Part B: Experimental Design and Protocol – ALL APPLICANTS MUST COMPLETE THIS FORM

All investigators must submit a completed Part B with their New Protocol or Continuing Review application. If a protocol from a corporate sponsor or cooperative group is available, this must also be submitted.

Each question in Part B should be answered thoroughly with answers that are specific to how the research will be conducted at Children's Hospital, Boston.

Do not cut and paste from the protocol or from a grant application to complete Part B. Instead, complete each question in Part B by referencing the applicable page and section number of the protocol which answers the questions in Part B. For some questions in Part B, such as those regarding recruitment methods, confidentiality provisions, and adverse event reporting, you will need to provide complete answers rather than references to the protocol, since the protocol will not address these items as they apply specifically to how the research will be conducted at CHB.
Further information may be obtained by referring to **the polices and procedures on the CCI website**

1. Abstract

This research protocol describes a randomized control trial to compare two different methods of managing home oxygen therapy in premature infants. This is a multicenter study involving 9 centers. We plan to enroll a total of 196 infants, of which 68 will be from Boston Children's Hospital (BCH). The current standard for oxygen management includes brief assessments of a patient's oxygen saturation status during monthly clinic visits. The patient's oxygen status between visits is assumed to be acceptable; although it is possible for significant hyperoxia or hypoxia to occur, providers have no data to help with decision-making. In many centers, final steps before discontinuing home oxygen therapy (HOT) often include polysomnography (PSG), which can be costly and requires the inconvenience of rehospitalization. Advances in data storage and pulse oximetry technology have expanded potential uses for recorded home oximetry (RHO) in the accurate assessment of hypoxemia. At Boston Children's Hospital, we have pioneered the use of recorded home oximetry (RHO) in other research protocols, and shown that it can be a simple and convenient method for parents to transmit oximetry data to providers.
In this trial, we will randomize premature infants who require HOT at time of discharge from the NICU, who are referred for follow-up at the Center for Healthy Infant Lung Development. At the time of their first outpatient appointment, infants will be randomized to one of two treatment arms:

Arm A ("Standard therapy"): Infants' oxygen will be increased, decreased, or maintained based on brief structured assessments during monthly clinic visits. Polysomnograms will be utilized prior to final discontinuation of oxygen. RHO will only be utilized on the night prior to and during the polysomnogram to compare these two modalities.

Arm B (RHO): Infants will have the same monthly clinic assessments as in Arm A, but also will utilize RHO to potentially increase, decrease or maintain oxygen between monthly visits. Parents will transmit a minimum of 25 hours (1500 minutes) of stored RHO data (approximately 4 days, 8 hours per day) every 4-7 days. Changes in oxygen needs will be made based on standardized objective criteria. To determine discontinuation of oxygen, RHO will be utilized instead of polysomnography.

Parents of all infants will be asked to complete a structured quality-of-life survey, the PedsQL Family Impact Module (PedsQL), at their initial (baseline) clinic visit, and monthly at each clinic visit until the infant is weaned. A follow-up PedsQL will be done 3 months after weaning either by phone or at a clinic visit. Health care utilization (emergency department visits and rehospitalizations) and information on growth and nutrition will be assessed at monthly clinic visits while the child is on oxygen, as well as 1 and 6 months after discontinuation of oxygen. Additionally, post-wean, but before their 6 month follow-up, parents of Arm B children will be approached in clinic, or contacted via phone, to collect a brief, 5 minute Home Oximetry Feasibility Questionnaire survey that helps to identify variables that may correlate with an increased or decreased likeliness to record and send home oxygen data.

Our overall objective is to determine whether RHO can improve caregiver quality of life, and can shorten HOT duration and eliminate need for PSG, without compromising safety. We will determine respiratory-related re-hospitalizations, emergency department (ED) visits, and growth parameters to confirm safety of the proposed weaning strategies.

Our specific aims include: **Specific Aim 1:**

To evaluate the impact of a data-driven HOT management protocol on duration of HOT. *We hypothesize that RHO will shorten duration of HOT therapy compared to the current standard HOT management protocol* **Specific Aim 2: To evaluate the effects of a data-driven HOT management protocol on parent quality of life.** *We hypothesize that RHO utilization will decrease emotional and financial stress compared to standard oxygen management approaches.*

Specific Aim 3*:*

To evaluate the extent to which a data-driven HOT management protocol can improve growth and respiratory outcomes.

We hypothesize that RHO utilization will not increase rates of respiratory-related re-hospitalizations and ED visits, and will not impair growth compared to standard oxygen management protocols.

2. Background and Significance

Improvements in neonatal intensive care have led to increased numbers of premature infants surviving with chronic lung disease, including requirement for supplemental oxygen (O_2). Current estimates indicate that over 50,000 premature infants are currently discharged home on supplementary O_2 each year.[1] At Boston Children's Hospital's Center for Healthy Infant Lung Development, we currently wean approximately 60-70 premature infants from home O_2 annually.

Consensus guidelines for safe management of HOT do not currently exist. Current strategies to manage outpatient HOT include arbitrary timing of decreasing O_2 delivery to lower flow rates prior to discontinuation, leading to potentially unnecessarily longer duration of HOT.[2-5] The final step before completely discontinuing HOT often includes polysomnography (PSG) [6-7], but the cost and inconvenience of this tool has led to a search for alternative strategies. PSG requires readmission to the hospital, and is relatively expensive. ***Inappropriate extension of HOT due to inefficient oxygen management strategies and use of potentially unnecessary, expensive weaning procedures both expose patients to potential toxicities and result in excessive cost to the health care system.***

In an effort to provide insight into resource utilization targets and best-practice guidelines, we performed a systematic review of the published clinical evidence. Surprisingly, we noted that guidelines exist but without any evidentiary basis. We then undertook a survey to identify best practice from the twenty top pulmonology programs in the country.[6] Many providers rely on brief outpatient assessments of O2 status in monthly outpatient clinic visits to assume oxygenation status in the subsequent month. Prior to discontinuing O_2, a majority of providers perform some form of nocturnal oximetry assessment, but there is no consensus on whether to perform the more expensive PSG versus inpatient or outpatient recorded oximetry.

The Center for Healthy Infant Lung Development (CHILD) program at Boston Children's Hospital (BCH) is one of the largest programs dedicated to the respiratory health of premature infants in the country. Through our extensive experience in clinical care of this of these patients, and through our experience in multicenter research collaborations, we have identified *recorded home oximetry* (RHO) as a potentially efficient, relatively inexpensive alternative tool to potentially save cost and improve the process of HOT management. RHO can provide extended O_2 saturation data during the outpatient weaning process, and also provides data comparable to the more expensive PSGs that have been more recently encouraged.[7]

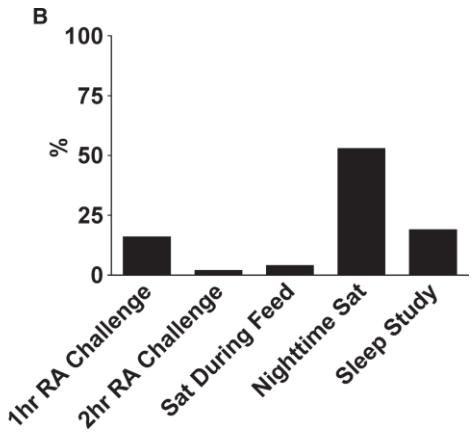
Based on these analyses above, several conclusions could be drawn regarding local and national HOT management practices: 1) Variability in O_2 weaning practice results in great variability in cost, 2) There is no evidence that more expensive O_2 management strategies are either safer or more efficient, and 3) Evidence-based practice guidelines for clinical decision-making and optimal resource utilization are currently lacking.

3. Preliminary Studies/Progress Report

Several preliminary studies have provided the basis for this proposed study.

Current HOT management strategies lack evidence for safety or efficacy. Our survey of US pulmonologists revealed striking variation in practice for weaning O_2 therapy in infants with BPD.[21] The majority of pediatric pulmonologists at major academic institutions rely on a combination of findings to aid them in establishing appropriate oxygen management practices for their patients. However, many of these practice determinants have never been prospectively studied or shown to actually predict safe discontinuation of O_2 therapy. Consistent and practical methods need to be determined and integrated into the care of these formerly premature infants. Such a consensus is lacking in published clinical practice guidelines.

These findings are consistent with other reports from Europe and Australia. [18, 39]



Expensive, inconvenient diagnostic testing is more common without substantial evidence for improved safety or efficacy. Recent studies have investigated the role of overnight polysomnography (PSG) in HOT management. PSG has been recommended by some as a more accurate test for assessing pulmonary reserve and for determining the appropriate timing for weaning of supplemental oxygen in preterm children with CLD.[22] There is little data to support the routine use of PSGs to manage supplemental oxygen needs in this population. Although there seems to be true equipoise regarding appropriate O_2 management methods, the methods have very different emotional and financial impacts on families. The discomfort of hospital admission for PSG for disabled patients and their families has been well-described [40], while Marcus described PSG studies as time-consuming, disruptive to families' lifestyle, expensive and not always feasible because of the limited number of sleep laboratory facilities.[41] **These studies support the need to evaluate more family-friendly, cost-efficient and safe alternatives to PSG.**

Simple, noninvasive methods of home oximetry data collection have been developed. We have completed pilot studies utilizing recorded home oximetry, which confirm feasibility of recording in the home, with accurate results. In one such study to assess intermittent hypoxia in former preterm infants, we recorded over 25,974 hours of analyzable recording from a total of 95 infants using the Masimo Rad-8 pulse oximeter interfaced with an Acumen serial data recorder, including recording in both the hospital and home. We have verified that simple, valid and time–saving strategies for automated software-based analyses can efficiently identify saturation parameters that can be used for clinical interpretation (accepted manuscript under revision, JAMA-Pediatrics).

In a separate study, we have identified reference values for nocturnal oximetry for use to identify readiness to wean from supplemental O_2,[42] which serve as the basis for the oxygen management protocol described in Table 1. In a population of 130 preterm infants weaned from HOT in our clinic, we have also determined the mean duration (144 +/- 66 days) of HOT (Manuscript in preparation). **The proposed study will build on these findings and methods and take this work in important new directions.**

4. Design and Methods

4a. Study Design

We plan a prospective, multicenter, randomized trial of premature infants who require HOT. We will follow infants, beginning at the time of their first outpatient pediatric pulmonary appointment and continuing until 6 months from discontinuation of HOT. Duration of HOT therapy for each arm of the study will be documented by each site investigator. Questionnaires throughout the HOT managing process and after oxygen discontinuation will assess the impact of each HOT managing process on the parent quality of life. Growth assessments throughout of the HOT managing process and after oxygen discontinuation will track safety of both protocols. Similarly, assessment of health-care utilization (respiratory-related emergency department visits or rehospitalizations) at 6 months after discontinuation of HOT will track safety as well.

4b. Patient Selection and Inclusion/Exclusion Criteria

This study will focus on premature infants with chronic lung disease of prematurity, or bronchopulmonary dysplasia (BPD). This population makes up the largest group of children that require supplemental O_2 and have an improving course that allows subsequent weaning. The results of our study will have more generalizability to several other populations (including both children and adults) that can wean from O_2, as standardized protocols to wean O_2 in those populations similarly do not exist.

Our intent is to select a representative target population of families of preterm infants with BPD that optimizes generalizability to preterm populations in general. Infants with conditions that may influence prolonged need for oxygen beyond lung disease of prematurity will be excluded.

Eligible parents will be recruited sequentially.

Inclusion Criteria:

Eligible parents will be:

(1) parents of an infant with birth gestational age ≤ 37 (37 0/7) wks postmenstrual age (PMA) who has requirement for supplemental O_2 at time of NICU discharge, as determined by primary NICU team.

(2) parent of a child receiving pediatric pulmonology care at the Center for Healthy Infant Lung Development.

(3) parent aged 18 years or older.

(4) English or Spanish-speaking. (Spanish instruments will be developed through translation services and a Spanish-speaking interpreter will assist with interviews as needed to allow participation of potential Spanish-speaking families).

Exclusion Criteria:

Ineligible parents will be:

(1) parents whose infants has presence of pulmonary hypertension at enrollment.

(2) parents whose infant with syndrome or other diagnosis with known high risk for persistent hypoxia (cardiac disease, Trisomy 21, Pierre-Robin Sequence, etc.).

(3) parents whose infant has requirement for O_2 flow rate > 1 L/min or tracheostomy

(4) any infants who also require caffeine at discharge from the NICU. One parent per child will be eligible. Parents will be asked to respond to a question about which parent takes primary responsibility for daily monitoring of the child; the primary caregiver will be the eligible parent for each family. If the child's parents share care-giving responsibilities equally, then parents may choose which parent will participate.

4c. Recruitment Methods

This is a multi-center study. Dr. Lawrence Rhein is the Principal Investigator at University of Massachusetts Medical Center (UMass)).UMass Medical Center will act as the coordinating center. The other sites include, Boston Children's Hospital (PI: Dr. Catherine Sheils) Baystate Medical Center (PI: Dr. Kathy Meyer), UConn Medical Center (PI: Dr. Tregony Simoneau), University of Vermont Medical Center (PI. Dr. Tom Lahiri), Dartmouth-Hitchcock Medical Center (PI: Dr. Tyler K Hartman), Tufts Medical Center (PI: Dr. Scott Schroeder), Boston Children's Hospital Physicians (PI: Dr. Sankaran Krishnan) and Kentucky Children's Hospital, University of Kentucky (PI: Dr. Elie Abu Jawdeh)

At BCH, potential eligible patients will be identified through one of two potential mechanisms: (1) identification of infants approaching readiness for discharge who will require supplemental home oxygen therapy (HOT) from Brigham and Women's Hospital (BWH) NICU or Beth Israel Deaconess Hospital (BIDMC) NICU or (2) identification of infants who present at their first outpatient appointment to the Center for Healthy Infant Lung Development (CHILD Clinic).

The site PI will review the NICU census at BWH and BIDMC once per week to identify infants who are approaching discharge and will require HOT, and to determine if there are contraindications to approaching families. They will then provide information about the study to parents in the NICU.

For infants who are eligible but not able to be approached due to logistics, or infants who are eligible but were discharged from other NICUs, the first provision of information will be at the first CHILD Clinic visit in their clinic room.

We will provide fliers to local referring NICUs to distribute to patients who will be discharged home on oxygen. These fliers will include contact information for study staff so that families may proactively ask questions or learn more about the study prior to their first clinic visit.

Subject recruitment will be performed by a team of research assistants in the study.

4.d. Description of Study Treatments or Exposures/Predictors

All participants will have the following study treatments:

1. Parents of enrolled infants will have parent reports/surveys to assess quality of life using the **PedsQL** at each monthly clinic visit until the infant has weaned and a 3 month post weaning follow-up PedsQL report/survey either by phone or in clinic.
2. All infants will have **growth assessments** at each monthly clinic visit before and after the wean.
3. **Nutrition regimen** will also be collected at each monthly clinic visit, and the 1 month and 6 month post-wean follow-up visits to capture factors that contribute to growth. Nutrition information will include any note on nutrition regimen made by a physician or nutritionist at the time of visit.
4. All infants will have **monthly clinic visits** with O2 challenges in clinic until oxygen is discontinued. (**This is standard clinical care and not a separate research treatment)
5. Infants in Arm A ("Standard" management) will have **polysomnogram** performed prior to discontinuation of HOT. (This is a clinically-indicated, although not mandatory test). They will have RHO on the night prior to and during the polysomnogram.
6. Infants in Arm B (RHO) will use an **additional oximeter to record data** and will transmit the data every 4-7 days to research staff.
7. Parents of infants in ARM B (RHO) will also be given a **post study Home Oximtery Feasibility Questionnaire** to complete. This is a questionnaire that will be used to determine the advantages and challenges of using home oximetry. This questionnaire would be conducted at the 1 month post-wean visit, however, if unable to obtain at this time point, due to missed visit or lost to follow-up it can be collected post wean at any time at a clinic visit or over the phone.

**For patients in ARM B who have completed the study and have not completed the Home Oximetry Feasibility Questionnaire, this will be obtained from the parents retrospectively by sending them a letter and the questionnaire or by calling and obtaining verbal consent to conduct the questionnaire before doing so. Additionally, for all past patients, nutrition notes will also be obtained for the clinic visits that they attended during the course of the study.*

4.e. Definition of Primary and Secondary Outcomes/Endpoints

Primary measures: (a) Total duration of home oxygen therapy (HOT) from the first outpatient pulmonary appointment to discontinuation of supplemental O_2; and (b) Parent quality of life, assessed by differences in the post-weaning PedsQL baseline.

Secondary measures: (a) Number of rehospitalizations and emergency department visits from 1st clinic visit through 6 months after discontinuation of HOT; (b) Change in weight and weight-for-length z-score from 1st clinic visit to 6 months after discontinuation of HOT; and (c) For patients who will receive a sleep study, percent time below designated O_2 saturation thresholds (<96%, <93%, and < 90%) will be calculated from both RHO and from the polysomnogram data. The number of desaturation events (defined as saturation drops below 90% for >10 seconds and > 20 seconds) will also be analyzed.

Duration of HOT was chosen as a primary outcome since it is the primary driver of caregiver emotional and financial health for families of infants on HOT. This outcome was driven by input from families themselves, through a process of including important stakeholders in the protocol development process. The PedsQL was chosen as an additional primary outcome because it is validated, accurate scale in which scores correlate with maternal psychiatric symptoms, poor child health, poor child adjustment, and increased child hospitalizations.

This protocol focuses on patient-centered outcomes that may demonstrate non-inferiority from a medical safety perspective, but may improve quality of life. While families place a priority on treatment strategies that optimize health, when there are multiple choices without a clear medically superior choice, then the impact of specific treatment choices on quality of life will help drive decision-making.

Although our primary outcomes focus on quality of life, the secondary outcomes were chosen to confirm that weaning strategies (that likely improve quality of life) are not less safe. Assessment of short-term outcomes after discontinuation of therapies may miss significant later morbidities. We therefore included clinically relevant secondary outcomes at 6 months post discontinuation of O_2 to assess the safety of the weaning strategies. Inadequate O_2 supplementation has been associated with poor somatic growth, [15] so growth parameters are an important outcome to confirm long-term safety of all studied weaning protocols. Higher O_2 target saturations, with subsequent increased exposure to supplemental O_2, have been linked to increased numbers of respiratory exacerbations.[12] We therefore are also including rates of respiratory-related emergency department visits and rehospitalizations as additional secondary outcomes.

4f. *Data Collection Methods, Assessments and Schedule*

Each enrolled patient will receive a coded deidentifier, which will be used in a RedCap database to preserve confidentiality of all data linked to that patient.

Informed Consent:

Consent for this study at BCH will be obtained by the site PI or study team.
Consent will be obtained at the first study visit at all sites. Adequate time will be allowed between the review of the consent form and the signing of the consent form to allow families to decide on their participation. We will gauge the parents' level of understanding by asking them questions about the various elements of the consent. Significant new findings during the course of the research would require changes to the informed consent document. Subjects would be re-consented with the new approved

consent form at their next study visit, prior to any procedures being performed. Because at BCH we feel it will be important for other healthcare providers to know if the child is participating in this study, the consent forms will be placed in the subjects BCH medical record.

ARM A																
Study Period											Follow-up					
Visit	Baseline (Initial Visit) V0	V1	--	V2	--	V3	--	V4	--	V5	1 mo post wean	--	3 mo post wean	--	--	--	6 mo post wean (Final visit)
Consent	X																
Eligibility Criteria	X																
NICU Discharge Summary	X																
Clinic O2 Setting	X	X		X		X		X		X							
PedsQL	X	X		X		X		X		X			X				
Growth Assessment	X	X		X		X		X		X	X						X
PSG																	
AE/ED/Rehospitalizations		X		X		X		X		X	X		X				X
Nutrition Assessment	X	X		X		X		X		X	X						X

ARM B																
Study Period											Follow-up					
Visit	Baseline (Initial Visit) V0	V1	--	V2	--	V3	--	V4	--	V5	1 mo post wean	--	3 mo post wean	--	--	--	6 mo post wean (Final visit)
Consent	X																
Eligibility Criteria	X																
NICU Discharge Summary	X																
Clinic O2 setting/Home Oximetry Data	X	X	X	X	X	X	X	X	X	X							
PedsQL	X	X		X		X		X		X			X				
Growth Assessment	X	X		X		X		X		X	X						X
AE/ED/Rehospitalizations		X	X	X	X	X	X	X	X	X	X		X				X
Nutrition Assessment	X	X		X		X		X		X	X						X
Home Ox. Feasibility Questionnaire*											X*						

***Home Oximetry Feasibility Questionnaire will be collected at the 1 month post wean follow-up visit. However, If a patient is missed or lost to follow-up, research staff may call the family to obtain this information as soon as possible before their last visit.**

- **Baseline Visit (First Initial Visit): V0**

(For all patients in ARM A and ARM B)

After confirming eligibility and obtaining the consent form, growth parameters, nutrition notes, NICU discharge summary, demographics and PedsQL survey will be obtained at this visit.

Medical records will be transferred to UMass using methods to ensure data safety, for abstraction by study staff. Dr. Rhein will train study staff in abstraction of medical records.

Each site PIs will perform the baseline growth assessment and perform randomization at time of enrollment. We will perform block randomization to ensure equal distribution within each site.

Study staff at BCH will ask parents to complete a PedsQL[38] at the initial (baseline) clinic visit. Research staff at BCH will hand the questionnaire to the parent for self-report in order to minimize response bias and standardize methods. If for some reason the PedsQL is not completed in clinic, staff at BCH or UMass will contact the family to complete the survey over the phone shortly after the visit. Growth and nutrition information from this visit will also be recorded.

At the end of the visit, contact information will be confirmed, and the parent will be reminded about the next planned phone/clinic visit and interview.

- **Monthly Visits: (ARM A and ARM B): (V1 onwards until wean)**

1. Parents will be asked to complete the PedsQL at follow-up monthly clinic visits until the infant is weaned. In case the PedsQL is not obtained during the clinic visit, due to time constraints, these surveys can be conducted over the phone in the privacy of their home. This is to ensure we have consistent data on all patients in our study.
2. Growth parameters (WHO) and nutrition notes will be obtained at all monthly visits (prior to weaning).

- **Post Wean Follow- Up visits**:

The Post-Wean follow- up (f/u) visits are at 1 month, 3 month and 6 month after the patient has been weaned off oxygen.

- 1 month post-wean f/u visit: At the 1 month post wean visit, growth parameters, nutrition notes and will be collected. For ARM B patients only, a **post study Home Oximetry Feasibility Questionnaire** will be given to parents to complete. This questionnaire would be conducted at the 1 month post-wean visit, however, if unable to obtain at this time point, due to missed visit or lost to follow-up it can be collected post-wean at any time at a clinic visit or over the phone.
- 3 Month post-wean f/u visit: At the 3 month post-wean visit, a **PedsQL will be obtained. If unable to complete at this time, study staff at BCH or UMass will contact to obtain the survey over the phone**.
- 6 month post-wean f/u visit (Final Visit): At the 6 month post-wean visit, growth parameters and nutrition notes will be collected. In addition, the provider will inquire about respiratory-related hospitalizations or emergency department visits that may have occurred since oxygen discontinuation. Medical records will be reviewed to confirm this data. This visit marks the completion of participation in the study

Study staff will complete a final disposition form for every subject as a way to declare them officially off of the study.

- **All Visits:**

Adverse events:

Rehospitalizations and emergency department visits will be determined through parent interview/phone calls during and in between the monthly clinic visits as well as during the post weaning period: (1 month, 3 month and 6 months after oxygen discontinuation), and will be verified through medical record review/parent/site communication. This will be recorded on the Adverse Event form.

- **ARM B only:**

Oximetry data for infants in Arm B will be transmitted by mail or email to study staff every 4-7 days, and after analysis will be transferred to structured data collection forms. For patients who do not have internet access, or who do not feel comfortable using a computer, pre-stamped envelopes with blank data cards will be provided. The data cards will be labeled with the patient's coded deidentifier so that no identifying patient information is on the card or envelope. The participants will simply mail their data card every 4-7 days. All participants will mail the data card to UMass Medical Center, which will serve as the central data coordinating center

- **ARM A Only:**

Polysomnogram data for infants in Arm A will also be extracted into data collection forms after completion of the polysomnogram.

Follow-up with sites: Every month, study staff, led by Dr. Rhein, will conduct a conference call with all site PIs to review recruitment progress and confirm status of currently enrolled patients. Notification of infants who have successfully discontinued HOT will be verified.

Removal of subjects from the study: If it is required to permanently discontinue the study intervention because of adverse effects the participant will be withdrawn from the study. The Investigator may also remove a subject from the trial if he or she feels this action is in the best interest of the subject. Parents can withdraw their children from the study at any time for any reason.

Study Procedures:

- **PedsQL:**

The PedsQL consists of 36 items that assess eight health domains labeled physical functioning, role limitations due to physical or emotional health, bodily pain, general health, vitality, social functioning and mental health. For the purpose of reporting results, the raw scores rating each health domain are transformed to a score that can range from 0 to 100, with higher scores reflecting better functioning. Considerable information about the validity and reliability of this measure is available. We have performed a preliminary review of the PedsQL with our Parent Advisory Board, and will work with them to augment these measures and ensure that planned measures adequately address the parent perspective.

- **Oxygen Management Protocols**

At time of enrollment, infants will be randomized to one of the oxygen management protocols (utilization of RHO or routine care). Infants randomized to utilization of RHO will receive a Masimo Rad-8 pulse oximeter and serial data recorder to record HbO_2 SAT and heart rate, and will receive instruction regarding when to record the infant and how to send in data.

- **Home Pulse Oximeter Recording Procedures**

The recording system we used for prior studies and plan to use for this study is the Masimo Rad-8 pulse oximeter with an attached data recorder and removable memory card with ample capacity (2 GB) to store the continuous data recorded for each infant. The oximeter will be set for the minimum (2 sec) averaging time. Since the study oximeter will not be used as a monitor but rather as a **(continuous) recorder**, it will be preset in the sleep lab mode; there will be alerts for "probe off" and "low battery," but no alarms for HbO2 SAT or heart rate, and no visual displays of HbO2 SAT. ***Infants will utilize their clinically-provided monitor as determined by their primary clinical team to serve as their monitor.***

During the 4-7 day evaluation periods to determine readiness to wean or status post wean, parents will be instructed to use the oximeter continuously during nocturnal sleep periods for a minimum of 25 hours (1500 mins/approximately 8 hours per day for 4 days). At the end of the 4-7 day period, data will be downloaded and electronically sent via secure email. For families who do not have access to a computer, and/or are uncomfortable with technology we will provide with data cards that can then be sent via provided protected express shipping envelopes with postage. All data cards will be sent to Dr. Rhein at UMass for analysis as soon as they are removed from the oximeter.

Over the 4-7 days, a minimum of 25 hours (1500 minutes) of data is to be sent to UMass and deemed interpretable before any change in supplemental oxygen management is made. If the data is deemed inadequate or unreadable, the parent will be notified and no change in oxygen management will be made. Infants randomized to routine care will be weaned at monthly outpatient clinic visits per structured clinic-based protocol. Weaning parameters for each arm are listed in Table 1.

Table 1. O2 WEANING PARAMETERS		
	STANDARD OXYGEN MANAGEMENT ARM	**CpOx OXYGEN MANAGEMENT ARM**
CRITERIA FOR **INCREASING** O2 FLOW RATE	INABILITY TO MAINTAIN **O2 SAT >93%** AT PATIENT'S CURRENT O2 LEVEL FOR 20 MINUTES IN CLINIC VISIT CHALLENGE	INABILITY TO MAINTAIN **O2 SAT >93%** FOR >95% OF RECORDED TIME
CRITERIA FOR **MAINTAINING** CURRENT O2 FLOW RATE	ABILITY TO MAINTAIN **O2 SAT >93%** AT PATIENT'S CURRENT O2 BUT UNABLE TO MAINTAIN **O2 SAT >93%** AT WEANED FLOW RATE FOR 20 MINUTES IN CLINIC VISIT CHALLENGE	ABILITY TO MAINTAIN **O2 SAT >93%** FOR >=95% OF RECORDED TIME BUT UNABLE TO MAINTAIN **O2 SAT >96%** FOR >=95% OF RECORDED TIME
CRITERIA FOR **WEANING** O2 FLOW RATE	ABILITY TO MAINTAIN O2 **SAT >96%** AT WEANED FLOW RATE FOR 20 MINUTES IN CLINIC VISIT CHALLENGE	ABILITY TO MAINTAIN **O2 SAT > 96%** FOR >=95% OF RECORDED TIME
* Clinic pass and fail will be determined per clinic assessment of oximeter alarms. ** CpOx pass and fail will be determined 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 any wean.		

For infants in both arms, O_2 weaning will proceed, when allowable per weaning criteria in the protocol, in 50% increments to a minimum of 125 cc/min. (For example, flow rate of 500 cc/min will be decreased to 250 cc/min, and 250 cc/min will be decreased to 125 cc/min.) Once infants achieve flow rates of 125 cc/min (or if they are discharged home from NICU on <125 cc/min), the next weaning step will be to room air during the day and nocturnal O_2 only at a flow rate of 125 cc/min.

When infants in arm A have weaned to the final stage before discontinuation (O_2 flow rate <= 125 cc/min, utilized only at night), they will be scheduled for an overnight polysomnogaphy (PSG). These infants will have overnight recording with the Masimo Rad-8 pulse oximeter and serial data recorder on the nights prior to and during the PSG. Final decision regarding safe discontinuation of supplemental O_2 therapy will be based on O_2 saturation and growth outcomes; infants who do not meet criteria on the first PSG will remain on overnight O_2 supplementation and repeat the PSG monthly until they pass.

To determine "Pass" of PSG or to determine ability to wean versus hold on current therapy versus escalate support, strict protocols to analyze O_2 saturation status will be followed:

For patients randomized to standard therapy weaning:
Clinic staff will monitor the patient for 20-minute intervals to determine whether infants maintain saturations above the target saturation limits defined in Table 1 to determine whether weaning can proceed at that visit.
For patients randomized to HRO-based weaning:
We will determine the number of seconds/hour with saturation >96, < 93, and < 90%, and the percentage of time below these thresholds for each recording interval (minimum 4-day epochs during weaning for

randomized infants, and 12 hour epochs for all infants both on the night before and during PSG) using target saturation limits defined in Table 1 to determine whether weaning can proceed.

For PSG evaluations:
Infants will "pass" the PSG when they can maintain O_2 saturation >93% for >95% of the time, with a minimum of 8 hours of nocturnal recording.

Control for Confounding Variables
Although this is a randomized trial, to account for potential confounding factors, we will extract demographic and NICU clinical variables. All clinical sites will complete a data collection form using a secure web portal. Family demographic data will include history of any fetal exposures (including smoking, alcohol, street drugs), parental ages and highest education levels achieved, marital status and other environmental or home influences affecting infant development. Infant data will include time to full oral feeds, breast feeding status at discharge and at home, and all diagnoses at enrollment, hospital discharge, and to study completion, including PDA ligation, and any documented fungal/bacterial sepsis or meningitis, and bronchopulmonary dysplasia or chronic lung disease. The severity-of-illness data collected will include last day of (1) intubation, (2) nasal continuous positive airway pressure, (3) high flow (>2 L) and low flow nasal cannula use, and (4) supplemental O_2. Weight, length and head circumference at birth, hospital discharge, and first clinic visit will be recorded. Other medications recorded will include postnatal steroids, and all prescribed medications at home.

g. Study Timeline (as applicable)

We expect to enroll the total of 68 patients from BCH over a 3.5-year period. (This is a multicenter study. Total enrollment will be 196 infants. We anticipate that our final patients will complete oxygen weaning after 6 months and 6-month follow-up for final outcomes assessment will be within 3 years of starting this project.

h. Adverse Event Criteria and Reporting Procedures

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, or other means, will be collected and recorded and followed as appropriate.

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study intervention even if the event is not considered to be related to study intervention. The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. the severity grade (mild, moderate, severe) or (grade 1-4)
2. its relationship to the study device(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

All adverse events should be treated appropriately. Such treatment may include changes in study treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study intervention, the interventions required to treat it, and the outcome. The IRB at

each site will be notified about adverse events in compliance with its policy of safety reporting. (e.g. according to BCH IRB policies, all adverse events that do not qualify the definition of an "reportable" event will be notified at the yearly continuing review).

Serious Adverse Events (SAE):

. A serious adverse event is an undesirable sign, symptom or medical condition which:

- is fatal or life-threatening
    - Non-infectious hypoxic events or Acute Life Threatening Events (ALTEs) between and during monthly clinic visits
    - Development of newly diagnosed pulmonary hypertension.

OR

- results in persistent or significant disability/incapacity

OR

- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for one of the following:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the patient's general condition

OR

- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

SAE Reporting: Information about all serious adverse events will be collected and recorded. To ensure patient safety, each serious adverse event must also be reported to the PI as soon as possible after learning of its occurrence

At BCH, according to its IRB policies, Serious Adverse Events that are **serious**, **unexpected** and **related** to the study, including rehospitalizations and emergency department visits will be reported to the study's DSMB and IRB promptly (within 72 hours of occurrence). At all other sites, the SAE reporting will comply to the site specific IRB policies). New diagnoses of pulmonary hypertension will similarly be reported to the DSMB and IRB within 72 hours of diagnosis.
All Adverse events and Serious Adverse events will be presented to the DSMB board every 6 months.

i. <u>If the Investigator is the Sponsor/Assignee (IND or IDE-holder)</u>, he/she is responsible for selecting a qualified monitor who will monitor the progress of all clinical investigations conducted under the IND or IDE. Please describe the monitoring plan for this protocol below:

↳ Note: the EQuIP office provides monitoring services and advice. For info, contact EQuIP @ 5-7052.

X Not applicable

5. Data Management and Statistical Analysis

a. Data Management Methods

Subjects will be provided with a unique ID code and only the study coordinator, Principal Investigator and study monitor will be able to view the link between participants' names and the unique ID. The link to all codes will be maintained in a secure, HIPAA compliant database in the study coordinator's office. The unique patient number will be used on all research documents, including case report forms, as well as on labels on samples collected. All information from this study will be kept in the same research binder in the study coordinator's private and locked office at UMass Medical Center. This will include all paperwork with identifying information, including tracking sheets, orders, consents, etc. After each clinic visit, the BCH study staff will transfer all essential documents including clinic notes, anthropometrics and study surveys to the research team based at UMass using secure file transfer methods.
Pre-enrollment/screening clinical and laboratory data may be collected by study staff from the medical record. Case report forms (CRFs) will be designed for collection of all clinical and laboratory data with input from the BCH Clinical Research Center (CRC) staff and statistician. The CRC staff includes experienced data managers who will be responsible for creating the data base and training study staff at all sites in data entry into the data base. The data manager will work with the study statistician to ensure that all appropriate measures are collected and coded correctly. The clinical research coordinator will work with study and coordinate with the site study monitor to ensure data quality and integrity.
The CRC clinical research staff provides data management expertise for many clinical trials that take place at Boston Children's Hospital. Data will be collected by the research coordinator who has been trained in how to collect the specific clinical and laboratory data from the medical record. All data will subsequently be entered into the electronic database created specifically for this study using RedCap. The database will be designed with rules to prevent entry of impossible values for relevant fields. Subjects will be identified only by a study identification number in the database. The database will be password protected with a password known only to study staff, who need to enter or access data. Files with the study ID number linked to the subjects' actual names and hospital medical record numbers will be kept separately by the site PI at each site.

The CRC representative will review the data entered in the eCRFs for completeness and accuracy and instruct the site team to make any required corrections or additions. Queries will be generated and sent to the site team using an electronic data query. Designated site team personnel will respond to the query and confirm or correct the data. Concomitant medications entered in the database will be coded using the WHO drug reference list. Adverse events will be coded using the medical dictionary for regulatory activities (CTCAE Coding) terminology.

b. Quality Control Method Monitoring Plan:

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes containing demographic and medical information, and the results of any other tests or assessments. All information on the eCRFs must be traceable to these source documents in the patients file. The investigator must also keep the original informed consent form signed by the parent/legal guardian.

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries.

Routine independent monitoring visits shall occur one or more times during the period after study initiation but before study closeout. Guidelines for scheduling monitoring visits shall be determined according to the stage of development, complexity of the study, the rate of subject accrual and other factors. Monitoring visits are conducted for routine monitoring only and are intended to ensure that the

protocol and applicable regulatory requirements are being followed, that subjects' rights and safety are protected, and to confirm data integrity and quality.

The CRC representative will perform reviews as follows:
100% source and data verification of 1st patient Visit 1 at all sites. Subsequently, 10% of the records will be reviewed quarterly at all sites. If significant discrepancies exist (more than 5% of responses), retraining and comprehensive crosschecking will be performed.

c. Data Analysis Plan

We employed a block randomization design for each site to ensure balanced distribution of treatment groups. Baseline characteristics and the duration of the O2 management in RHO and control groups will be compared using the independent sample test for continuous measures and the $\chi 2$ test for categorical measures. To compare the oximetry in the sleep study and the home recording studies, we will use generalized estimating equation (GEE) gamma regression models for longitudinal count data. Gamma regression models are appropriate for highly skewed measurement or count outcome data, and exponentiating the regression parameters from these models gives estimates of the percent change in the mean outcome corresponding to a change in the independent variable.

d. Statistical Power and Sample Considerations

Analyses for Aim 1:

Aim 1: To evaluate the effects of a data-driven HOT management protocol on parent(s) quality of life.	**Hypothesis 1.1: Parents of patients weaned from HOT using a data-driven management protocol will have improved quality of life compared to their status at time of NICU discharge compared to patients weaned using the current standard HOT management protocol.**

For the impact of oxygen management protocol on the family's emotional health, we will use the PedsQL . We are performing these scales at the beginning of the outpatient HOT management process, to establish a baseline, and then will repeat these measures at the end of the HOT weaning process (6 months after discontinuation of HOT). We will test the association of oxygen management protocol with change in each measure using the Student's *t*-test to analyze the difference between intervention groups. Multivariate linear regression models will adjust for potential confounding variables, including parent and medical attributes.

Power calculation for hypothesis 1.1:
Power calculations are based on the primary analyses (t-test). A sample size of 130 will give 80% power, with 0.05 two-sided type I error rate, to detect a 20% absolute difference in emotional role limitation on the PedsQL, which we consider to be clinically significant.

Analyses for Aim 2:

Aim 2: To evaluate the impact of a data-driven HOT management protocol on duration of HOT.	**Hypothesis 2.1: A data-driven HOT protocol will shorten duration of HOT therapy compared to the current standard HOT management protocol.**

For the primary outcome, duration of HOT, the interval from date of first outpatient clinic visit/enrollment to discontinuation of HOT will be determined. Mean duration of HOT between the two groups will be compared.

Based on our experience weaning over 130 premature infants from O_2, we expect the mean duration of HOT in our standard treatment group (clinic-based weaning) to be 144+/-66 days, and we anticipate that RHO weaning strategies will decrease the median duration by 25% (36 days) to 108 days. A total sample of 98 infants per group provides 97% power to detect this effect of the RHO strategy (two-tailed, alpha=0.05, see Table 2).

TABLE 2

The power of detecting an effect of RHO on duration of HOT, indexed by the enrolled sample size and the difference in mean duration between the RHO and standard oxygen management group, assuming 85% completing all components of the study, a standard deviation of 66 days, and testing at the 2-tailed .05 level.

	Enrolled n per group (double for total sample size)				
Difference in duration of HOT (days)	33	44	53	60	98
30	45%	57%	65%	70%	89%
36	60%	73%	80%	85%	97%
49	85%	94%	97%	98%	>99%

Analyses for Aim 3:

Aim 3: To evaluate the extent to which a data-driven HOT managing protocol can improve growth and respiratory outcomes.	**Hypothesis 3.1: Patients weaned from HOT using a data-driven protocol will have improved growth and decreased respiratory rehospitalizations compared to patients weaned using the current standard HOT weaning protocol.**

The incidence of emergency department visits during HOT management process is estimated to be 30% in the RHO group and 40% in the standard weaning protocol. The two rates will be considered clinically noninferior if the difference was 10 percentage points or less (with a significance threshold of P=0.05 on a one-tailed test and 80% statistical power). On this basis, the number of patients required for each of the two treatment groups was calculated to be 65.With 98 patients per group the power increases to 93%.

e. Study Organization

This is a multicenter study with University of Massachusetts Medical Center as the lead center and Dr. Lawrence Rhein as PI. Dr. Catherine Sheils will serve as the site PI at Boston Children's Hospital and oversee the study at this location. Monitoring will be performed at each site. De-identified data from both sites will be stored in the RedCap database.

f. Data and Safety Monitoring Plan

A Data Safety and Monitoring Board (DSMB) will provide oversight for this study. The DSMB will be constituted to oversee the safety of patients on this trial. The DSMB will meet after the first 8 patients have been enrolled, and subsequently not less than twice yearly. The DSMB will include 2 neonatologists (not associated with the study) and two pediatric pulmonologists (not associated with the study) as well as one primary pediatrician from the community (also not associated with the study). We will also include a member of our Parent Advisory Board, a parent of a premature infant who had required oxygen supplementation in the home in the past.

At the beginning of each meeting, Dr. Rhein and the primary research coordinator will be present to discuss study enrollment and any issues, and then they will leave the meeting so the DSMB can review

any adverse events. If one of the arms is noted to have more than 3 respiratory re-hospitalizations, the committee will come together and decide what, if any part of the study needs to be altered and/or stopped.

Stopping Rules:
The study will be stopped, if there are least 3 *related* respiratory related hospitalizations in one arm *and* the majority of the DSMB votes that these are study related and cannot be remedied.

6. Risks and Discomforts

By definition, patients enrolled in the "Standard Therapy" arm will not have additional risk from usual practice. Infants in the "RHO" arm may have changes made in their oxygen delivery between clinic visits. However, these infants will continue to have their clinically-indicated, NICU-supplied monitors to ensure safety, and weans will have been made using patient data. We therefore believe patients enrolled in the "RHO" arm will have less risk compared to the standard care.
Patients in the "RHO" arm will have an additional oximetry probe, identical to the ones utilized for their clinically-indicated oximeter. These will be rotated every 12 hrs. Theoretically, if left on the same area for extended periods without rest, probes can cause skin irritation. In their use in the NICU and in the CHILD clinic with thousands of infants, this complication has not been realized.
We will also instruct each family to use different sites for the probes to minimize risk.

7. Potential Benefits

Patients in the "RHO" arm will have the benefit of data-driven oxygen management and may have shorter duration of HOT due to increased frequency of weaning opportunities.

8. Costs:

Neither third party payers, subjects, nor their families will be charged for performance of this study. Only studies that are performed for clear clinical reasons, such as in response to symptoms or laboratory data abnormalities will be charged for the clinical care of the subject.

Reimbursement is available for travel expenses related to participation in the study. Participants may receive up to $100 as incentives for their participation. The participant will receive $50 at the initial study and $50 at the completion of the study.

University of Massachusetts Medical Center will be using a service called ClinCard® by the company Greenphire, www.greenphire.com, to manage all payments associated with subject's participation in study visits

9. Privacy Provisions

Patients will be approached in the privacy of their clinic room, or in the privacy of their NICU bedspace, to maximize privacy.

10. Confidentiality Provisions

Data will be securely stored using coded deidentifiers. All data will be analyzed in aggregate and coded deidentifiers will be used. Data will be secured using password-protected files and any hard-copy forms will be stored in locked storage cabinets.

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11. Appendix Materials – please check off as appropriate if included with submission.

- ☐ Sponsor's Protocol
- ☐ Investigator brochure (3 copies)
- ☐ Flow charts, schemas
- X Other
- ☐ Federal grant application (3 copies)
- ☐ Survey, questionnaires, assessments
- ☐ Recruitment letters, postings, flyers
- ☐ Materials given to subjects (reminders, letters, thank-you, etc.)*

** see instructions for further information*