations not encountered in everyday life. In this context, situations not encountered in everyday life may be considered to include diagnostic or therapeutic procedures.

2. Before seeking consent for a child's participation in medical research, an investigator must fully inform the child's custodial parent(s) or guardian about what is proposed. Information should be provided orally and in writing. The nature of the procedures involved in the research should be discussed with the parents and their views sought on the child's likely response. The possibility of the child objecting to participation and the type of behaviour that should be regarded as an expression of objection should also be discussed. The investigator should also explain what is to happen in the event of the child objecting. The consent obtained from the parents should include agreement to the proposed procedure for dealing with expressions of objection by the child.

3. The consent statement signed by parents should stipulate that, if the child should object to participation in the research, consent for its further participation will be invalidated.

4. If prior to the research there is doubt as to whether a child should participate, consideration may be given to involving the patient in the research for an agreed pilot period.

5. While the research is in progress, the behaviour of the child should be continually assessed at the research location to determine whether the child's behaviour is within the bounds normally associated with the child when confronted with situations not encountered in everyday life. If a child's behaviour is not within these bounds, he or she should be deemed to have expressed an objection in the sense of the WMO.

6. The parents, the investigator(s) and possibly a behavioural scientist should be involved in assessment of a child subject's behaviour. Assessment of a child subject's behaviour should not be a one-off exercise, but should continue through all phases of the research.

7. The parents of a child subject should be able to withdraw their consent at any point during the research. If a child subject expresses an objection, the child's participation should be discontinued.

8. In all medical research involving child subjects, the burden associated with participation should be minimised; where non-therapeutic research is concerned, the law stipulates that it must be negligible. Medical studies often involve the combination of research procedures with diagnostic procedures necessary in connection with the subject's treatment. Where research involves an invasive procedure, such as a finger prick or venapunction, this should if possible be combined with a procedure necessary for diagnostic or treatment purposes, such as blood sampling. If possible, a needle or line that has already been inserted should be utilised, so that the number of 'jabs' is kept to the minimum. The burden can also be reduced by the use of plasters with local anaesthetic. The various steps to be taken with a view to minimising the burden should be detailed in the research protocol and in the information given to the parents and subjects.

9. The following should be noted in the research file or the medical (status) report, as appropriate:
   (a) the outcome of any trial participation;
   (b) the consent of the custodial parent(s) or guardian, including the procedure to be followed in the event of a possible expression of objection;
   (c) an account of the subject's participation in the research, stating whether objection was expressed;
   (d) an assessment as to whether the subject's behaviour constitutes objection, as referred to above;
   (e) the names of the people responsible for assessing the subject's behaviour, as described above;
   (f) an assessment as to whether the subject's behaviour in the course of the study constitutes objection;
   (g) the steps taken to minimise the burden associated with participation.

The protocol for a medical research project in which minors are to be used as subjects should state that the NVK's code of conduct for dealing with subjects' expressions of objection in the course of the research will be adhered to.

10. This code of conduct will be evaluated in consultation with the research community two years after its initial publication and amended as necessary.

This code of conduct was approved by the Board of the Netherlands Association for Paediatric Medicine (NVK) on 21 May 2001 and published in NVK Newsletter no. 3, June

11.4 Benefits and risks assessment, group relatedness

The main treatment for BPD is supplemental oxygen but the optimal oxygen saturation (SpO_2) target that should be obtained by supplemental oxygen in children with established BPD after 36 weeks PMA is not known. There is wide practice variability between hospitals in lower SpO_2 targets, with most hospitals accepting a lower SpO_2 limit of 90%. However, this limit may be too low as according to a number of observational studies, supplemental oxygen may decrease respiratory symptoms, prevent pulmonary hypertension, be beneficial for neurodevelopment and improve weight gain when BPD is present. (11-14) On the other hand, hyperoxia (e.g. too much oxygen) may result in increased levels of reactive oxygen species and subsequent oxidative damage. (19) This may negatively influence lung development but also the development of other organs such as the brain. (20) Hyperoxia is associated with retinopathy of prematurity (ROP), although after 36 weeks PMA children are much less vulnerable for this complication. (37)
The possible benefit for children who participate in the study is that their oxygen supplementation is closely monitored and decreased based on frequently recorded SpO_2 profiles. Usual care now varies widely. In some hospitals parents stop supplemental oxygen on their own, while on the other end children are admitted to monitor nocturnal oxygen before withdrawing supplemental oxygen.
If our study shows that there is no difference between the two SpO_2 targets, this may avoid prolonged supplemental oxygen use in the future.
However, if the higher target has better outcomes, this may benefit children during the rest of their lives. The risk of the lower target group includes less weight gain, higher breathing frequency or work of breath.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives (if applicable)

Not applicable.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Collected data and samples will be coded complying with the Dutch Personal Data Protection Act. The code will not include patient initials and date of birth, but will include a code of the hospital were inclusion took place. The key to link patients and their genotypes or biomarkers will be securely stored, and accessible only to the database programmers and to the principal investigators of each participant centre.
Information gathered by the study will be used only for aggregate analysis, and will not be released with any information that identifies research participants.

12.2 Monitoring and Quality Assurance

Study monitoring

The study will be monitored by an experienced monitor throughout its duration by means of personal visits to the Investigator's facilities and through other communications (e.g., telephone calls, written correspondence).
Monitoring visits will be scheduled at mutually agreeable times periodically throughout the study and at a frequency deemed appropriate for the study.
These visits will be conducted to evaluate the progress of the study, ensure the rights and wellbeing of the subjects are protected, check that the reported clinical study data are accurate, complete and verifiable from source documents, and the conduct of the study is in compliance with the approved protocol and amendments, GCP and applicable national regulatory requirements. A monitoring visit will include a review of the essential clinical study documents (regulatory documents, CRFs, source documents, subject informed consent forms, etc.) as well as discussion on the conduct of the study with the investigator and staff. The investigator and staff should be available during these visits to facilitate the review of the clinical study records and resolve/document any discrepancies found during the visit.

Quality assurance audits and inspections

The Sponsor's (or an authorized representative's) Quality Assurance department may conduct audits of all aspects of the clinical study either during the study or after the study has been completed. By participating in this trial the investigator agrees to this requirement.
The clinical study may also be subject to inspection by regulatory authorities as well as the accredited Medical Ethical Committee to ascertain that the study is being or has been

conducted in accordance with protocol requirements, GCP, as well as the applicable regulatory requirements.

For more details we refer to the monitoring plan.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

We will follow the basic principles of the CCMO statement on publication policy. The protocol will be published at clinicaltrials.gov and trialregister.nl before the first patient is included in the study. The results of this research will be submitted for publication to peer-reviewed scientific journals, and will also be updated at clinicaltrials.gov and trialregister.nl.

Consortium agreements (with AMC and UMCG) and trial agreements (with all other centres, the statistician and HTA expert) will be set out in a contract to be signed by all parties. Agreements involve the participation in publication, based on the rules of the Vancouver convention.

13. STRUCTURED RISK ANALYSIS

Not applicable.

14. REFERENCES

1. www.longfonds.nl.
2. Balfour-Lynn IM, Field DJ, Gringras P, Hicks B, Jardine E, Jones RC, et al. BTS guidelines for home oxygen in children. Thorax. 2009;64 Suppl 2:ii1-26.
3. www.neonatologiestudies.nl/home/page.asp?page_id=1050.
4. Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med. 2003;349(10):959-67.
5. Baraldi EF, M. Chronic lung disease after premature birth. . N Eng J Med. 2007;357:1946-55.
6. Doyle LW, Anderson PJ. Pulmonary and neurological follow-up of extremely preterm infants. Neonatology. 2010;97(4):388-94.
7. McGrath-Morrow SAR, T. Riekert, K. Lefton-Greif, M.A. Eakin, M. Collaco, J.M. The impact of bronchopulmonary dysplasia on caregiver health related quality of life during the first 2 years of life. Pediatr Pulmonol. 2013;48:579-86.
8. Manja V SO, Lakshminrusimha S. Oxygen Saturation Targets in Preterm Infants and Outcomes at 18-24 Months: A Systematic Review. Pediatrics. 2017;139.
9. Askie LM, Henderson-Smart DJ, Ko H. Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants. Cochrane Database Syst Rev. 2009(1).
10. www.nvk.nl/kwaliteit/richtlijnenoverzicht.
11. Cherian S, Morris I, Evans J, Kotecha S. Oxygen therapy in preterm infants. Paediatr Respir Rev. 2014;15(2):135-41.
12. Poets CF. When do infants need additional inspired oxygen? A review of the current literature. Pediatric Pulmonology. 1998;26(6):424-8.
13. Statement on the care of the child with chronic lung disease of infancy and childhood. Am J Respir Crit Care Med. 2003;168(3):356-96.
14. Groothuis JR, Rosenberg AA. Home oxygen promotes weight gain in infants with bronchopulmonary dysplasia. Am J Dis Child. 1987;141(9):992-5.
15. Van Mastrigt EK, E. Ciet, P. den Dekker, H.T. Joosten, K.F. Kalkman, P.M. Swarte, R.M. Kroon, A.A. de Jongste, J.C. Tiddens, H.A. Reiss, I.K. Duijts, L. Pijnenburg, M.W. . Structural and functional ventilatory impairment in infants with severe bronchopulmonary dysplasia. Pediatr Pulmonol. 2017.
16. Sanchez-Solis M P-FV, Bosch-Gimenez V, Quesada JJ, Garcia-Marcos, L. Lung function gain in preterm infants with and without bronchopulmonary dysplasia. Pediatr Pulmonol. 2016;51:936-42.
17. Kotecha S AJ. Oxygen therapy for infants with chronic lung disease. Arch Dis Child Fetal Neonatal Ed. 2002;87:F11-4.
18. Huysman WA dRM, de Bruin NC, van Helmond G, Terpstra N, Van Goudoever, JB SP. Growth and body composition in preterm infants with bronchopulmonary dysplasia. Arch Dis Child Fetal Neonatal Ed. 2003;88:F46-51.
19. Saugstad OD. Bronchopulmonary dysplasia - Oxidative stress and antioxidants. Semin Neonatol. 2003;8(1):39-49.
20. Reich B HD, Bendix I, Felderhoff-Mueser U. Hyperoxia and the Immature Brain. . Dev Neurosci. 2017.
21. http://statline.cbs.nl/statweb/publication/.
22. Shah PS, Lui K, Sjors G, Mirea L, Reichman B, Adams M, et al. Neonatal Outcomes of Very Low Birth Weight and Very Preterm Neonates: An International Comparison. J Pediatr. 2016;177:144-52 e6.
23. Harigopal S, Satish HP, Taktak AF, Southern KW, Shaw NJ. Oxygen saturation profile in healthy preterm infants. Arch Dis Child Fetal Neonatal Ed. 2011;96(5):F339-42.
24. Thoracic Society of A, New Z, Fitzgerald DA, Massie RJ, Nixon GM, Jaffe A, et al. Infants with chronic neonatal lung disease: recommendations for the use of home oxygen therapy. Med J Aust. 2008;189(10):578-82.

25. Ellsbury DL, Acarregui MJ, McGuinness GA, Eastman DL, Klein JM. Controversy surrounding the use of home oxygen for premature infants with bronchopulmonary dysplasia. J Perinatol. 2004;24(1):36-40.
26. Konig K, Holberton JR. Current practice of pulse oxygen saturation targets and limits in neonatal intensive care units in Australia and New Zealand. Acta Paediatr. 2012;101(6):e253-5.
27. Peter C, Boberski B, Bohnhorst B, Pirr S. Prescription of home oxygen therapy to very low birth weight infants in Germany: a nationwide survey. Clin Pediatr (Phila). 2014;53(8):726-32.
28. Everitt LH, Awoseyila A, Bhatt JM, Johnson MJ, Vollmer B, Evans HJ. Weaning oxygen in infants with bronchopulmonary dysplasia. Paediatr Respir Rev. 2020.
29. Terrill PI, Dakin C, Edwards BA, Wilson SJ, MacLean JE. A graphical method for comparing nocturnal oxygen saturation profiles in individuals and populations: Application to healthy infants and preterm neonates. Pediatr Pulmonol. 2018;53(5):645-55.
30. Sanchez-Solis M, Perez-Fernandez V, Bosch-Gimenez V, Quesada JJ, Garcia-Marcos L. Lung function gain in preterm infants with and without bronchopulmonary dysplasia. Pediatr Pulmonol. 2016;51(9):936-42.
31. van Mastrigt E, Kakar E, Ciet P, den Dekker HT, Joosten KF, Kalkman P, et al. Structural and functional ventilatory impairment in infants with severe bronchopulmonary dysplasia. Pediatr Pulmonol. 2017;52(8):1029-37.
32. DeBoer MD, Lima AA, Oria RB, Scharf RJ, Moore SR, Luna MA, et al. Early childhood growth failure and the developmental origins of adult disease: do enteric infections and malnutrition increase risk for the metabolic syndrome? Nutr Rev. 2012;70(11):642-53.
33. Wang LY, Luo HJ, Hsieh WS, Hsu CH, Hsu HC, Chen PS, et al. Severity of bronchopulmonary dysplasia and increased risk of feeding desaturation and growth delay in very low birth weight preterm infants. Pediatr Pulmonol. 2010;45(2):165-73.
34. Brouwer WB, van Exel NJ, van Gorp B, Redekop WK. The CarerQol instrument: a new instrument to measure care-related quality of life of informal caregivers for use in economic evaluations. Qual Life Res. 2006;15(6):1005-21.
35. Parade SH, Leerkes EM. The reliability and validity of the Infant Behavior Questionnaire-Revised. Infant Behav Dev. 2008;31(4):637-46.
36. Putnam SP, Helbig AL, Gartstein MA, Rothbart MK, Leerkes E. Development and assessment of short and very short forms of the infant behavior questionnaire-revised. J Pers Assess. 2014;96(4):445-58.
37. van Mastrigt E, Logie K, Ciet P, Reiss IK, Duijts L, Pijnenburg MW, et al. Lung CT imaging in patients with bronchopulmonary dysplasia: A systematic review. Pediatr Pulmonol. 2016;51(9):975-86.