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BPD Saturation TARgeting (BPD STAR)

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Title: **The Bronchopulmonary Dysplasia Saturation TARgeting Pilot Trial**

Short Title: BPD STAR Pilot Trial

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ABBREVIATIONS AND DEFINITIONS OF TERMS

NICU	Neonatal Intensive Care Unit
BPD	Bronchopulmonary dysplasia
SpO2	Oxygen saturation
IH	Intermittent hypoxemia
CA	Corrected age
PMA	Postmenstrual age
ROP	Retinopathy of Prematurity
ATS	American Thoracic Society
NC	Nasal Cannula

ABSTRACT

Context: Bronchopulmonary dysplasia (BPD), or chronic lung disease of prematurity, is most commonly defined as oxygen dependence at 36 weeks postmenstrual age (PMA). BPD affects nearly half of surviving extremely preterm (<28 weeks gestational age) infants, and the incidence of BPD has increased over time. Infants with BPD face more than doubled odds of death after 36 weeks PMA or disability at 5 years compared to preterms without BPD. BPD is associated with abnormal lung function throughout childhood and significantly increases health care costs. Cognitive and respiratory outcomes are closely linked throughout the life course; thus, optimal long-term management of BPD during infancy may ultimately improve cognitive outcomes of this high-risk population.

Objectives: The primary objective is to compare the incidence of intermittent hypoxemia (IH) and total duration of hypoxia up to 6 months corrected age (CA) among infants with BPD randomized to higher versus lower oxygen saturation (SpO2) target ranges. The secondary objective is to describe clinically relevant outcomes over the first 6 months in the two study groups.

Study Design: This is a randomized pilot clinical trial. Since the two SpO2 target groups in the current trial represent the currently accepted range of clinical practice, neither group is labeled as "intervention" or "control."

Setting/Participants: In collaboration with Hospital of the University of Pennsylvania (HUP) and its affiliate hospitals, potential participants will be enrolled from the Neonatal Intensive Care Units (NICUs) at The Children's Hospital of Philadelphia (CHOP), Pennsylvania Hospital (PAH) and HUP. We will enroll up to 50 infants who were born <30 weeks and who remain on respiratory support at 34-44 weeks PMA (ie, have moderate or severe BPD). CA.

Study Interventions and Measures: Enrolled infants will be randomized to higher or lower SpO2 target ranges (a target SpO2 of >=96% or 90-94%). The study intervention will begin in the hospital and will continue at home until 6 months. We will utilize 2-second sampling and averaging times and measure IH longitudinally throughout the study period in all participants regardless of home oxygen use. We define IH as SpO2<80% for ≥30 seconds. Primary outcomes are incidence of IH and total duration of hypoxemia up to 6 months CA. Specifically, these are measured as differences between the two groups in incidence of IH at 40 weeks PMA, 3 months CA, and 6 months CA and percent of recording time spent <80%, <85% and <90% SpO2 over the study period. Secondary outcomes are growth, feeding development, health-related resource utilization and quality of life.

The study team will use novel technology to perform overnight continuous oximetry after discharge and until 6 months CA. These data will be transmitted wirelessly to the study team using a novel, compact and low-cost device, whenever relevant, supplemental oxygen will be titrated according to a study algorithm, in order to maintain study participants within the target SpO2 ranges.

PROTOCOL SYNOPSIS

Study Title	The Bronchopulmonary Dysplasia Saturation TARgeting Pilot Trial
Funder	Thrasher Research Fund
Clinical Phase	Phase I (Pilot Study)
Study Rationale	Supplemental oxygen is a lifesaving therapy for premature infants and a common post-discharge treatment for BPD. There is limited evidence to guide the use of supplemental oxygen beyond the immediate newborn period. No controlled studies have described continuous oxygen saturation monitoring post-discharge for infants with established BPD or evaluated the safety and efficacy of reducing IH to improve outcomes of infants with established BPD.
Study Objective(s)	**Primary** • To compare the incidence of IH (SpO2 <80% for >=30 seconds) up to 6 months corrected age among infants with moderate or severe BPD randomized to higher versus lower SpO2 target ranges. **Secondary** • To explore clinically relevant outcomes over the first 6 months in the two study groups.
Test Article(s)	Preterm born infants who remain on respiratory support at 34-44 weeks PMA will be randomized to higher or lower oxygen saturation target ranges, which will be maintained until 6 months corrected age. Both of these target ranges are within the wider range commonly used in clinical practice. • For the lower target group our goal is to keep oxygen saturations between 90-94%. In hospital, inspired oxygen will be adjusted as needed to maintain target SpO2. Monitoring will continue after discharge, and whenever children are discharged on supplemental oxygen, oxygen flow will be titrated monthly according to a standardized algorithm. • For the higher target group our goal is to keep oxygen saturations greater than or equal to 96%. In hospital, inspired oxygen will be adjusted as needed to maintain target SpO2. Monitoring will continue after discharge, and whenever children are discharged on supplemental oxygen, oxygen flow will be titrated monthly according to a standardized algorithm.
Study Design	Randomized controlled pilot study.

Subject Population key criteria for Inclusion and Exclusion:	**Inclusion Criteria** **1.** Pre-term male or female infants born at <30 0/7 weeks gestation **2.** Current age 34 0/7 to 43 6/7 weeks postmenstrual age **3.** Diagnosis of moderate or severe Bronchopulmonary Dysplasia based on the NIH consensus definition **4.** Infant has never been discharged to home from the hospital **Exclusion Criteria** **1.** Congenital anomaly or oncologic process likely to affect growth or respiratory status **2.** Hemoglobinopathy or other blood disorder likely to affect oxygen saturations **3.** Contraindication to nasal cannula use (for example, severe nasal septal breakdown) **4.** Pulmonary hypertension requiring pharmacotherapy at the time of screening/enrollment **5.** Tracheostomy **6.** Intubated during entire eligibility period
Number Of Subjects	50 enrolled (42 evaluable) between CHOP, HUP, and PAH
Study Duration	Each subject's participation will last up to 8 months. The entire study is expected to last 3 years.
Study Phases **Screening** **Study Treatment** **Follow-Up**	1) Baseline/Screening: screening for eligibility and obtaining consent 2) Phase 1: Inpatient 3) Phase 2: Outpatient oxygen Saturation Monitoring (discharge to 6 months CA) 4) Phase 3: Outcomes assessment at 3 and 6 Months CA
Efficacy Evaluations	**1.** Oximetry **2.** Growth checks **3.** Developmental assessment **4.** Parent questionnaires
Safety Evaluations	1. Close supervision from study physician. 2. All adverse events will be recorded and reported in accordance with CHOP and all other regulatory requirements. All adverse events and near misses will be discussed during monthly study team meetings to continually evaluate participant safety and prevent future adverse events.
Statistical And Analytic Plan	The primary endpoints are the incidence of IH (SpO2 <80% for >=30 seconds) and total duration of hypoxia up to 6 months CA

among infants with BPD randomized to higher versus lower SpO2 target ranges.

All secondary endpoints in this pilot study are exploratory and descriptive. The primary clinical outcome is growth in kilograms between 36 weeks PMA and 6 months CA. In addition, the study will also report:

- The change in other growth parameters - length (cm), weight for length, and head circumference (cm) - between 36 weeks PMA and 40 weeks PMA, 3 months CA, and 6 months CA.
- Differences between groups on a standardized feeding questionnaire at 3 and 6 months CA.
- Differences between groups in parent and child quality of life at 3 and 6 months CA.
- Differences between the groups in health care utilization at 3 and 6 months CA.
- Differences between the groups in development at 6 months CA.
- Safety, assessed as differences in growth, re-hospitalizations, and any safety events at 3 and 6 months CA.

DATA AND SAFETY MONITORING PLAN

Data will be managed and stored in a password-protected database using REDCap (Research Electronic Data Capture). Only study team members will have access to the REDCap database for data entry under the supervision of and after training by the PI. Hard copies of data collection instruments will be stored in a locked cabinet in the PI's locked office. Participants will be assigned a unique identifier that contains no protected health information (PHI). PHI will be coded as identifiable information in REDCap using REDCap's built-in security features. Access to the identifiers of the coded data will be controlled by the PI and only study team members will have access to the electronic and paper data.

The PI will be responsible for monitoring the data and safety of all participants. All study procedures will receive IRB approval prior to recruitment or enrollment of participants. In addition to the data management procedures outlined above, the PI will hold monthly study team meetings to evaluate the safety and progress of all research procedures. Standard procedures for all data collection methods will be reviewed at the start and periodically throughout the study. Data checks for errors will be performed prior to analysis. Adverse events and serious adverse events will be reported to the

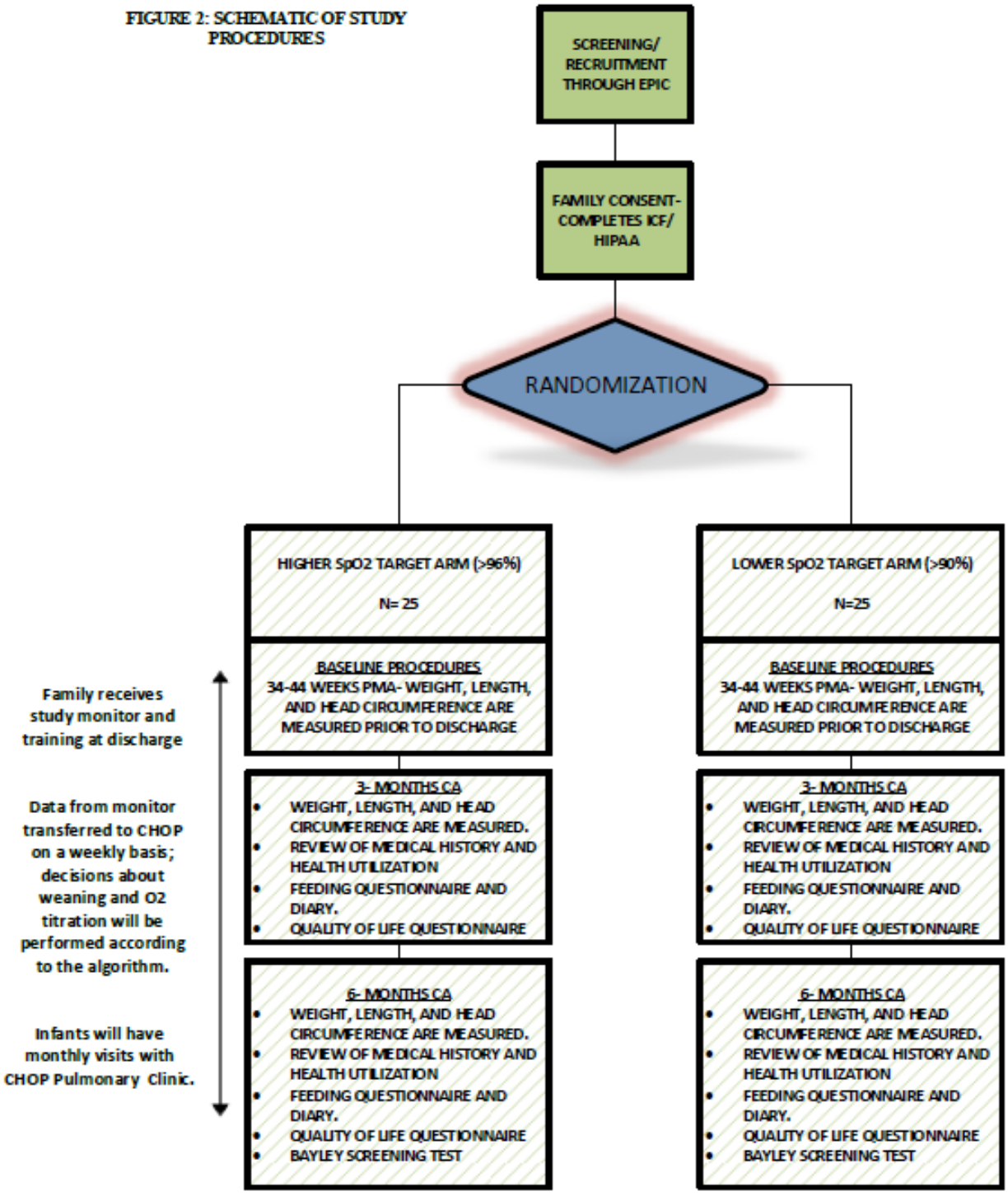
	CHOP IRB and other regulatory authorities in accordance with federal and other relevant regulations.

TABLE 1: SCHEDULE OF STUDY PROCEDURES

Study Activity	*Recruitment Phase & Screening*	**Enrollment Phase**	**Study Timeframe**					
			Baseline 34-44 (weeks)	**Discharge**	**Weekly after discharge**	**Monthly after discharge**	**3 Months CA**	**6 Months CA**
Pre-Enrollment Pool EPIC-CHOP/PENN/PAH	X							
Medical Record Review	X							
Conduct Eligibility Screen	X							
Approach Families (Beginning 34weeks, PMA)		X						
Parental Consent			X					
Participant Randomization			X					
Weight, length, and head circumference are measured			X				X	X
Placement of SPO2 study monitors/ training with families					**Continuous over 6 months**			
Feeding questionnaire and diary							X	X
Data from monitor are reviewed by study team and family is contacted if needed					**Weekly data transfers to CHOP**			
Feeding Questionnaire**							X	X
ITQOL-SF47 (Parent/Child quality of life) **							X	X
Health care utilization data is collected							X	X
Bayley Scales of Infant Development Screener								X
Participant Compensation. Payments issued monthly($50/visit; up to 6 visits)						X		

Adverse Event/Serious Adverse Event Assessment			X	X	X		X	X

FIGURE 1: SCHEMATIC OF STUDY PROCEDURES



1 BACKGROUND INFORMATION AND RATIONALE

Bronchopulmonary Dysplasia affects up to half of very preterm infants, yet little is known about how this condition is best managed in the outpatient setting, especially in the time immediately following discharge from the neonatal hospitalization. The proposed trial will be the first study of oxygen saturation targeting for infants with established BPD and the first study to evaluate the efficacy and safety of home oxygen saturation targeting for this vulnerable population.

1.1 Introduction

Bronchopulmonary dysplasia (BPD) is most commonly defined as oxygen dependence at 36 weeks postmenstrual age. BPD affects nearly half of surviving extremely preterm (<28 weeks gestational age) infants, and the incidence of BPD has increased over time. Infants with BPD face more than doubled odds of death after 36 weeks PMA or disability at 5 years compared to preterms without BPD. BPD is associated with abnormal lung function throughout childhood and significantly increases health care costs. Cognitive and respiratory outcomes are closely linked throughout the life course; thus, optimal long-term management of BPD during infancy may ultimately improve cognitive outcomes of this high-risk population.

Supplemental oxygen is a lifesaving therapy for premature infants; yet, there is limited evidence to guide the use of supplemental oxygen beyond the immediate newborn period. The American Thoracic Society (ATS) has been quite definitive in stating that "oxygen is increasingly viewed as a safe and relatively convenient means for maximizing growth and development" in infants with BPD. But supplemental oxygen also carries potential risk, as it is implicated in the causal pathway for morbidities such as retinopathy of prematurity (ROP). In addition, targeting high oxygen saturations (SpO2) with supplemental oxygen may be associated with increased pulmonary oxygen toxicity and decreased quality of life, without improving neurologic outcomes. In the absence of sound evidence to guide medical decisions, there is currently a significant variation in practice with regard to use of oxygen therapy in this population. No controlled studies have evaluated the safety or efficacy of supplemental oxygen for improving outcomes of infants with established BPD. This is a critical knowledge gap in neonatal and pediatric pulmonary medicine. This study will test whether targeting higher versus lower oxygen saturations in infants with BPD influences rates of hypoxemia and clinical outcomes during the first 6 months of life.

1.2 Name and Description of Investigational Product or Intervention

The intervention that will be tested in the current study is higher versus lower oxygen saturation target ranges for infants with established BPD.

1.3 Relevant Literature and Data

Several recently published randomized trials have compared oxygen saturation (SpO2) target ranges for extremely preterm infants immediately after birth, up to only 36 weeks PMA. These trials have differing methodology and conflicting results.(1-3) Two older trials compared SpO2 target ranges for slightly older preterm infants. The BOOST trial randomized 358 preterm infants who were *oxygen dependent at 32 weeks* to higher (95-98%) or standard (91-94%) saturation target ranges. (4) Participants remained on the study intervention until oxygen was discontinued: a median of 2.5 weeks in the standard target group and 5.7 weeks in the high target group. Only about half of the infants still required supplemental oxygen at 36 weeks. The BOOST Trial did not demonstrate any

benefits associated with targeting higher SpO2 in this population. The STOP-ROP multicenter trial randomized 649 infants with pre-threshold retinopathy and a median SpO2 of <94% to conventional oxygen targets (SpO2 89-94%) and supplemental oxygen targets (96-99%). (5) These targets were continued for two weeks or until the infants met the ophthalmologic endpoint of the study, whichever occurred later. STOP-ROP was stopped early for futility and a loss of equipoise in favor of the high saturation arm. The adjusted odds ratio for progression to threshold retinopathy in the supplemental arm as compared to the conventional arm, which was the primary outcome of the trial, was 0.72 (95%CI 0.52-1.01). In these trials, there were no differences between the groups in growth at 36 weeks or 12 months (BOOST) or 2 months (STOP-ROP).(4,5) In summary, RCTs in the acute newborn period up to 36 weeks have conflicting results; and studies from 32-36 weeks show no benefit but potential harm. Crucially, no trials have compared the impact of prolonged SpO2 targeting for very preterm children with moderate or severe BPD after 36 weeks.

Secondary analyses of a large randomized trial comparing higher versus lower SpO2 targeting for newborn extremely preterm infants(6) demonstrated that IH, and in particular events <80% for at least one minute, are common in this population between birth and at least 9-10 weeks of age.(7) The duration of time with SpO2 <80% is associated with the combined outcome of death after 36 weeks or disability at 18 months, cognitive or language delay, motor impairment, and severe retinopathy of prematurity. Importantly, this effect is significantly stronger when IH occurs 9- 10 weeks after birth than when it occurs earlier. While the neonatal community has been striving to minimize events in the weeks prior to discharge, these data force us to evaluate the value of reducing IH throughout infancy. It is unknown whether infants with BPD continue to have IH after 36 weeks PMA or after hospital discharge, or whether ameliorating this with longer-term use of supplemental oxygen would improve outcomes of these high-risk infants. IH is an important and novel therapeutic target in BPD, and may be a key component of decisions regarding safe and appropriate use and weaning of supplemental oxygen.

A recent trial of late caffeine therapy enrolled infants who were at least 33 PMA and in room air.(8) The control group had an average of 8.4 episodes of intermittent hypoxemia (decline in SpO2 by at least 5% from baseline to <90% and lasting at least 5 seconds) per hour at 35 weeks PMA, which declined to 3.0 events per hour at 39 weeks PMA. The total time spent with saturations <90%, <85%, and <80% declined dramatically between 35 and 39 weeks. The clinical relevance of these more minor IH episodes and periods of hypoxia have not yet been demonstrated.

Our study collaborators have developed a simple, low-cost device for the BPD STAR Trial that securely transmits oximetry data wirelessly from the home environment. This device will enable us to implement a novel approach to studying management and outcomes of BPD. This study will provide critical data about whether infants with BPD continue to have IH after discharge; whether targeting higher SpO2 ameliorates IH; and whether this management strategy is associated with improved outcomes until 6 months of age.

1.4 Compliance Statement

This study will be conducted in full accordance all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46 and the Good Clinical Practice: Consolidated Guideline approved by the

International Conference on Harmonisation (ICH). All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with The Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

The purpose of this study is to test whether targeting higher, as compared to lower, oxygen saturations reduces the incidence of IH and improves clinical outcomes for preterm infants with established BPD.

2.1 Primary Objective

The primary objectives of this study are to compare the incidence of intermittent hypoxemia (defined as: SpO2 <80% for >=30 seconds) and total duration of hypoxemia between 36 weeks PMA and 6 months corrected age among infants with BPD randomized to higher versus lower SpO2 target ranges.

2.2 Secondary Objectives

The secondary objectives are to describe clinically relevant outcomes over the first 6 months in the two study groups. These outcomes include quality of life, respiratory health-related resource utilization, feeding, and growth.

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

The proposed study will be a randomized clinical pilot trial. Enrolled infants with moderate or severe BPD will be randomized to higher or lower oxygen saturation (SpO2) target ranges, which will be maintained until 6 months corrected age.

The two SpO2 target groups represent the currently accepted range of clinical practice. Therefore, neither group is labeled as "intervention" or "control."

Please reference Table 1 above for an overall visual explanation of study procedures. The study procedures will be discussed in detail in section 4.

3.1.1 Screening- Baseline

Potential subjects will be screened using the protocol inclusion and exclusion criteria. Parental/guardian permission (informed consent), will be obtained prior to any study related procedures being performed. Randomization occurs when infants have been extubated. However, parents of infants who are on higher levels of support, may be approached to introduce the study. Consent will be obtained at time of extubation. Once the infant meets all eligibility criteria (, the

subject will be randomized to higher or lower oxygen saturation (SpO2) target ranges and study monitoring (3.1.2) will begin.

3.1.2 Phase 1 – Inpatient monitoring

After randomization, the alarm settings on the standard hospital equipment will be adjusted according to the participant's group assignment. The study SpO2 ranges are similar to the standard of care ranges in the CHOP NICU, where the clinical alarms for infants born <30 weeks are 95% (high) and 87% (low) until 36 weeks PMA. After 36 weeks PMA, alarms are set at 98% (high) and 90% (low). Participants will continue on the study-mandated alarm settings until discharge to home.

In addition, participants will be placed on the study monitor in order to facilitate collection of study data. This is similar to the approach previously used in the CHOP and HUP NICUs for the Canadian Oxygen Trial. Nurses will be instructed to follow alarms from the clinical monitors, not the study monitor, while the infant is in the NICU. Per standard of care, the infant will be on the clinical monitor continuously. Every effort will be made to also keep the infant on the study monitor continuously; however, it is sufficient to have minimum of 4 days per week/8 hours per day of data. This is consistent with the minimum planned data collection planned for the outpatient phase of the study.

If patients are reintubated, oxygen saturation targets will be at the discretion of the clinical team. However, they will be encouraged to maintain the study mandated targets.

3.1.3 Phase 2 – Outpatient monitoring

At the time of hospital discharge, as detailed below, families will be given a Masimo oximeter along with a device that will transmit the oximetry data back to the study team at CHOP. They will be instructed how to use the device nightly while the child is sleeping at home.

Infants who are discharged per clinical recommendations on supplemental oxygen will have frequent visits in the CHOP Pulmonary Clinic. Oxygen titration and weaning will be standardized according to the algorithm in Table 2, below.

Table 2: Home Nasal Cannula Flow Titration Algorithm*

	HIGHER SpO2 TARGET ARM (≥96%)	**LOWER SpO2 TARGET ARM (≥90%)**
Criteria for **INCREASING** O2 flow rate	**SpO2 < 96%** for > 10% of recorded time	**SpO2 < 90%** for > 10% of recorded time
Criteria for **MAINTAINING** current O2 flow rate	**SpO2 >= 96%** for 90-95% of recorded time	**SpO2 > 90%** for >= 90% of recorded time but NOT > 94% for >= 90% of recorded time
Criteria for **WEANING** O2 flow rate	**SpO2 >= 96%** for >95% of recorded time	**SpO2 > 94%** for >= 90% of recorded time

*Decisions will be made by assessment of recorded oximetry. A minimum of 4 days of data, with a minimum of 8 hours per day, will be required for analysis to make a wean. Oxygen flow rates will be decreased stepwise: 2 LPM – 1.5 LPM – 1 LPM – 1/2 LPM – 1/4 LPM – 1/8 LPM. Once the child is stable on 1/8 LPM, he/she will be weaned off for increasing duration of time: first 6 hours, then 12 hours per day, and finally off completely.

Downloaded oximetry data will be reviewed and decisions about weaning will be made each week by the study team (including Dr. Howard Panitch from the Division of Pediatric Pulmonology). In the home setting, weans may be performed as often as every week. If an infant loses >5% of body weight in any month, no oxygen weans will be made until the weight is regained. If an infant is discharged without oxygen or weans off but then meets the criteria for increasing flow on two subsequent recordings, the family will be instructed to attend pulmonary clinic for assessment and then home oxygen therapy will be instituted.

3.1.4 Phase 3 – 3 and 6 month corrected age outcomes assessment

Per standard of care, participants will be evaluated in the CHOP Neonatal Follow-up Program at 3 and 6 months corrected ages. Several study outcomes, clinical outcomes in particular, will be assessed during these clinical visits. Based on the limited existing literature, average age of weaning from supplemental oxygen in infants with BPD is between 2-4.5 months corrected age.(9,10) For the current study, the oxygen titration protocol and study oximetry will continue until 6 months corrected age, with the expectation that nearly all participants will have weaned to room air by the end of the study period. If participants remain on oxygen after the conclusion of the study, the pediatric pulmonologist primarily responsible for the child's ongoing BPD care will make decisions about further weaning. For all other participants, ongoing clinical care will be provided by the neonatal follow-up clinic and pediatrician.

3.2 Allocation to Treatment Groups and Blinding

Infants will be randomized to higher or lower oxygen saturation (SpO2) target ranges. The randomization sequence will be determined in advance, stratified by gestational age (<27 and 27-29 6/7 weeks at birth) and severity of BPD (moderate or severe, see Table 3 below) and balanced in random blocks of 2 or 4 patients. Allocation will be concealed in sequentially numbered opaque envelopes. The envelope with the lowest number will be opened by study staff. This plan for allocation concealment and stratification by key biologic variables will protect the scientific rigor of the study. After randomization, study group assignments will not be blinded. Multiples will be randomized separately. The two target SpO2 ranges in the current trial represent the middle and upper range of the currently accepted range of clinical practice in our center.

Table 3: Screening Definition of BPD

Level of respiratory support at 36 weeks PMA	**Eligibility**
Room Air	Not Eligible (No or Mild BPD)
<2 L nasal cannula and <30% oxygen*	Eligible (Moderate BPD)
<2 L nasal cannula and >=30% oxygen**	Eligible (Severe BPD)
>=2 L nasal cannula or any positive pressure	Eligible (Severe BPD)

** <30% but receiving supplemental oxygen (22-29%) for at least 12 hours per day*
*** >=30% for 12 hours or more per day*

3.3 Study Duration, Enrollment and Number of Sites

3.3.1 Duration of Study Participation

The study duration per subject will be up to 8 months, not including the screening and consent procedures. The baseline phase will last from the time of hospitalization until discharge, the

treatment phase and follow-up phase will take place during the time between discharge and the 6 month corrected age follow-up appointment.

Many of the children eligible for the study will be followed by the CHOP Chronic Lung Disease Program, which has both inpatient and outpatient components. In addition, all children will be eligible for routine care in the CHOP Neonatal Follow-up Program (NFP). It is anticipated that most outcomes assessments will be performed during routine pulmonary or NFP follow-up appointments. Growth parameters between 36 weeks PMA and 40 weeks PMA, 3 months CA, and 6 months CA will take place during scheduled follow-up appointments. Questionnaires will be collected at 3 and 6 months CA. All questionnaires will take approximately 15-30 minutes to complete.

3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

Infants will be recruited from 3 neonatal intensive care units (NICUs): The Children's Hospital of Philadelphia (CHOP) NICU, the adjacent Hospital of the University of Pennsylvania (HUP) NICU, and Pennsylvania Hospital (PAH) NICU. All outpatient care will take place at CHOP. Up to 50 participants may be enrolled to reach our target sample of 42 patients with evaluable data.

3.4 Study Population

We will enroll male and female infants born less than 30 0/7 weeks at birth of all ethnicities who have been diagnosed with moderate or severe Bronchopulmonary Dysplasia; gender and race/ethnicity of the sample is expected to mirror the proportions of the Children's Hospital of Philadelphia, the Hospital of the University of Pennsylvania, and Pennsylvania Hospital patient populations. Subjects will be identified through EPIC. Because data about parent quality of life will be collected, subjects will be enrolled as parent-child dyads.

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the study.

3.4.1 Inclusion Criteria

1) Patient at CHOP,HUP, PAH (including both inborn and outborn infants)
2) Pre-term males or females infants born at <30 0/7 weeks gestation
3) Current age 34 0/7 to 43 6/7 weeks postmenstrual age
4) Diagnosis of moderate or severe Bronchopulmonary Dysplasia (as above)
5) Infant has never been discharged to home from the hospital

3.4.2 Exclusion Criteria

1) Family unlikely to be available for follow-up for 6 months
2) Congenital anomaly or oncologic process likely to affect growth or respiratory status
3) Hemoglobinopathy or other blood disorder likely to affect oxygen saturations
4) Contraindication to nasal cannula use (for example, severe nasal septal breakdown)

5) Pulmonary hypertension requiring pharmacotherapy at the time of screening/enrollment

6) Intubation at the time of screening/enrollment. (Infants may be approached while requiring higher levels of support, but may not enroll until extubation).

7) Tracheostomy

8) Parents/guardians or subjects who, in the opinion of the Investigator, may be non-compliant with study schedules or procedures

Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

4 STUDY PROCEDURES

The Schedule of Study Procedures (Table 1) summarizes the study procedures to be performed at each point throughout the study. Individual study procedures are described in detail below.

4.1 Inpatient screening and enrollment

Data elements to be collected are listed in section 5.

4.2 Inpatient study procedures and data collection

Details of randomization are provided above in section 3.2.

4.2.1 Oxygen Saturation Monitoring

- While inpatient patients will have two monitors, a clinical monitor and a research monitor
- Alarm limits on the clinical monitor will be changed to reflect randomization assignment.
- Study oximeter will be placed on baby with the alarms off to ensure consistent data collection throughout.
- Orders in EPIC will be changed to reflect randomization

Data elements to be collected after enrollment and during the inpatient phase are listed in section 5. An interpreter will be used to administer questionnaires to non-English speaking subjects.

4.3 Outpatient study procedures and data collection

4.3.1 Oxygen Saturation Monitoring

- Prior to discharge, the family will receive a Masimo oximeter which will transmit data to the study team at CHOP.
- The study team will instruct the family how to use the oximeter correctly.
- The family will "teach back," demonstrating that they understand correct use of the monitor.
- After discharge, the family will attach the probe to the toe and turn on the monitor each night while the child is in the crib. It will be disconnected and turned off in the morning, *unless* the child has been ordered for continuous home pulse oximetry by the discharging

physician. If clinical orders are for increased monitoring, the clinical orders will be followed.

- Oximetry data will be transmitted to the study team at CHOP nightly between discharge and 6 months CA.
- Each week the study team will review a report of the transmitted oximetry data.
- If the child is discharged on supplemental oxygen (based on clinical judgment), this will be weaned based on the child's assigned target saturation range and the study algorithm. This algorithm standardizes the typical approach to weaning used by the CHOP Division of Pulmonary Medicine. Downloaded data will be reviewed weekly and decisions about weaning will be made by the study team. In the home setting, weans may be performed as often as every week. If an infant loses >5% of body weight in any month, no oxygen weans will be made until the weight is regained. If an infant is discharged without oxygen or weans off but then meets the criteria for increasing flow on two subsequent recordings, the family will be instructed to attend pulmonary clinic for assessment and then home oxygen therapy will be instituted.
- Families will be instructed how to evaluate the infant in the case of an alarm, just as with home clinical monitoring. If the infant is kicking/moving and the alarm seems related to motion, they will ensure that the probe is well secured and follow for further events. If the alarms are recurrent and the infant has respiratory distress, response will differ based on the infant's situation: If the child is on oxygen, the family will be instructed to turn up the oxygen and call the pulmonary team. If the child is not on oxygen and has mild distress or cold symptoms, they will be instructed to call the pediatrician. All children with severe respiratory distress and persistent low alarms should go to the emergency room. This is all consistent with the instructions given to all families of children with BPD at the time of discharge from the neonatal hospitalization.

4.3.2 Study outcomes and safety data

Nearly all participants will have a clinical visit with either the Neonatal Follow-up Program, the Chronic Lung Disease Program, or the Pulmonary clinic at about 3 months corrected age. If none of these are scheduled, at visit at the CTRC will be arranged. If this is not possible, the PI will arrange a home visit with the family. The 3 month assessments can be conducted in any of these locations. Specific data elements to be collected during these clinical or study visits are listed in section 5.

4.3.3 End of Study

Protocol mandated monitoring of oxygen saturations will continue until the child reaches 6 months corrected age. At that time, if the child remains in supplemental oxygen, decisions about subsequent monitoring will be made by the child's pulmonologist.

If the infant is at home in room air without intermittent hypoxemia (definition below) for 8 continuous weeks, study monitoring may be discontinued at parental request (earliest possible discontinuation of study monitoring at 48 weeks PMA) before 6 months corrected age. All study data will still be collected at 3 and 6 months CA.

4.4 Unscheduled Visits

It is likely that the participant will have interim clinical visits to the Neonatal Follow-up Program, Pulmonary clinic, and the pediatrician. Wherever possible, study visits will be arranged to align with these visits.

4.5 Concomitant Medication

The majority of infants at our center are discharged without caffeine therapy; clinicians will be encouraged to continue this practice because caffeine is likely to impact incidence of intermittent hypoxemia.(8) The study will not dictate diuretic use either in hospital or after discharge, but clinicians will be strongly encouraged to wean diuretics before oxygen.(11) Ultimately, however, this will be a clinical decision. Exposure to caffeine, diuretics, bronchodilators, steroids, and any other medications will be recorded throughout the study. The dates of administration, dosage, and reason for use will be included.

4.6 Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence or tolerance to testing procedures. Participants will not be withdrawn from the study for missing follow up appointments. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the CRF.

4.6.1 Early Termination Study Visit

Subjects who withdraw from the study will be asked to notify the study team of their decision. If participants indicate that they do not want us to collect, use, or share their health information any longer, we will ask them to inform a research team member or the Principal Investigator, Dr. Sara DeMauro.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Screening and Monitoring Evaluations and Measurements

5.1.1 Medical Record Review: Screening

The CHOP/HUP/PAH electronic medical record (EMR) will be accessed to identify potential candidates who are CHOP/HUP/PAH patients. Screening for eligibility based on medical record review will include:

- Date of birth (inclusion criterion)
- Gender
- Gestational age (inclusion criterion)
- Race

- Ethnicity
- Moderate or severe BPD based on the NIH consensus definition at 36 weeks postmenstrual age (inclusion criterion)(12)
- Presence of any exclusion criteria

5.1.2 Inpatient Data Collection

After enrollment and randomization, the following data will be collected from the EMR while the patient is in the hospital:

- Birthweight
- Birth hospital
- Date of transfer to CHOP,HUP, of PAH (if applicable)
- Antenatal steroid treatment
- Reason for preterm birth
- Respiratory support
- Growth parameters at 36 weeks PMA
- Growth parameters at 40 weeks PMA
- Treatment with the following medications for BPD: iNO, postnatal steroids, inhaled bronchodilators, inhaled steroids, other
- Any surgeries
- Neonatal morbidities (surgical NEC, PDA ligation, ROP surgery, etc).
- Screening for pulmonary hypertension

5.1.3 Discharge Data Collection

- Discharge feeding plan
- Discharge respiratory support
- Discharge medications
- Discharge growth parameters
- Discharge date

5.1.4 Outpatient Data Collection

During the remainder of the study period, the following data will be collected:

- Rehospitalizations: location, duration, and ICU care, primary reason for hospitalization
- Medication use
- Visits to doctor or emergency room, with reason
- Procedures or surgeries
- Growth parameters as assessed at any clinical visit(s)
- Mode of feeding
- Developmental assessment (Bayley screener)

5.1.5 Parental Data Collection

- Infant quality of life questionnaires

5.2 Efficacy Evaluations

5.2.1 Efficacy Evaluations: Oximetry

This pilot trial is designed to assess the efficacy of continuous transmission of pulse oximetry from the home environment, for use in oxygen titration and monitoring for clinical care and research purposes. Therefore the study outcomes are designed to assess the efficacy of the study monitoring itself as well as the intervention of randomization to higher or lower oxygen saturation target ranges for infants with BPD.

For this study, we define intermittent hypoxemia as SpO2<80% for >30 seconds. In keeping with the prior literature, we will also report severe IH events, defined as SpO2<80% for >60 seconds. In the current study, we will utilize 2-second sampling and averaging times. IH will be measured longitudinally throughout the study period in all participants regardless of home oxygen use. IH will be reported as weekly average number of events per "night" based on 8 hours of recorded oximetry data per night. If data are not available for all nights in a week, the available data will be used to estimate average number of events per night for that week. Specific outcomes of interest are differences between the two groups in incidence of IH at 40 weeks PMA, 3 months CA, and 6 months CA. In addition, we will report percent of recording time spent <80%, <85% and <90% SpO2 over the study period.

Duration of exposure to supplemental oxygen will be measured as the number of weeks between 36 weeks PMA (the time of formal diagnosis of BPD) and complete discontinuation of supplemental oxygen. This outcome is defined in weeks, not days, because this more closely matches the pace

with which changes are made in the outpatient setting. Prior studies demonstrated that it can be challenging, but nevertheless possible to keep infants in goal SpO2 ranges during hospitalization. However, no studies have performed this maneuver after discharge. To demonstrate successful implementation of our study intervention and monitoring technology, percent of usable data and percent of time with SpO2 in target range over time will be reported. Time with SpO2 in the target range will be reported as a percent of oximeter recordings with SpO2 in range, out of total recorded time. These outcomes are key components of demonstrating feasibility of the study intervention for future research and clinical use.

5.2.2 Efficacy Evaluations: Clinical

In this pilot study, physiologic (oximetry) data are the primary outcomes. All clinical outcomes/assessments of efficacy are exploratory and descriptive. Methods and timing of measures that will be used to assess efficacy are:

Primary Clinical Outcome:

Growth in kilograms between 36 weeks PMA and 6 months CA as well as other growth parameters.

- Change in Length (cm)
- Weight for length
- Head circumference (cm)

Secondary Clinical Outcomes:

- Feeding questionnaire: The questions that will be asked at 3 and 6 months are selected assess feeding skills and estimate caloric intake. The questions are selected from longer questionnaires administered as part of the Millennium Birth Study, with permission from the author of the original study.(13)

- The ITQOL---SF47- Parent and child quality of life survey: The Infant Toddler Quality of Life Questionnaire™ (ITQOL) was developed for use in infants and toddlers at least 2 months of age up to 5 years. The Infant Toddler Quality of Life Questionnaire™ (ITQOL) adopts the World Health Organization's definition of health, as a state of complete physical, mental and social wellbeing and not merely the absence of disease. The survey was developed following a thorough review of the infant health literature and a review of developmental guidelines used by pediatricians. The ITQOL includes questions that assess the impact of health on both child and parent quality of life.

- Medical resource utilization recorded at 3 and 6 months corrected age: medications (including dose, route, frequency, and indication), doctor and emergency room visits, hospitalizations (whether or not in ICU, duration, and indication), therapies (type and frequency), and home equipment use. These data will be extracted from the EMR wherever possible and verified with the participant's parent(s).

- Development: Per standard of clinical care, the Bayley Scales of Infant Development- 3rd Edition Screening Test is administered to all children who attend the Neonatal Follow-up Program (NFP) at 6 months corrected age. (All children eligible for this study will be

followed at the NFP per standard of care) Results of this clinical evaluation will be recorded for the study.

5.3 Safety Evaluation

Subject safety will be monitored by adverse events, as well as the clinical outcomes as described above. Potential adverse clinical outcomes based on the prior literature are pneumonia/BPD exacerbations and detrimental effects on parental quality of life.

6 STATISTICAL CONSIDERATIONS

6.1 Primary Endpoint

The primary endpoints are the incidence of intermittent hypoxemia (IH, SpO2 <80% for >=30 seconds) and total duration of hypoxia up to 6 months corrected age among infants with BPD randomized to higher versus lower SpO2 target ranges.

6.2 Secondary Endpoints

All secondary endpoints in this pilot study are essentially exploratory and descriptive. The primary clinical outcome is growth in kilograms between 36 weeks PMA and 6 months CA. In addition, the study will also report:

- The change in other growth parameters - length (cm), weight for length, and head circumference (cm) - between 36 weeks PMA and 40 weeks PMA, 3 months CA, and 6 months CA.
- Differences between groups on a standardized feeding questionnaire at 3 and 6 months CA.
- Differences between groups in parent and child quality of life at 3 and 6 months CA.
- Differences between the groups in health care utilization at 3 and 6 months CA.
- Differences between the groups in development at 6 months CA.
- Safety, assessed as differences in growth, re-hospitalizations, and any safety events at 3 and 6 months CA.

6.3 Statistical Methods

6.3.1 Baseline Data

Standard descriptive statistics will be used to compare baseline characteristics of the two groups, which may be different despite randomization in this small pilot study.

6.3.2 Efficacy Analysis

The primary analysis will be based on an intention to treat approach and will include all randomized subjects. Interpretation and analysis of downloaded saturation data throughout the study will be managed in two ways. Saturation data will be cleaned, processed, and analyzed weekly. This will allow real-time assessments in order to ensure that the oximeter is being applied routinely and sufficient usable data are available. In addition, the data will be analyzed to determine whether the participant is having SpO2 below the target range that would necessitate either increase in flow or medical attention.

Generalized estimating equations will be used for continuous primary outcomes such as frequency of IH and growth and logistic models for binary outcomes. Models will be adjusted for potential confounders that are significantly different in bivariate testing, because differences may exist despite randomization due to small sample size. Variables that will be considered for inclusion in the model are gender, gestational age, birth weight, race, small size for gestational age, and severity of BPD. The remaining exploratory outcomes will be compared between groups with simple bivariate tests such as t-tests and x^2 tests. Exploratory subgroup analyses will be performed to evaluate the effect of the intervention on the gestational age and severity of BPD strata. Lastly, we will test for PMA week-specific differences between study groups through regression models controlling for key covariates, and using adjustments to account for multiple testing across PMA weeks. Given the sample size of this pilot study, we will likely not have sufficient power to draw definitive conclusions in these exploratory analyses; however, these approaches to the data are likely to be valuable in planning future studies.

6.3.3 Safety Analysis

All subjects entered into the study will be included in the safety analysis. The frequencies of AEs by type, body system, severity and relationship to study arm will be summarized. SAEs (if any) will be described in detail.

6.4 Sample Size and Power

No preliminary data about incidence of IH in infants with moderate or severe BPD are available. Therefore, our sample size is based on extrapolations from the existing studies. Rhein reported 8.2 +/- 11.5 events of 5 seconds or longer per hour (197 per day) at 36 weeks PMA.(8) Poets reported a median 88.4 events of 10 seconds or longer per day in the Canadian Oxygen Trial.(7) We assume that fewer than half of these will be longer events that meet our study definition of IH, and estimate that our study participants will have between 20-30 IH events per 8-hour period at baseline. We plan to recruit 42 participants with useable data, which will provide sufficient power to detect a relative reduction of 30% between the high and low SpO2 target groups if the baseline rate is 30 events per 8 hours. Therefore, our target sample size is 42 children *with complete data*.

Mean weight at 36 weeks PMA based on the Olsen growth curves is 2.8 kg,(14) and mean weight at 6 months CA based on the WHO growth curves is 7.9 kg.(15) Therefore, we assume a mean growth of 5.1 kg in the higher SpO2 group and less weight gain in the lower SpO2 group. The target sample size of 42 children will provide >80% power to detect a mean difference in growth of 0.5kg between the two study groups.

6.5 Interim Analysis

Interim analyses will be performed after 10 and 20 participants complete the study observation period (25% and 50%). The goal of the two interim analyses is to evaluate rates of drop-out, ensure that sufficient useable data are acquired, assess mean rates of IH across the entire population, and review accumulating safety data.

7 STUDY INTERVENTION

7.1 Description

We will randomize infants with moderate or severe BPD to lower (target SpO2 of 90-94%) or higher SpO2 target ranges (target SpO2 of >=96%). The study team will then use novel technology to monitor infants starting at randomization, continuing after discharge and until 6 months corrected age, titrating supplemental oxygen to achieve these target SpO2 ranges.

All trial participants will be provided with a study oximeter. Families will be instructed to use the study monitor continuously each night or when the baby is napping. The research monitor will stay in the child's sleep space and set with alarm limits of 79% and 101% and will be attached nightly when the infant is placed in the bed (in addition to the clinical monitor if prescribed). The research oximeter will be set for 2 second averaging and sampling. In addition, we will collect photoplethsymgraphy (PPG) data at a rate not greater than 100 Hz to aid in identifying errors in the SpO2, likely caused by motion artifact.

Infants enrolled in the current study who are discharged on home oxygen will be provided with standard clinical monitors by their home care companies, which will be set with alarm limits of 88% and 101%, and used with a frequency determined by the discharging clinician.

7.1.1 Treatment Compliance and Adherence

Data will be transmitted continuously from the home oximeter to the study team at CHOP. Data will then be reviewed weekly to ensure that families are using the device nightly as required per protocol, as well as to evaluate the integrity of transmitted data. If families are not using the monitor, the study team will contact them to facilitate adherence to the study protocol.

8 SAFETY MANAGEMENT

8.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

8.2 Adverse Event Reporting

The Investigator is responsible for recording and reporting unanticipated problems related to research that occur during and after study treatment. Unanticipated problems related to the research involving risks to subjects or others that occur during the course of this study (including SAEs) will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

8.3 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a subject who has received an intervention (drug, biologic, or other intervention). The occurrence does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable or unintended sign

(including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All AEs (including serious AEs) will be noted in the study records and on the case report form with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event.

8.4 Definition of a Serious Adverse Event (SAE)

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A distinction should be drawn between serious and severe AEs. A severe AE is a major event of its type. A severe AE does not necessarily need to be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but would not be an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE

8.4.1 Relationship of SAE to intervention

The relationship of each SAE to the study intervention should be characterized using one of the following terms in accordance with CHOP IRB Guidelines: definitely, probably, possibly, unlikely or unrelated.

8.5 IRB/IEC Notification of SAEs and Other Unanticipated Problems

The Investigator will promptly notify the IRB of all on-site unanticipated, serious Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed using the eIRB system and in accordance with the timeline below. External SAEs that are both unexpected and related to the study intervention will be reported promptly after the investigator receives the report.

Type of Unanticipated Problem	Initial Notification (Phone, Email, Fax)	Written Report
Internal (on-site) SAEs Death or Life Threatening	24 hours	Within 2 calendar days
Internal (on-site) SAEs All other SAEs	7 days	Within 7 business days
Unanticipated Problems Related to Research	7 days	Within 7 business days
All other AEs	N/A	Brief Summary of important AEs may be reported at time of continuing review

8.5.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

8.6 Medical Emergencies

It is possible that a home monitor will alarm repeatedly for low saturations. In this case, the family will be instructed to contact the child's doctor and if necessary bring the child to the emergency room. Such events will be monitored closely and reported to the IRB as necessary according to the above guidelines about adverse event reporting.

9 STUDY ADMINISTRATION

9.1 Treatment Assignment Methods

9.1.1 Randomization

The plan for randomization is described above in section 3.2.

9.1.2 Blinding

The plan for allocation concealment is described above in section 3.2. Given the nature of the intervention to be evaluated participants and research staff will not be blinded to group assignment.

9.2 Data Collection and Management

The proposed research will be carried out using, in part, computing facilities available at the PRECISE (Penn Research in Embedded Computing and Integrated Systems Engineering) Center at the University of Pennsylvania. The PRECISE center has a large dedicated facility for embedded system development and prototyping with an array of electronic measurement and instrumentation equipment.

The oximeters each have a port into which a small computer/dongle designed for this study is plugged. The dongle contains a wi-fi device ("hot spots") that will transmit the data continuously. The dongle can store data in the case of dropped wi-fi signal. We will transmit SpO2 data and pulse rate, along with some data that indicate the quality of the signal, but not the waveforms. Only oximeters on loan from Masimo will be used for this study. In addition only cellular modems provided by CHOP will be used for this study.

The lab provides secure storage in addition to the hardware and computing resources necessary to maintain a large-scale monitoring system. The PRECISE center has developed the device that will transmit data from the Masimo monitor to the study team at CHOP wirelessly. They will maintain these devices and the data transmission throughout the study. This team will not have access to patient identifiers; data streams will be labeled only with study ID numbers. However, the data streams will be date and time stamped, which is essential in order to ensure data integrity. PRECISE will then strip dates and may perform analyses on de-identified and coded data set with dates

removed, therefore they will not be considered engaged in human subject's research nor is there a need for a data sharing agreement.

As mentioned, data may be managed and stored in a password-protected database using the research-focused electronic web-based data capture system REDCap (Research Electronic Data Capture). REDCap is a secure software solution and workflow methodology for supporting clinical research databases developed by the informatics core at Vanderbilt University. Automated time-stamped backup files are made daily from the replicated database by CHOP Research Information Systems. Backup files are encrypted and transferred to the secure CHOP Research Information Systems Storage Area Network (SAN) accessible only to designated personnel. REDCap provides automated export procedures for seamless data downloads to Excel and commonly-used statistical packages. The database will incorporate range and consistency checks to ensure quality control and will signal the presence of questionable items. Only study team members will have access to the REDCap database for data entry under the supervision of and after training by the PI. Hard copies of data instruments will be stored in a locked cabinet in a locked office in the Division of Neonatology at CHOP.

To maintain confidentiality, participants will be assigned a unique identifier that contains no protected health information. All source documents will have the study identifier only. Access to the identifiers of the coded data will be controlled by the PI and only study team members will have access to the electronic and paper data.

Individuals who withdraw from the study after enrollment will be removed from the main study database (s) and placed in to a separate encrypted, password-protected database maintained at CHOP. This file will be deleted at the end of the study. Records will be retained in compliance with CHOP Policy A-3-9

9.3 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy. Study personnel will not use data and records for any purpose other than conducting the study. To maintain confidentiality, informed consent will occur privately and all study data will be coded as described above in 9.2 Data Collection and Management.

No identifiable data will be used for future study without first obtaining IRB approval. The investigator will obtain a data use agreement between the provider (the PI) of the data and any recipient researchers (including others at CHOP) before sharing a limited dataset (PHI limited to dates and zip codes).

9.4 Regulatory and Ethical Considerations

9.4.1 Data and Safety Monitoring Plan

The PI will be responsible for monitoring the data and safety of all participants. All study procedures will receive IRB approval prior to recruitment or enrollment of participants. In addition to the data management procedures outlined above, the PI will hold monthly study team meetings to evaluate the safety and progress of all research procedures. The PI will also be responsible for overseeing training of the research staff in the recruitment of subjects according to the participant

inclusion criteria and maintaining the study protocol set forth in this study. Standard procedures for all data collection methods will be reviewed at the start and periodically throughout the study. Data checks for errors will be performed prior to analysis. The PI and research staff will also review adverse events and any concerns about participant distress that might not qualify as an adverse event. Adverse events and serious adverse events will be reported to the CHOP IRB and other regulatory authorities in accordance with federal and other relevant regulations.

In addition, an independent data monitor for the BPD STar study has been identified. This person is a biomedical engineer with expertise in streaming oximetry data and clinical studies of newborn infants utilizing oximetry. She will be responsible for participating in assessments of data quality as pretain to the oximetry data and analyses.

9.4.2 Risk Assessment

Confidentiality. Protected health information will be collected as part of study records, and breaches of this information outside of the study team resulting in loss of confidentially is a potential risk. Every precaution will be taken to secure participants' personal information to ensure confidentiality. Our institution maintains strict policies, systematic procedures and sufficient resources for data management in compliance with HIPAA and IRB regulations for safeguarding participant information. Electronic data will be stored in secure, password-protected systems. Paper data will be stored in a locked cabinet in the locked Neonatology office suite at CHOP. Participants will be assigned a unique identifier that contains no protected health information. Access to the identifiers of the coded data will be controlled by the PI and only study team members will have access to the electronic and paper data.

Saturation Targeting. Targeting high oxygen saturations with supplemental oxygen may be associated with increased pulmonary oxygen toxicity, retinopathy of prematurity, decreased quality of life, without improving neurologic outcomes. Targeting lower oxygen saturation ranges with less supplemental oxygen may be associated with more episodes of hypoxia which might impact growth and development. Subjects will be monitored simultaneously with a clinically indicated pulse oximeter monitor. There are subject discontinuation and study stopping criteria as well as monitoring procedures in place and, in addition to the PI, an independent monitor will conduct data safety monitoring.

Oxygen saturation monitors. Oxygen saturation monitors are routinely used in the NICU and also frequently indicated for home use in infants with BPD. Participants will follow routine clinical routines for frequent site relocation of the oximeter sensors (probes), which will eliminate the risk of any significant skin irritation. The monitor will have an alarm, which will sound if the sensor is not working or if the infant's oxygen level is too low, which may be bothersome to families.

Questionnaires. Risks are not greater than minimal. Completing questionnaires in regards to health behavior activities could potentially be distressing for some parents/caretakers, however it is not likely that these activities will create additional distress beyond that which is already present.

9.4.3 Potential Benefits of Trial Participation

Direct benefits are that participants may have improved symptoms and/or disease management or improved growth and development and decreased cost. It is possible that infants with BPD,

who are at high risk for adverse outcomes, might benefit from targeted management of oxygen saturations over the first few months of life.

Indirect study benefits include benefitting infants with BPD in the future by increasing our understanding of effective oxygen saturation targets. This study will yield important knowledge about the post-discharge care of infants with BPD.

9.4.4 Risk-Benefit Assessment

The potential benefits of participation exceed any minimal risks.

9.5 Recruitment Strategy

Research will take place at The Children's Hospital of Philadelphia (CHOP), Hospital of the University of Pennsylvania (HUP), and Pennsylvania Hospital (PAH). Infants will be recruited from the neonatal intensive care unit (NICU) at the Children's Hospital of Philadelphia, which is a 97-bed quaternary referral center, and the adjacent Hospital of the University of Pennsylvania NICU, which is a 36-bed tertiary inborn unit. In addition, Infants will be recruited from Pennsylvania Hospital, Which is a 50- bed tertiary inborn unit. The research coordinator or PI will approach families of eligible infants for consent while the infant is still hospitalized in the CHOP, HUP, or PAH NICU and has reached at least 34 weeks corrected age. Adequate time to review the consent, consider risks and benefits of participation, and ask questions will be provided. Signed informed consent will be obtained from a parent before a child is enrolled and randomized.

9.6 Informed Consent/Assent and HIPAA Authorization

Potential study candidates will be screened for eligibility based on the inclusion and exclusion criteria. Parent or legal representative of each potential participant will receive a verbal and written explanation of the purposes, procedures and risks of the study. Families will have time to consider participation and make a decision at a later time. A study physician will be available to explain the medical aspects of the study and answer questions during the consent process. Informed consent procedures will occur in the participant's room or remotely. A combined informed consent-HIPAA authorization document will be used. Parents will have the opportunity to ask questions. The parent or legal representative must provide written informed consent prior to the start of any study activities. Consent will be documented and a copy of consent documents will be provided to the parent or caregiver. Decision not to participate in this study will not affect access to or quality of clinical services.

Due to Covid-19 and with reduced access to the workplace and social distancing that is enforced, we will provide the option to consent parents and enroll subjects remotely in one of two ways –

1) The REDCAP survey method with an eConsent that will be emailed to the parents with telephone and/or video-conferencing to follow, if feasible, to answer questions, and a signed copy returned automatically if they agree, or

2) By making a paper copy of the consent available to the parents ahead of time with either the research team mailing, emailing or faxing the consent or the research team or clinical staff providing a paper copy, followed by either telephone and/or video-conferencing or face-to-face to address their questions or concerns.

A valid electronic signature will be obtained via RedCap that the signature is logically associated with the individual. The consent form/HIPAA authorization will include instructions to print or save a copy of the page(s) presented on the electronic device. The subject will be able to print (or save) a copy of the consent form (with or without signature). Alternatively, the form could be emailed to the subject.

Regardless, the method by which consent is obtained, a study physician will be available to explain the medical aspects of the study, risks and benefits of the study, and answer questions during the consent process.

A short form will be available and translated into the subjects preferred language during the consent process for participants with limited English proficiency. The short form consent process will not occur remotely or via electronic form. Potential participant will receive a verbal and written explanation of the purposes, procedures and risks of the study. A translator will be available either in person or over the phone whenever needed. The study summary document and short form consent form (signed by the interpreter) will be obtained in person or via fax, scan or email.

9.6.1 Waiver of Assent

A waiver of child assent is requested due to the age of the children participating in the study.

9.7 Payment to Subjects/Families

Participants will be compensated up to a total of $300 ($50 per month, up to 6 months CA), through a ClinCard (loadable debit card) for their time and inconvenience, given that the study monitor must be used nightly and the family will have at least weekly interaction with the study team. Participants will also receive a BPD Star Tote at discharge to aid in convenient transportation of the study equipment.

10 PUBLICATION

Study findings will be disseminated in peer-reviewed scientific publications and at scientific meetings. The CHOP investigators will have access to complete trial data. Published data will be deidentified.

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