Monitoring Oxygen Levels of Premature Babies at Home and in the Clinic—The RHO Trial

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ABSTRACT

Background: Thousands of premature infants are discharged from neonatal intensive care units (NICUs) on supplemental home oxygen therapy (HOT) annually. Evidence-based strategies to determine safe timing of discontinuation of HOT have not been described. Recorded home oximetry (RHO) provides objective data to allow data-driven weaning protocols that potentially shorten duration of HOT.

Methods: This was a prospective multicenter randomized trial. We enrolled 196 premature infants from 9 centers between November 2013 and December 2017, discharged from the NICU on HOT, who were attending their first outpatient pulmonary clinic visit. Infants were randomly assigned to a standardized outpatient weaning protocol (monthly clinic visits with in-clinic weaning attempts) vs the identical protocol with the addition of RHO data sent between clinic visits. The protocol for weaning during clinic visits was identical for infants in both arms and consisted of 20-minute challenges to ensure infants could maintain oxygen (O₂) saturations >93%, assessed by in-person observation of monitor alarms. Infants who could successfully maintain saturations for the 20-minute interval were subsequently rechallenged at lower O₂ flow rates (50% of previous flow rate) until the O₂ flow rate was <125 cc/min, at which time a 20-minute room air challenge was performed. Because infants whose parents were randomly assigned to send data between clinic visits provided more opportunities for assessment of oxygenation and opportunities to adjust O₂ flow rates, we hypothesized that infants randomly assigned to this protocol would decrease the duration of HOT.

For infants randomly assigned to RHO, oximetry data were analyzed using a structured algorithm to determine whether to increase, maintain, or decrease HOT flow rates between monthly clinic visits. Data were sent by parents to a data coordinating center, and the recommendation for potential adjustment of the O₂ flow rate based on the algorithm was communicated to the site provider and parents within 48 hours of receipt of data. The primary outcomes were duration of HOT and parental quality of life (QOL). Data for secondary outcomes, including growth data and the number of adverse events, were also collected for analysis. In a sub-cohort, we also compared RHO data with oximetry obtained simultaneously on the night before and the night of a full polysomnography (PSG) study.

Results: Our final cohort included 196 infants, a total of 99 infants randomly assigned to the standard-of-care arm and 97 randomly assigned to the RHO interventional arm. Approximately two-thirds of our cohort was male, and the mean birth gestational age was 26.9 weeks (±2.6 weeks) with a mean birth weight of 933 g (±440 g). No significant differences were found in demographic or clinical characteristics between infants in the 2 arms of the study.

Our primary outcome, mean time to discontinue HOT, was shorter in infants randomly assigned to RHO than to standard of care (53 days vs 74 days, respectively; P = .03). The effect of reporting frequency of RHO data was dose dependent; the greater the reporting frequency of RHO, the shorter the duration of home O₂. For each level of increased RHO reporting, duration of HOT decreased by 26% (P = .0006). The estimated mean duration of HOT for ≤3
reports/month was 85 days; for >3 reports/month, the mean was 47 days, a reduction of 53% ($P = .0001$).

Especially considering the fragility of this study cohort, there were relatively few significant adverse events in the entire study, with fewer adverse events in those randomly assigned to RHO. After discontinuation of HOT, no significant change in growth was observed in either cohort. Parent-reported QOL improved after discontinuation of HOT and was not significantly different in parents randomly assigned to either protocol.

**Conclusions:** RHO is a safe and effective protocol to assist in the management of HOT in premature infants. The greater the reporting frequency of RHO, the shorter the duration of HOT. Use of RHO is safe (ie, it does not increase adverse events); in our study, it was associated with fewer negative effects on growth, and did not have a significant positive or negative effect on parent-reported QOL, compared with standard of care. RHO is a reasonable alternative to PSG to determine when it is safe to discontinue HOT.

**Study Limitations:** Our study used a consensus guideline for target $O_2$ saturations to determine when to adjust HOT flow rates. It is possible that slight alterations in these HOT adjustment parameters would have altered the weaning schedule and therefore affected the duration of HOT. We had a relatively high nonresponse rate for our QOL outcome in parents.
BACKGROUND

Improvements in neonatal intensive care have led to increased numbers of premature infants surviving with bronchopulmonary dysplasia (BPD), including thousands with a requirement for supplemental oxygen ($O_2$) after neonatal intensive care unit (NICU) discharge.\(^1\) BPD, the lung disease resulting from abnormal lung development in premature infants, is defined by the need for supplemental $O_2$ at 36 weeks postmenstrual age (PMA).\(^2\) Current estimates indicate that approximately a third of premature infants diagnosed with BPD will require home oxygen therapy (HOT) after NICU discharge.\(^{1,3-5}\) When used, HOT is an option to facilitate discharge of infants with BPD as an alternative to prolonged hospitalization, but its use in US NICUs is highly variable.\(^6\) Controlling for clinical risk factors, institutional variation still accounts for 4- to 5-fold differences in use of HOT in premature infants. Some of this institutional variation may be explained by varying recommendations and decision-making strategies from providers regarding use of HOT.\(^{3,5,7}\) Some studies show that neonatologists who use less HOT appear to prolong NICU hospitalization, potentially putting undue burden on families and creating increased parental stress while impairing neurodevelopmental and bonding outcomes for the infant.\(^{8,9}\)

An obstacle to increased use of HOT is the lack of evidence-based consensus guidelines for safe management of HOT. Current strategies to manage outpatient HOT include arbitrary timing of decreasing $O_2$ delivery by gradually lowering flow rates before discontinuation, leading to potentially unnecessarily longer durations of HOT.\(^{4,10}\) Inefficient $O_2$ management strategies may lead to inappropriate extension of HOT. Use of potentially unnecessary, expensive weaning procedures also exposes patients to potential toxicities of prolonged $O_2$ and may result in excessive cost to the health care system and families.\(^{11,12}\) Families have also reported that prolonged use of HOT increases stress,\(^{9,8,13,14}\) so shortening duration of HOT may improve parent quality of life (QOL).

Parent stakeholders were asked to explain some of the stressors involved in having an infant at home who requires HOT. Infants who are discharged on HOT are required to wear a pulse oximeter continuously while receiving supplemental $O_2$. While on continuous $O_2$, an
infant will have a nasal cannula in their nose and wear a pulse oximeter attached by a sensor wrapped around either their foot or wrist. A burden on parents of infants receiving HOT is that they need to carry O₂ tanks and a bulky oximeter, often causing parents to be isolated in their homes and to limit outings to the infant’s medical appointments. HOT weaning strategies could limit stress on parents and decrease the total time they spend being isolated from friends and family.

Little evidence is available to guide the increase and decrease of HOT flow rates or to show how to ultimately discontinue HOT safely. A survey of pediatric pulmonologists revealed that some form of recorded oximetry study is often used before discontinuation of HOT to provide a longer duration of oximetry data. For many providers, the final step before completely discontinuing HOT often includes, instead of oximetry alone, a full polysomnography (PSG; also known as a formal sleep study), but the cost and inconvenience of this tool has led to a search for alternative strategies. PSG requires an overnight stay in the hospital or sleep laboratory, is relatively expensive, and can be stressful for families and the infant. PSG is also not representative of a typical night’s sleep due to the difference in location, bed, and requirement for connection of the infant to multiple different leads and probes throughout the night.

To provide insight into resource use targets and best practice guidelines, we performed a systematic review of the published clinical evidence. Surprisingly, we noted that some guidelines existed but without any evidentiary basis. Providers commonly rely on brief outpatient assessments of O₂ status at monthly outpatient clinic visits to manage oxygenation status for the subsequent month. Roughly a third of infants are weaned based on parental decision alone, without physician guidance or recommendation.

Through our extensive experience using oximetry data in the inpatient and outpatient clinical settings and in multicenter research collaborations using such data, we identified recorded home oximetry (RHO) as a novel and potentially efficient and cost-effective tool to potentially improve HOT management. RHO uses the same oximeter device commonly distributed by home care companies but adds a small attached data storage recorder to capture
the oximetry data, allowing potential transmission of this stored data to health professionals between clinic visits. Requiring only oximetry devices like those commonly used by clinicians, RHO can provide $O_2$ saturation data during the outpatient weaning process that is similar, if not identical, to that obtained during a PSG, which has been encouraged as a suggested tool in HOT management. More importantly, the availability of data between clinic visits allows for more frequent adjustment of HOT than would be possible if adjustment took place only during an outpatient clinic visit.

With recent availability of better oximeters as well as portable data storage capability, clinic-based weaning protocols could be enhanced by RHO, allowing data-based weaning between clinic visits. As a first step in the current study, clinician stakeholders from all participating sites reviewed the available data on optimal $O_2$ saturations in infants, including those with BPD, to develop a consensus algorithm, guide data-driven RHO weaning, and, specifically, determine the $O_2$ saturation thresholds to increase, maintain, or decrease HOT levels.

To determine the threshold for increasing $O_2$ flow rates, we first defined hypoxemia. The American Thoracic Society (ATS) recently published guidelines for $O_2$ target saturations in premature infants with BPD. These guidelines are consistent with the study consensus protocol developed by our panel of pediatric pulmonology experts and include a definition of hypoxemia of (1) ≥5% of recording time spent with $O_2$ saturation ≤93% as measured by pulse oximetry (if measurements are continuous); or (2) at least 3 separate findings of $O_2$ saturation ≤93% if measurements are obtained intermittently.

To determine the threshold to decrease $O_2$ flow rates, we identified the $O_2$ saturation standards in healthy infants. Per the American Academy of Sleep Medicine, healthy infants should have $O_2$ saturation values >96% for ≥95% of recorded time. These values are also consistent with the recently published ATS guidelines.

The use of a structured protocol for both in-clinic weaning and for application of RHO allowed comparison of the specific effects of RHO on HOT management. The goals of this study
were therefore to evaluate the effects of a recorded data-driven O₂ weaning strategy on duration of HOT, to determine the effects of RHO on parental QOL, and to describe and compare the growth and respiratory outcomes between HOT management strategies.

This study addressed these 3 specific aims:

Specific aim 1: To evaluate the impact of a data-driven HOT management protocol on duration of HOT.

Specific aim 2: To evaluate the effects of a data-driven HOT management protocol on parental QOL.

Specific aim 3: To evaluate the extent to which a data-driven HOT management protocol affects growth and respiratory outcomes.
PARTICIPATION OF PATIENTS AND OTHER STAKEHOLDERS

Stakeholder Engagement

The design and implementation of RHO was the result of a collaboration of stakeholders representing primary care pediatrics, pediatric pulmonologists, neonatologists, representatives from the insurance industry, and providers of home durable medical equipment. We used established methods on engagement\textsuperscript{28} and PCORI’s Methodology Standards.\textsuperscript{29} First, we identified families and pediatricians who would be interested in participating in focus group discussions about their experiences with HOT. Several parents from these focus groups were already participating as ongoing members of our parent advisory boards (PABs). The project was further developed based on the numerous concerns expressed by each group of stakeholders about the extreme variability in management of HOT and the effects of such variability and lack of evidentiary basis on each stakeholder group. Primary care pediatricians expressed clear interest in obtaining guidance to manage their patients on HOT. Families expressed concern about whether, in the absence of available data, their infants were being weaned too quickly or too slowly. Providers of home durable medical equipment, who were frequently being asked to obtain intermittent recorded studies, expressed concern about the seemingly arbitrary timing of such studies and of discontinuation of HOT.

In response to these stakeholder concerns, Rhein et al\textsuperscript{19} looked at O\textsubscript{2} weaning strategies through surveying pediatric pulmonologists at large academic pediatric pulmonary practices across the country, and found that no clear guidelines existed, and none were data driven. To plan for this project, Dr. Rhein held several stakeholder meetings to validate the anecdotal described concerns. The collaboration between the different groups of stakeholders and the findings from Dr. Rhein’s survey project determined the critical need to find safe and effective O\textsubscript{2} weaning strategies for pediatric pulmonologists caring for infants diagnosed with BPD and receiving HOT.
Parent Advisory Board

We engaged multiple families of premature infants in the study planning phase. We also solicited input from the PAB at Boston Children’s Hospital through focus groups, to inform development of the proposal including research objectives and outcome measures important to families with infants with BPD. Parent stakeholders confirmed that prolonged HOT adds significant emotional and financial stress, above and beyond the stresses of caring for premature infants after NICU discharge.\textsuperscript{8,9,12,13} Therefore, we prioritized parent satisfaction and QOL and duration of HOT as outcomes. The RHO trial had a PAB of 12 parents, with at least 1 representative from each participating site. The PAB met biannually to provide parental guidance in the protocol and development of the study. Parents also provided valuable input regarding the selection of study questionnaires and all aspects of the study design, including the frequency of data transmission, wording of consent documents, and determination of which adverse outcomes should be prioritized for analysis. The PAB continued to meet biannually throughout the trial until completion of all study procedures, and it will continue to provide insightful feedback on the implementation of RHO into clinical practice.

Data and Safety Monitoring Board

For this project, we assembled a multidisciplinary data and safety monitoring board (DSMB). The DSMB included parents of premature infants, pediatric pulmonologists, neonatologists, primary care physicians, and a statistician. The DSMB met biannually to review the progress of the study, identify adverse events, and formally evaluate project effectiveness. When serious adverse events (SAEs) were identified, the DSMB would review these events within 24 hours of the study team’s awareness. The DSMB reviewed the SAE in real time and provided feedback to the principal investigator (PI) and research coordinator. After the biannual closed meetings, the DSMB provided written feedback that included determination of whether the study could proceed, clarification of documentation for specific adverse events as needed, and improvements in processes for reporting to the IRBs at each site.
METHODS

Study Overview

The RHO clinical trial was conducted at 9 academic centers: Boston Children’s Hospital, Dartmouth-Hitchcock Medical Center, University of Vermont, University of Massachusetts, Tufts University, University of Connecticut, Maria Fareri Children’s Hospital, University of Kentucky, and Baystate Medical Center. Although all of these centers had some type of program for respiratory follow-up of premature infants, the programs at each center varied in size and in whether there was a specific BPD component for such follow-up. Dr. Rhein founded the Center for Healthy Infant Lung Development program at Boston Children’s Hospital (July 2004) and more recently at the University of Massachusetts Memorial Medical Center (UMMMC; July 2016). These are 2 of the largest programs dedicated to the respiratory health of premature infants in the country. Through extensive experience in clinical care of these patients, and through experience using RHO in other multicenter research cohorts, the study team identified RHO as a potentially efficient, relatively inexpensive tool to potentially save costs and improve the process of HOT management.

The RHO trial design, participant eligibility criteria, and recruitment strategies were described in Procaskey et al. We randomly assigned patients to 1 of 2 arms. The standard-of-care arm included monthly clinic visits with structured in-clinic weaning attempts. PSGs were used before final discontinuation of HOT, and RHO was used both the night before the PSG and during the PSG for comparison. The RHO arm (intervention arm) included the identical protocol but also included the addition of RHO to potentially increase, decrease, or maintain O₂ flow rates between monthly visits. Parents of RHO participants were instructed to record and transmit RHO data every 4 to 7 days (ideally 4 reports per month) whenever it was convenient for them. Oximetry was analyzed using a structured algorithm to decide whether to increase, decrease, or maintain the HOT flow rate based on the consensus guidelines determined by a panel of experts, including all of the pediatric pulmonologists involved in the study. Data downloads were sent from parents directly to the main data coordinating center (UMMMC) and analyzed the same business day by research staff. The resulting recommendation, based on
the algorithm in Table 1, was then communicated to the parent and their local provider. If data were transmitted by the parent over the weekend or on a holiday, research staff analyzed and reported the results on the next business day.

For infants in the intervention arm, RHO alone was used throughout the HOT weaning process and for ultimate discontinuation of HOT. Infants in the standard-of-care arm used PSG because it is the most common tool described in the literature and was agreed on by our consensus panel. To determine whether the additional parameters recorded during PSG added value to HOT discontinuation decisions in a subset of infants in the standard-of-care arm, we also compared RHO data with oximetry obtained simultaneously on the night before and the night of a full PSG.

The primary outcomes were (1) duration of HOT, and (2) the effects of RHO on parental QOL measured by a validated questionnaire, the Pediatric Quality of Life Inventory (PedsQL) Family Impact Module v.2.0. Secondary outcomes, specifically growth and respiratory outcomes, included safety data identified by family stakeholders, pediatric pulmonologists, and primary care pediatricians.

All study activities were approved by the IRBs at all participating sites, with the University of Massachusetts Medical School (UMMS) as the primary site. The RHO trial was recorded in the ClinicalTrials.gov national registry of randomized trials (ClinicalTrials.gov ID NCT01994954).
Table 1. Oxygen Weaning Parameters

<table>
<thead>
<tr>
<th>Criteria for increasing O₂ flow rate</th>
<th>Standard-of-care O₂ arm</th>
<th>RHO arm</th>
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<tbody>
<tr>
<td><strong>Criteria for increasing O₂ flow rate</strong></td>
<td>Inability to maintain O₂ sat &gt;93% at patient’s current O₂ level for 20 min in clinic visit challenge</td>
<td>Inability to maintain O₂ sat &gt;93% for &gt;95% of recorded time</td>
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| 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 min 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 min in clinic visit challenge | Ability to maintain O₂ sat >96% for ≥95% of recorded time |

Abbreviations: RHO, recorded home oximetry; sat, saturation.

*Clinic pass (weaning) and fail (increasing or maintaining) were determined per clinic assessment of oximeter alarms. RHO pass and fail were determined by assessment of recorded oximetry. For each episode of transmitted data, a minimum of 4 days of recorded data, with a minimum of 8 hours per day, would be required for analysis to make any determination. RHO participants also received monthly in-clinic weaning attempts (the same as the standard-of-care arm participants described earlier).*

**Eligibility and Recruitment**

**Inclusion Criteria**

1. An infant with birth gestational age ≤37 0/7 weeks who had a requirement for supplemental O₂ at the time of NICU discharge, as determined by the primary NICU team.

2. Infants attending their first visit to the outpatient pediatric pulmonary clinic or NICU follow-up clinic that has a pulmonary component.

3. Infants with a parent aged ≥18 years.
4. Infants with parents who speak English or Spanish. (Spanish instruments were developed through translation services, and a Spanish-speaking interpreter assisted with interviews as needed to allow participation of potential Spanish-speaking families).

**Exclusion Criteria**

1. Infants with presence of echocardiography-confirmed pulmonary hypertension.

2. Infants with known syndrome or other diagnosis with high risk for persistent hypoxia (cardiac disease, trisomy 21, Pierre Robin sequence, etc).

3. Infants with a supplemental O₂ requirement with flow rate >1 L/min or tracheostomy.

4. Infants who require caffeine at discharge from the NICU.

5. Infants with diagnosed laryngomalacia or tracheomalacia.

Eligible patients were identified via 2 primary modes: (1) Site PIs identified infants with impending discharge from the NICU with anticipated requirement of HOT determined by the discharging NICU clinical team; or (2) site PIs identified potentially eligible infants scheduled for a first outpatient assessment in a pediatric pulmonary clinic or NICU follow-up clinic. The study team at each site received approval for a HIPAA waiver to screen for eligibility before NICU discharge and pediatric pulmonary clinic visit.

Following identification, the study team approached eligible families. A description of the study was provided in lay terms, and the potential risks were explained in detail to the family. Informed consent was subsequently obtained at the first study visit at all participating sites. If consent was not received at the first pulmonary visit the child was excluded because duration on HOT from time of NICU discharge until successful discontinuation of HOT was the primary outcome.

**Randomization**

We used a block randomization design for each site to ensure balanced distribution of treatment arms. Study participants were randomly assigned to either RHO or standard of care in the order they were enrolled using the blinded set supplied to their site. The randomization
blocks were generated by the study biostatistician and distributed by the study project coordinator. Envelopes were sequentially numbered, opaque, and sealed by the biostatistician. Individual sites were given their randomization envelopes in sequential order and marked with the sequential randomized IDs. To keep the researcher unbiased, study participants were given the envelope to open themselves, and the randomized study arm was revealed by the patient’s family at the time of randomization at the first clinic visit. Only the study biostatistician had access to the randomization lists to ensure quality of the randomization scheme. If infants from a multiple birth were consented, they were randomly assigned as individual patients and not necessarily clustered into the same arm. The RHO trial enrolled 9 sets of twins. Each family was able to remain compliant with both arms of the protocol when enrolled in separate arms. In one instance, an infant from a set of twins was withdrawn; the other twin continued in the study.

**Interventions and Controls**

All infants were scheduled to have monthly clinic visits with 20-minute O₂ weaning evaluations until O₂ was discontinued. The protocol for weaning during clinic visits was identical for infants in both arms. Infants were observed for 20 minutes on their preclinic HOT flow rate to ensure they could maintain saturations >93%, assessed by in-person observation of monitor alarms. Infants who could not maintain saturations >93% on that flow rate had their flow rates increased (doubled). Infants who could successfully maintain saturations >93% for the 20-minute interval were subsequently rechallenged at a lower O₂ flow rate (50% of prior flow rate) until the flow rate was <125 cc/min, at which time a 20-minute room air challenge was performed. If possible, the infant could wean multiple decrements in the same clinic visit as long as they were successfully monitored for 20 minutes at each decrement.

The O₂ weaning proceeded, when allowable per weaning criteria in the protocol, in 50% decrements to a minimum of 125 cc/min (or an eighth of a liter of O₂). For example, an initial flow rate of 500 cc/min was decreased to 250 cc/min, and 250 cc/min was decreased to 125 cc/min. Once all enrolled infants achieved flow rates of 125 cc/min (or if they were discharged
home from the NICU on <125 cc/min), the next weaning step was to discontinue O₂ during the day\textsuperscript{34} and continue only nocturnal O₂ at a flow rate of 125 cc/min.

Parents of enrolled infants were given reports/surveys to assess their QOL using the PedsQL Family Impact Module v.2.0\textsuperscript{35,37,39} at each monthly clinic visit until the infant’s O₂ was discontinued, and at the 3-month postdiscontinuation point, a follow-up PedsQL report/survey was given either by phone or in clinic. The PedsQL v2.0 is a validated and accurate pediatric QOL scale, used in various cohorts of pediatric patients, including those with acute and chronic pediatric diseases.\textsuperscript{35,37-39}

All infants had growth assessments performed at each monthly clinic visit while on HOT. Growth assessments were also performed at the 1-month post–HOT discontinuation visit and 6-month post–HOT discontinuation visit. Nutrition regimens were collected at each of these follow-up visits as well, to capture factors that contributed to growth. Nutrition information included any notes on the patient’s nutritional regimen made by a physician or pediatric nutritionist at the time of the visit. This information was collected for future studies investigating the relationship between nutrition and O₂ requirement and the impact on growth outcomes.

Rehospitalizations and emergency department (ED) visits were determined through medical record review of the monthly clinic visits during HOT management as well as the clinic visits during the postweaning period (1 month, 3 months, and 6 months after HOT discontinuation). The primary site was notified by research staff at participating sites between visits if an SAE occurred and was provided the documents in a timely manner so that the DSMB could be notified and make their assessment.

**Interventions**

In the RHO arm, families received a Masimo Rad-8 pulse oximeter and serial data recorder (Acumen) to record O₂ saturation and heart rate data. They received instructions regarding when to record the infant and how to send data to the central data coordinating center (UMMMC).
Home Pulse Oximeter Recording Procedures

The recording system we used for this study was used in prior studies and included the Masimo Rad-8 pulse oximeter with an attached data recorder (Acumen) and removable memory card (SanDisk) with ample capacity (2 GB) to store the continuous data recorded for each infant. The oximeter was set for the minimum (2 second) averaging time. Because the study oximeter was not to be used as a monitor but rather as a (continuous) recorder, it was preset in the Sleep Lab mode; there were alerts for “probe off” and “low battery,” but no alarms for O$_2$ saturation or heart rate and no visual displays of O$_2$ saturation or heart rate. The clinically provided monitors were used as determined by the infant’s primary clinical team to provide visual and audible alarms when the O$_2$ saturations were too low. The RHO oximeter was exclusively used as a data recording device.

During the 4- to 7-day evaluation periods to determine readiness to wean or status postwean, parents were instructed to use the oximeter continuously at least during nocturnal sleep periods for a minimum of 25 hours (1500 minutes or approximately 8 hours per day for 4 days), and they were encouraged to use it as often as possible when convenient. Parents were asked to only record while the infant was on O$_2$, so for infants on nocturnal O$_2$, recording would only take place at night. If the infant was on continuous O$_2$ at any flow rate, parents were asked to record when it was convenient or when the infant was not going to be too mobile. No minimum or maximum amount of time was set for an individual recording session; the only requirement was a total of 1500 minutes for analysis. At the end of the 4- to 7-day period, data reports were downloaded and sent electronically via secure email by the parents to the data coordinating center at UMMMC. For families who did not have access to a computer and/or were uncomfortable with technology, we provided them with data cards that could be sent via provided protected express shipping envelopes with postage. All data cards were sent to the single data coordinating center at UMMMC for analysis as soon as they were removed from the oximeter.

Over the 4 to 7 days of recording, a minimum of 25 hours (1500 minutes) of data was to be sent to the UMMMC and deemed interpretable before any change in supplemental O$_2$
management was made. If the data were deemed inadequate or unreadable, the parent was notified, and no change in O₂ management was made. If data were under the minimum 1500 minutes, the parents were encouraged to continue recording, and no changes were made to supplemental O₂ flow rates until adequate time (at least 1500 minutes) of recordings were made available to the primary study site.

RHO infants were weaned only when data demonstrated a decrease in the flow rate. Once results were shared with the families, they were reminded to record again for the next 4 to 7 days to demonstrate that the wean was appropriate. The families were also instructed to notify staff if the infant consistently desaturated once the flow rate was lowered. Once the infant was ready to wean completely to room air, the family was instructed to record data on room air for 4 nights. Study staff analyzed the data on room air while the infant was sleeping to demonstrate that the infant could maintain appropriate target O₂ saturations while sleeping.

Parents of infants using RHO were also given a poststudy Home Oximetry Feasibility Questionnaire to complete, which determined the advantages and challenges of using home oximetry to wean infants from HOT. The questionnaire was conducted at the 1 month postwean visit when possible. If the research team was unable to obtain this data at this time point, due to missed visit or lost to follow-up, it was collected postwean at any time at a clinic visit or by phone with the primary caregiver.

For infants in the standard-of-care arm (no RHO), families received RHO recording equipment when they reached the last step before discontinuation of HOT, when infants were scheduled for their PSG. Parents were instructed to record data, using identical procedures for the RHO arm of the trial, but the recordings only occurred on the night before the PSG and were brought to the PSG for simultaneous recording in addition to the sleep laboratory’s monitoring equipment. The simultaneous recordings were used to correlate RHO recordings and PSG recordings to determine readiness to wean off supplemental O₂ permanently.
Study Outcomes

Primary Measures

Primary measures were (1) total duration of HOT from the NICU discharge date to successful discontinuation of supplemental O$_2$, and (2) parental QOL, assessed by differences in postdiscontinuation PedsQL scores compared with baseline scores (during weaning).

Secondary Measures

Secondary measures were (1) number of rehospitalizations and ED visits from the first clinic visit through 6 months after discontinuation of HOT; (2) change in weight and weight-for-length z score from first clinic visit to 6 months after discontinuation of HOT; and (3) for patients who received a PSG, percentage time below designated O$_2$ saturation thresholds (<96%, <93%, and <90%) were calculated from both RHO and from the PSG data. The number of desaturation events (defined as saturation drops <90% for >10 seconds and >20 seconds) were also analyzed.

Duration of HOT was chosen as the primary outcome because it is the primary driver of caregiver emotional and financial health for families of infants on HOT, per our focus groups and published data. 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 a validated, accurate scale in which scores correlate with maternal psychiatric symptoms, poor child health, poor child adjustment, and increased child hospitalizations.

This protocol focused on patient-centered outcomes that possibly demonstrated no improvements from a medical safety perspective but might have improved QOL. Although families place a priority on treatment strategies that optimize health, when there are multiple choices without a clear medically superior choice, the impact of specific treatment choices on QOL likely helps drive decision-making.
Although our primary outcomes focused on parental QOL, the secondary outcomes were chosen to confirm that weaning strategies (that likely improve parental QOL) 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 3 and 6 months after discontinuation of O₂ to assess the safety of the weaning strategies in both arms. Inadequate O₂ supplementation has been associated with poor somatic growth, so growth parameters are an important outcome to confirm long-term safety of all studied weaning protocols. Higher O₂ target saturations, with subsequent increased exposure to supplemental O₂, have been linked to increased numbers of respiratory exacerbations. We therefore tracked health care use during HOT and up until 6 months post–HOT discontinuation by collecting rates of respiratory-related ED visits and rehospitalizations as additional secondary outcomes. Rates of respiratory- and nonrespiratory-related events were collected through the electronic medical record and parent report at clinic visits.

Covariates

To assess potential bias due to covariates, we collected additional demographic and NICU clinical variables at the time of randomization. The NICU information collected included common premature morbidities and their treatments, including severity of BPD. A BPD diagnosis was determined by O₂ use at 36 weeks PMA and defined using the National Institute of Child Health and Human Development (NICHD) definition of BPD. Data on days of use of mechanical ventilation, noninvasive positive pressure ventilation, and nasal cannula were collected at baseline. Weight, length, and head circumference at birth and hospital discharge were also documented, along with a feeding discharge plan and all prescribed medications at time of discharge.

Statistical Methods

Power Analysis

For each aim, we considered the trade-offs between power, sample size, and magnitude of detectable effect. Calculations for aims 1 and 2 were conservatively based on the
independent \( t \) test and 5% 2-sided type 1 error rate, without consideration of the reduction in variance (and accompanying increase in power) to be expected from adjustment for covariates. The calculation for aim 3 was framed as a noninferiority hypothesis with a 1-tailed test. The following results indicate either (1) the sample size needed to detect a specified difference in outcome with 80% power, or (2) the power to detect the anticipated effect, given the planned sample size.

**Primary aim 1.** Based on our experience weaning premature infants from \( O_2 \), we estimated the mean duration of HOT in our standard-of-care arm (clinic-based weaning) would be 144 days \( \pm 66 \) days. We anticipated that RHO weaning strategies would decrease the mean duration by 25% (36 days). A sample of 98 infants per arm would provide 97% power to detect this effect of the RHO strategy (see Table 2).

<table>
<thead>
<tr>
<th>Difference in duration of HOT, d</th>
<th>No. enrolled per arm (double for total sample size), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>33</td>
</tr>
<tr>
<td>30</td>
<td>45</td>
</tr>
<tr>
<td>36</td>
<td>60</td>
</tr>
<tr>
<td>49</td>
<td>85</td>
</tr>
</tbody>
</table>

Abbreviations: HOT, home oxygen therapy; RHO, recorded home oxygen.

**Primary aim 2.** Our study design called for the PedsQL measures of the family’s emotional health to be made during weaning and at 3 months after discontinuation of HOT. Accordingly, our calculations were based on the detectable pre-post change, indicating that a sample of 130 participants (65 per arm) would provide 80% power to detect a 20% absolute difference in emotional role limitation on the PedsQL v.2.0, which we considered to be clinically significant.
**Primary aim 3.** Power analysis for aim 3 was based on the expected impact of RHO on incidence of ED visits or rehospitalization for respiratory problems. Published literature suggested the rate would be approximately 30% in the RHO arm and 40% in the standard-of-care arm.\(^1\) The 2 rates were to be considered clinically noninferior if the difference was ≤10 percentage points. This rate was set as the noninferiority margin and prespecified before the start of the trial. On that basis, to attain 80% power, the number of patients required for each of the 2 treatment arms was calculated to be 65. With 98 patients per arm, the power increased to 93%.

**Data Analysis Plan**

**Primary aim 1.** To compare duration of HOT between study arms, we performed nonparametric time-to-event analysis, constructing Kaplan-Meier curves to illustrate the onset of weaning in the 2 arms. All 196 randomly assigned patients were included in this analysis; those with unknown weaning times were censored at last contact with the study (ie, the analytic method took account of whatever unweaned time we observed). Further comparisons were made by several parametric methods. We log-transformed the known durations and compared the study arms by analysis of variance (ANOVA) with either 1 factor (study arm only) or 2 factors (adjusting for categories of initial O\(_2\) flow rate). The fitted means, standard errors, and differences were retransformed to natural units and percentage differences for reporting. We also divided the duration of HOT into 30-day intervals and compared the study arms using the Fisher exact test. Finally, we subdivided the RHO patients according to their compliance with the intervention, as measured by the frequency of reports returned during weaning, and performed ANOVAs to assess the trend across categories of increasing compliance and the difference between standard-of-care patients and noncompliant RHO patients (no reports returned).

**Primary aim 2.** The PedsQL instrument, measuring the family’s emotional health, was filled out multiple times during HOT and at the 3-month postweaning visit. We constructed a mixed-effects linear model for each summary measure. The fixed factors were study arm and
time, with an interaction term to test whether the change over time was equal in the 2 arms. A random effect was included to account for correlation of a given family’s responses, both within time (multiple HOT measures) and across time (HOT to postweaning). We performed a similar analysis replacing study arm (intention to treat) with the frequency of oximetry reports (regardless of study arm), dichotomized at ≤3 or >3 reports per month between the initial clinic visit and weaning.

Primary aim 3. We compared the incidence of respiratory rehospitalizations and ED visits between study arms using a left-sided Fisher exact test as specified in the protocol and power analysis. Weight and length were measured in each patient multiple times both during and after HOT. The rate of growth was estimated with a mixed-effects linear model, using continuous time as the independent variable; study arm and time period (pre- or postweaning) as fixed factors; and interaction terms to allow the growth rate to differ across periods and arms. Random effects were included in the model to account for correlation with participants and variability of growth rates within levels of the fixed effects. To reduce the influence of extreme values and measurement errors, we applied an iterative reweighting procedure, discarding outliers further than 3.37 residual SDs from the fitted model and repeating the regression until no such outliers occurred.41

Changes to the Original Study Protocol

It was the goal of the PI to limit changes to the protocol to remain unbiased and produce the most effective results. Therefore, minimal changes were made throughout the duration of the study.

Increase to our enrollment goal. The original target of enrollment for the RHO trial was 146 participants. This would have given us adequate numbers to provide enough power to show that RHO shortens the duration of HOT in premature infants. After receiving permission from PCORI to add the University of Kentucky and Maria Fareri Children’s Hospital as enrolling sites, our target enrollment increased from 146 to 196. This change gave us 96% statistical
power to detect a 26-day reduction in the duration of HOT per patient, a significant change from our previous 87% power.

*Increase to the number of sites.* The original study plan was for the RHO trial to take place at 6 academic institutions in southern New England. In 2016, the PI received permission from PCORI to increase the number of sites to 9. Adding sites outside of New England optimized our opportunity to meet our enrollment goal of 196 participants and increase generalizability.

*Exclusion criteria.* The PI went on to clarify exclusion number 2 (ie, infants with known syndrome or other diagnosis with high risk for persistent hypoxia) by adding a fifth exclusion criterion. This exclusion criterion was added to clarify that infants with conditions that may influence prolonged need for $O_2$ beyond lung disease of prematurity were excluded (eg, infants with laryngomalacia and/or tracheomalacia).

*RHO arm feasibility survey.* After completing our pilot study, we found that to gauge whether parents liked or disliked a data-driven $O_2$ weaning protocol, we needed to ask them directly. By asking parents about the benefits or obstacles to this protocol, we could better understand implementing it into practice. We therefore added a feasibility survey to be given at the 1 month postwean visit; the survey was only completed by our intervention arm participants.

*Analytic plan.* After writing the original analytic plan, we changed statisticians. The new trial statistician used an ANOVA instead of the planned generalized estimating equation $\gamma$-regression models given for poor fit with the completed data set. The ANOVA was more fitting to the final data set. The new statistician completed some post hoc analysis on aims 1, 2, and 3 to show further effects of RHO and managing HOT.
RESULTS

Baseline Characteristics

A total of 253 infants were identified at the time of NICU discharge or first outpatient pulmonary clinic visit as requiring HOT. After assessing for eligibility, 223 families of infants diagnosed with BPD and a requirement of HOT were approached for participation in the RHO trial (Figure 1). A total of 30 potential eligible participants were excluded due to not meeting eligibility criteria; the most common reason for ineligibility was pulmonary hypertension (21 infants). We enrolled 197 infants in the RHO trial, but 1 infant was not randomly assigned due to the family immediately withdrawing consent: 99 infants were randomly assigned to the standard-of-care arm (monthly clinic visits without RHO), and 97 infants were randomly assigned to the interventional arm (monthly clinic visits with RHO). A total of 172 infants were weaned successfully from HOT using 1 of our 2 methods, and a total of 144 (73%) participants completed all study procedures through 6 months of follow-up after discontinuation of HOT. Overall, 25 participants withdrew consent before completing all study procedures. The most common reason for withdrawal was that parents reported feeling too overwhelmed taking care of their infant at home on HOT. This was true in both arms of the study. A total of 7 standard-of-care arm participants were withdrawn by a parent or their site PI, and a total of 17 participants were withdrawn from the RHO arm by either a parent or the site PI. Another 18 participants were lost to follow-up, with many of them lost in the 6-month postwean follow-up period. In the standard-of-care arm, 5 participants were lost to follow-up after weaning from HOT, and another 9 in the RHO arm whose duration on HOT was known and therefore could be included in analysis for aim 1.

Table 3 shows the characteristics of the RHO trial’s final cohort. Approximately two-thirds of our cohort were male, and mean (SD) birth gestational age was 26.9 weeks (2.6 weeks) with a mean (SD) birth weight of 934 g (440 g); no significant differences in demographic or clinical characteristics were found between the 2 arms of the study. BPD was defined using the NICHD definition and was based on respiratory support at 36 weeks’ PMA.40
A total of 23 infants had missing data on weaning status due to unknown status or withdrawing before discontinuing HOT. The participants missing data were equally balanced between the standard-of-care arm and the RHO arm ($P = .12$), with no difference in distribution of sex ($P = .82$), race ($P = .46$), or ethnicity ($P = .24$). There was also no difference in illness severity based on respiratory support at 36 weeks’ PMA ($P = .23$) or diuretic use at time of NICU discharge ($P = .54$).

**Figure 1. Flow Diagram of Recruitment for the RHO Trial**

Abbreviations: HOT, home oxygen therapy; RHO, recorded home oximetry.
Table 3. Study Cohort Demographics

<table>
<thead>
<tr>
<th></th>
<th>Standard-of-care arm ((n = 99))</th>
<th>RHO (intervention) arm ((n = 97))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Male</td>
<td>58 (59)</td>
<td>64 (66)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>57 (57)</td>
<td>59 (60)</td>
</tr>
<tr>
<td>Black</td>
<td>12 (12)</td>
<td>13 (13)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (1)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>29 (29)</td>
<td>21 (22)</td>
</tr>
<tr>
<td><strong>Hispanic ethnicity</strong></td>
<td>12 (12)</td>
<td>6 (6)</td>
</tr>
<tr>
<td><strong>Respiratory support at 36 wk PMA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilator</td>
<td>3 (3)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>CPAP/high-flow O₂</td>
<td>52 (53)</td>
<td>48 (49)</td>
</tr>
<tr>
<td>Low-flow nasal cannula</td>
<td>36 (36)</td>
<td>32 (33)</td>
</tr>
<tr>
<td>Room air</td>
<td>2 (2)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (6)</td>
<td>6 (6)</td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td>52 (53)</td>
<td>51 (53)</td>
</tr>
<tr>
<td>NEC</td>
<td>8 (8)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>PDA</td>
<td>55 (56)</td>
<td>58 (60)</td>
</tr>
<tr>
<td>ROP</td>
<td>63 (64)</td>
<td>58 (60)</td>
</tr>
<tr>
<td><strong>BPD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>2 (2)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>24 (24)</td>
<td>20 (21)</td>
</tr>
<tr>
<td>Severe</td>
<td>71 (72)</td>
<td>69 (71)</td>
</tr>
<tr>
<td><strong>Surfactant</strong></td>
<td>72 (73)</td>
<td>83 (86)</td>
</tr>
<tr>
<td><strong>Mean ± SD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>938 ± 439</td>
<td>929 ± 443</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>26.8 ± 2.5</td>
<td>26.9 ± 2.7</td>
</tr>
<tr>
<td>Length of NICU stay, d</td>
<td>98 ± 33</td>
<td>104 ± 37</td>
</tr>
</tbody>
</table>

Abbreviations: BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity.

*BPD severity diagnosis was based on the National Institute of Child Health and Human Development definition.*
Specific Aim 1: To Evaluate Impact of Data-Driven HOT Management Protocol on Duration of HOT

Our final cohort included 196 infants. A total of 99 infants were randomly assigned to monthly in-clinic weaning and final discontinuation of HOT after a PSG (standard-of-care arm). Ninety-seven infants were randomly assigned to use RHO and to be weaned from HOT using the interventional method (RHO arm). We successfully obtained discontinuation dates in 172 of the infants (88%). The percentage of unknown discontinuation dates did not differ significantly between arms (8/99 vs 16/97; \( P = .08 \)). The infants with unknown discontinuation dates had lower gestational age and birth weight and longer length of NICU stay than the others, but the magnitude of difference was not significant between the study arms (\( P > .40 \)). No other baseline characteristics differed significantly between infants with known or missing times.

The time to discontinue HOT was 21% shorter in infants randomly assigned to RHO (77.6 ± 6.5 days; retransformed mean ± SE) than in the standard-of-care arm (97.8 ± 7.8 days; \( P = .04 \)). The respective median times were 71 and 90 days. Time-to-event analysis, including the 24 infants with unknown weaning times as censored observations at last contact as well as the 172 infants with known times (Figure 2a), showed the onset of weaning in the RHO arm began at 15 days post-NICU discharge, whereas the first weaning in the standard-of-care arm began at 37 days. The separation in onset curves persisted up to 90 days. Weaning in the first 30 days of HOT was markedly more frequent in RHO infants (14/81 vs 0/91; \( P < .0001 \); Figure 2b).

To detail further the effect of RHO data use on HOT duration, we classified the RHO infants according to their frequency of data transmission between the initial clinic visit and weaning: no reports (9 [11%]); up to 1 report per month (16 [20%]); up to 3 reports per month (22 [27%]); up to 5 reports per month (25 [31%]); and >5 reports per month (9 [11%]). We included standard-of-care arm infants in this analysis as a separate group with no reports. Higher reporting frequency of RHO was inversely related to duration of HOT (Figure 2c). For each level of increased reporting per month, the duration of \( O_2 \) decreased by 28% (SE, 7%; \( P = .0003 \)). The duration did not differ significantly between standard of care and those RHO arm participants who provided no reports (\( P = .36 \)). With reporting frequency combined into 2
categories only, the duration of HOT for families with \( \leq 3 \) reports per month was 100 ± 6 days (mean ± SE); for families with >3 reports per month, 50 ± 6 days, a difference of 50% \( (P < .0001) \). Treating reporting frequency as a continuous measure, we found a decrease in HOT time of 13% per report per month (SE, 3%; \( P < .0001 \)).

We found that the duration of HOT was related to the \( O_2 \) flow setting at the first clinic visit, particularly in the RHO arm, where many infants starting at 125 cc/min were weaned in <30 days (24%). Accordingly, we repeated these analyses adjusting for the influence of initial \( O_2 \) flow, even though confounding was not of serious concern because of the randomized design and because the low setting was equally prevalent in the 2 arms \( (P > .20) \) (Figure 2d). The results did not change materially, indicating that the influence of RHO on weaning time was independent of initial \( O_2 \) settings.

We also found that the mean duration of HOT varied significantly among the 9 clinical sites \( (P < .003) \). Accordingly, we repeated the analysis adjusting for site. Site by arm interaction was not significant \( (P = .37) \), indicating that the RHO effect was uniform across sites. The other regression results, including the magnitude and significance of differences in duration of HOT by arm and by reporting frequency, did not change materially, indicating that the finding of an RHO effect was not confounded by site variation.
**Figure 2a. Duration of HOT by Randomized Arm**

(Duration from NICU Discharge Date to Date HOT was Discontinued)

Abbreviations: HOT, home oxygen therapy; NICU, neonatal intensive care unit; RHO, recorded home oximetry.

**Figure 2b. Percentage Weaned From Oxygen Within Set Categories**

Abbreviation: RHO, recorded home oximetry.
Abbreviations: HOT, home oxygen therapy; RHO, recorded home oximetry.

**Figure 2c. Duration of HOT by RHO Reports Per Month**

![Graph showing duration of HOT by RHO reports per month]

**Figure 2d. Comparison of Duration on HOT by Arm and Initial O₂ Flow Rate**

![Graph showing comparison of duration on HOT by arm and initial O₂ flow rate]

Abbreviations: HOT, home oxygen therapy; NICU, neonatal intensive care unit; RHO, recorded home oximetry.

**PSG Comparison with RHO**

We enrolled a total of 99 infants in the standard-of-care arm (no RHO) who, per clinical protocol, were to complete a PSG whose results would determine eligibility to wean from HOT and use RHO only the night before and during the PSG for comparison. Overall, 53 participants
completed a formal PSG to determine discontinuation of HOT (55%). Only 32 participants completed a PSG and had at least 1 night of RHO to compare with the PSG oximetry (33%). There were 27 simultaneous recordings during a formal PSG that we could compare saturation times <90%, <93%, and <96%. Of the 27 reports, there was correlation between RHO and PSG oximetry, and results were comparable in 26 cases (96%). In 25 cases, both RHO and PSG indicated discontinuing HOT, and in 1 case both RHO and PSG recommended continuing HOT; the remaining case suggested that RHO allowed discontinuation, whereas the PSG interpretation recommended continuation. For 16 of the infants randomly assigned to the standard-of-care arm, the parents refused the PSG.

**Specific Aim 2: To Evaluate Effects of Data-Driven HOT Management Protocol on Parental QOL**

Our final cohort included 196 infants. Parents of 170 infants completed at least 1 preweaning QOL survey, and among them 108 completed 1 survey post–HOT discontinuation. Nonresponding parents did not differ significantly from respondents with respect to the infants’ demographic and clinical characteristics, except for 1.3-week lower median gestational age, 110 g-lower birth weight, and 16 day-longer NICU stay. Among respondents, none of the infants’ demographic and clinical characteristics differed between study arms. The PedsQL is designed to measure health-related QOL in parents and caregivers. Scores on the PedsQL were relatively high, indicating a favorable self-reported QOL in both arms before weaning HOT, and no significant difference was found between the intervention and nonintervention arms (Table 4). In both arms, scores improved significantly from baseline to 3 months postdiscontinuation of HOT ($P \leq .002$), but the degree of improvement did not differ significantly between arms. Comparing PedsQL scores according to frequency of the parents’ oximetry reports, divided at ≤3 or >3 reports per month irrespective of study arm, gave similar results (Table 4). This finding indicates that parents in our cohort were satisfied with their child’s health and health care both at baseline and after discontinuing HOT.
Table 4. Parents’ QOL Scores (PedsQL) During and After Weaning

<table>
<thead>
<tr>
<th></th>
<th>Preweaning</th>
<th>Postweaning at 3 mo</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean ± SE</td>
<td>n</td>
</tr>
<tr>
<td>Arm A</td>
<td>90</td>
<td>72.1 ± 1.7</td>
<td>52</td>
</tr>
<tr>
<td>Arm B</td>
<td>80</td>
<td>72.2 ± 1.8</td>
<td>56</td>
</tr>
<tr>
<td>Difference (P value)</td>
<td></td>
<td>0.1 ± 2.5 (0.96)</td>
<td></td>
</tr>
<tr>
<td>≤3 reports/mo</td>
<td>136</td>
<td>72.3 ± 1.4</td>
<td>82</td>
</tr>
<tr>
<td>&gt;3 reports/mo</td>
<td>34</td>
<td>71.5 ± 2.9</td>
<td>26</td>
</tr>
<tr>
<td>Difference (P value)</td>
<td></td>
<td>−0.8 ± 3.2 (0.81)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: QOL, quality of life; PedsQL, Pediatric Quality of Life Inventory.

aThe P tests for significant difference between arms or significant change over time.

Specific Aim 3: To Evaluate Extent to Which Data-Driven HOT Management Protocol Affects Growth and Respiratory Outcomes

Growth Outcomes

Growth points were reported in z scores, based on the sex-specific World Health Organization growth charts, for each participant’s clinic visits while on HOT, and at the 1-month and 6-month postwean visits. We had data for 87 and 72 infants in the standard-of-care arm and RHO arm, respectively, during the HOT weaning process, and 80 and 73 infants, respectively, after HOT discontinuation. The subsamples did not differ significantly from the full sample in sex, race/ethnicity, birth weight, or gestational age at birth. We first compared weight z score changes from the time of enrollment through the time of HOT discontinuation.

Infants randomly assigned to standard of care (no RHO) experienced a minimal but statistically significant decrease in their weight z score of −0.043 per month throughout the duration of weaning (P = .02). Infants randomly assigned to RHO grew appropriately, with an average change in weight z score of 0.004 per month (P = .83) (Figure 3). After HOT discontinuation, RHO participants had significantly better growth, with an average 0.045 increase in weight z
score per month ($P = .007$), compared with those in the standard-of-care arm who only experienced a 0.018 weight $z$ score increase per month ($P = .24$).

We then compared weight-for-length $z$ score change from the time of enrollment through the time of HOT discontinuation. Participants in both arms of the study had a highly statistically significant decrease in their weight-for-length $z$ score ($P = .0001$). This decrease continued after weaning from HOT for participants in the standard-of-care arm and remained statistically significant ($P = .01$). The decrease in weight-for-length (reporting body weight in proportion to growth in length, a marker available in infants when body mass index is not available) $z$ score change leveled out for RHO participants (~0.018 per month decrease) after weaning, suggesting that their level of growth was appropriate ($P = .53$).

**Figure 3. Weight and Weight-for-Length $z$ Score Change Pre- and Postweaning by Study Arm**

Abbreviations: HOT, home oxygen therapy; RHO, recorded home oximetry.

**Adverse Event Outcomes**

Relatively fewer adverse events occurred throughout the weaning process than anticipated based on previous literature, indicating that both monthly clinic weaning and monthly clinic weaning plus RHO are both safe protocols to manage HOT in infants with BPD. In infants randomly assigned to clinic-based weaning without RHO (standard of care), 28 of 99 participants (28%) had an SAE, defined as an event that required a NICU hospitalization or
intubation, or that was life threatening. All events were reviewed by the DSMB; determination of whether a specific event was life threatening was also determined by the DSMB and included apparent life-threatening events or brief resolved unexplained events. Our DSMB evaluated all SAEs and determined that none were related to study protocol; for example, although all virus-confirmed bronchiolitis episodes requiring hospitalizations were classified as SAEs, none were attributed to the study protocol by our DSMB. In infants randomly assigned to receive RHO, 19 of 97 (20%) experienced an SAE; no significant difference was found between study arms ($P = .18$). For total adverse events requiring intervention, infants randomly assigned to use RHO experienced fewer events. An event was categorized as any ED visit or hospitalization; if an infant was seen in the ED and then admitted to the hospital, this counted as 1 event. If an infant was seen in the ED but not admitted to the hospital, this counted as a grade 2 event and was not considered a serious event; 25% of infants randomly assigned to RHO had an event compared with 40% of infants randomly assigned to weaning without RHO ($P < .05$) (Table 5).

At least 1 respiratory rehospitalization was reported for 31 patients and at least 1 respiratory ED visit for 22 patients. Ten patients had both a respiratory hospitalization and ED visit. The fraction of patients with at least 1 respiratory rehospitalization was slightly smaller in the RHO arm (14/97 [14%]) than in the standard-of-care arm (17/99 [17%]) but not enough for statistical significance (1-sided $P = .37$). Similar findings prevailed for respiratory ED visits (9/97 [9%] RHO vs 13/99 [13%] standard of care; 1-sided $P = .27$) and for the composite outcome of either hospitalization or ED visit (17/97 [18%] RHO vs 26/99 [26%] standard of care; 1-sided $P = .10$).

The timing of adverse events differed significantly between arms for respiratory-related events compared with nonrespiratory events ($P = .003$). Overall, nonrespiratory events were higher in the initial months of weaning for both arms (Figure 4).
<table>
<thead>
<tr>
<th>Event type</th>
<th>Frequency in standard-of-care arm (n = 99), %</th>
<th>Frequency in RHO arm (n = 97), %</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All events</td>
<td>41</td>
<td>26</td>
<td>.02&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>SAEs</td>
<td>28</td>
<td>20</td>
<td>.18</td>
</tr>
<tr>
<td>Life threatening, ICU admission, or intubation (grade 4)</td>
<td>7</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Hospitalization, grade ≥3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>30</td>
<td>19</td>
<td>.1</td>
</tr>
<tr>
<td>Intervention without hospitalization, drug/nondrug therapy (grade ≥2)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>39</td>
<td>26</td>
<td>.05&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>October-April (respiratory virus season)</td>
<td>29</td>
<td>17</td>
<td>.06</td>
</tr>
<tr>
<td>May-September</td>
<td>26</td>
<td>15</td>
<td>.08</td>
</tr>
<tr>
<td>Respiratory-related events</td>
<td>26</td>
<td>20</td>
<td>.4</td>
</tr>
<tr>
<td>Nonrespiratory-related events</td>
<td>25</td>
<td>14</td>
<td>.07</td>
</tr>
</tbody>
</table>

Abbreviations: ICU, intensive care unit; SAEs, serious adverse events.

<sup>a</sup> P ≤ .05.

<sup>b</sup>Hospitalization (grade ≥3) percentage age includes grade 4 events.

<sup>c</sup>Intervention without hospitalization: drug/nondrug therapy (grade ≥2) percentage age includes grade 3 and 4 events.
Intervention Feasibility, Acceptability, and Unintended Consequences

We aimed for participants in the RHO arm to send data every 4 to 7 days, as feasible and convenient. Research staff would encourage families to send data but would not remind them again to send data regularly if they were demonstrating noncompliance in transmitting reports every 4 to 7 days. A total of 72% of families randomly assigned to this intervention sent data at least once during the study period. The number of reports per month ranged from 0 to 7.5. The mean number of reports was 2.4 per month.

Nine of the 97 RHO infants’ families were noncompliant with the intervention, sending in no oximetry reports. These infants were no different from the others in the RHO arm with respect to baseline demographic and clinical characteristics. Nor were they more likely to have incurred at least 1 adverse event (3/9 [33%] vs 22/88 [25%]; P = .69) or at least 1 SAE (3/9 [33%] vs 16/88 [18%]; P = .37).

For those infants randomly assigned to RHO, we also administered feasibility surveys to determine potential obstacles to use of RHO. The feasibility surveys were added to the trial’s protocol after it had started, so not every RHO arm participant had the opportunity to complete
the survey. A total of 49 families in the RHO arm completed the feasibility survey. Of the families that responded to the survey, 91% indicated they would use RHO as a tool for managing HOT if offered a choice. These surveys demonstrated that the most common obstacles to RHO use (25%) were technological malfunctions (ie, oximeter not recording, difficulty uploading data, etc). Parents who experienced technological issues would reach out to study staff, who helped troubleshoot until the problem was resolved. The second most common obstacle was that infants had to wear 2 oximeter probes (one for their clinical monitor and a second for the RHO recorder). This was felt to be a burden to the infant, and some families ultimately did not place the second probe, resulting in less frequent recording.

In analysis of the feasibility responses from both compliant and noncompliant families, some statistically significant findings were associated with increased RHO reporting frequency. The correlation between reporting frequency and a parent’s level of education was statistically significant (mother’s education level $P = .002$; father’s education level $P = .05$). Reporting frequency was not correlated with the number of siblings or children living in the home (Spearman $r = 0.11; P = .51$), but it was correlated with the number of bedrooms ($r = 0.6; P = .01$). Families with more obligations were likely to have less reporting ($r = 0.48; P = .05$). We also asked families if they sent data more often, less often, or at about the same frequency as they had expected at the time of enrollment. The families who were compliant with the protocol and transmitted data every 4 to 7 days answered that they sent data more often than they had expected ($r = 0.62; P < .0001$).

Of note, 80% of barriers/obstacles described by families in this cohort can now be eliminated with recent advances in technology since initiation of the trial, and the fact that use of RHO clinically instead of as part of a study would also eliminate the need for a second oximeter. Recent technological upgrades have also eliminated the need for parents taking the active steps in recording and transmitting data.
DISCUSSION

The RHO trial represents a novel approach to HOT weaning and management of former premature infants diagnosed with BPD, and our study demonstrated the safety of 2 distinct HOT management protocols in this population. Use of RHO in addition to monthly clinic visits was safer and shortened the duration of HOT vs not using RHO; frequency of data transmission by parents was inversely correlated with decreased duration of HOT. Use of RHO did not reduce QOL for parents, and the discontinuation of HOT did not result in adverse effects on growth or adverse respiratory events for RHO participants.

Our study provides important descriptive data regarding the duration of HOT in premature infants. Compared with previous studies of premature infants requiring HOT, which were primarily descriptive single-center observational cohorts, our multicenter randomized trial demonstrated significantly shorter durations of HOT in both arms. For infants who had monthly clinic visits without RHO, the average duration of HOT was approximately 3 months from NICU discharge. It is unlikely that our cohort was healthier than those described in previous cohorts, based on comparisons of clinical and demographic data.

Our cohort of premature infants was typical of those sent home on HOT, in which it tends to be the sicker infants who will require HOT after NICU discharge. Infants enrolled in our study were discharged according to their site’s NICU policy on HOT, and all participating sites had appropriate procedures in place for sending infants home on HOT. A total of 140 participants (72%) had severe BPD, 103 (52%) required diuretics while in the NICU, and 113 (57%) had a patent ductus arteriosus confirmed by echocardiogram.

We did exclude infants with pulmonary hypertension (8% of infants screened for eligibility) and infants with hypoxemia potentially explained by other causes, to cleanly capture the natural course of hypoxemia resolution in premature infants without other confounders. Infants with pulmonary hypertension also have different O₂ saturation targets that would not have aligned with our predetermined algorithm. Our relatively large cohort from multiple sites is likely more generalizable for premature infants with BPD with a HOT requirement. Previous
studies also were purely descriptive and did not use a standardized protocol to wean or discontinue HOT. It is therefore possible that simply using a standardized protocol, regardless of the specific O_2 threshold parameters, allows earlier discontinuation of HOT. Either of the 2 management strategies described in our study seem to allow shorter duration of HOT for premature infants with BPD.

As expected, infants discharged from the NICU with higher O_2 flow rates took longer to discontinue HOT compared with infants discharged with lower initial O_2 flow rates. Adjusting for this variability in status at time of NICU discharge, we still saw significant differences in HOT duration between the intervention and nonintervention arms.

The RHO trial used consensus guidelines from pediatric pulmonologists, primary care physicians, and neonatologists to determine when to wean, increase, or maintain HOT. The specific O_2 saturation targets used in our protocol to determine need to increase, maintain, or decrease O_2 flow rates also may have allowed shorter duration of HOT. Optimal O_2 saturation targets remain controversial in neonatology, but the guidelines used in this protocol are consistent with published national guidelines.\textsuperscript{16,25} Infants in both arms of our study had relatively few adverse events compared with previous reports in the literature of infants on HOT, suggesting that the thresholds used in this protocol were not unsafe.\textsuperscript{3,6,14} Similarly, the growth data after discontinuation of HOT was reassuring. Future research needs to be conducted in optimizing O_2 saturation targets in former premature infants with BPD on HOT. This alone could help shorten duration of HOT in this specific population.

Our study showed that use of RHO did in fact shorten duration of HOT in a dose-dependent manner. It is likely that, in the absence of available oximetry data to inform HOT management, pediatric pulmonologists and primary care physicians err on the side of extending HOT to minimize risk of hypoxic episodes. Our data demonstrated that infants are often ready to wean their O_2 flow rates between clinic visits, and RHO allowed earlier identification of this readiness to wean, suggesting that in the absence of recorded oximetry, infants are being exposed to unnecessary supplemental O_2.
Some studies have suggested that use of HOT can improve growth, and as a corollary, that early discontinuation of necessary HOT results in unwanted weight loss.\textsuperscript{32,33} Interestingly, infants randomly assigned to the nonintervention arm (no RHO) did experience some change in their weight status (−0.043 z score units per month) during the HOT weaning process, whereas infants who were randomly assigned to RHO did not (0.004 z score units per month). This difference between the 2 arms was statistically significant. We observed no weight loss in infants in either arm after discontinuation of HOT. The decrease in weight z score during HOT in infants who were not randomly assigned to RHO may have been due to clinically inapparent hypoxia that was undetected due to lack of RHO data. However, the extended duration of HOT in the patients in this cohort would suggest that they were on HOT longer than needed, so these infants should not have been hypoxic.

Alternatively, families of infants randomly assigned to RHO were necessarily more actively engaged in their infant’s HOT management and were therefore potentially more attentive to their infant’s nutritional needs, compared with families who did not use RHO. The lack of weight loss seen in both arms after discontinuation of HOT is reassuring in that none of the infants in the study were weaned off O\textsubscript{2} too early. Alternatively, weight and O\textsubscript{2} status in our study were not as tightly correlated as some past studies have suggested they are, and other nutritional factors may have accounted for the weight z score patterns we observed in our cohort.

Previous studies of infants discharged from the NICU on HOT have reported high adverse event rates; in some studies, up to 80% of infants on HOT required at least 1 readmission to the hospital.\textsuperscript{1,6,14} Overall, our cohort of infants on HOT had fewer respiratory-related events than anticipated. Infants who were randomly assigned to use RHO experienced fewer respiratory-related adverse events when compared with infants randomly assigned to those without the intervention. The use of RHO may have encouraged increased parent participation in infant care that allowed closer monitoring. Previous studies showed that infants exposed to higher levels of O\textsubscript{2} have increased respiratory exacerbations.\textsuperscript{20} Although the
relatively low levels of $O_2$ exposure from a nasal cannula are not thought to be toxic, it is possible that shorter duration of HOT led to decreased adverse events due to less $O_2$ toxicity.

Duration of HOT was chosen as the primary outcome due to its hypothesized role in caregiver emotional health. The significance of this outcome was supported by the personal remarks of former HOT patient families that participated as key stakeholders during our protocol development.

For participants randomly used to use RHO, parents had to take an active role that required numerous steps to be compliant. The infant had to wear 2 oximeters for recording; 1 oximeter was to be worn to monitor the infant clinically, while the second was acting as a recorder. Parents also had to remember to hit the record button at the start of each recording session. To transmit the data electronically to research staff, parents had to use a secure digital card reader and download the data files to their computer and then use a secure login website provided through UMMS to email the data. The feasibility data did suggest that reporting frequency was correlated with parental education level and socioeconomic status. With recent technology, the burden of recording and transmitting RHO data can be significantly decreased and almost eliminates all active parental steps.

To best implement RHO into clinical practice, both neonatologists and pediatric pulmonologists need to understand the risks and benefits of HOT in former premature infants diagnosed with BPD. Pediatric pulmonologists will need to feel comfortable using the technology, which has already improved since the implementation of this trial. With the recent technological advances in home oximeters, most of the obstacles experienced by parents of RHO participants could be eliminated. Neonatologists also must recognize the benefit of sending patients home on supplemental $O_2$ and understand the safety profile of HOT, which includes decreased adverse events and optimal growth. If RHO were to be implemented clinically with the use of new technology that eliminates the need for a second oximeter, researchers would need to investigate how to optimize implementation of this evidence-based protocol. There is a strong likelihood that the duration of HOT would be further decreased and could increase parental satisfaction more than what we found in this trial.
Decisional Context

In this randomized controlled trial, we found that an intervention encouraging parental participation in the HOT weaning process through intermittent transmission of RHO data resulted in significant shortening of HOT duration. Both interventions had very favorable safety profiles, with fewer adverse events in the RHO arm. In both interventions, parent-reported health-related QOL increased compared with baseline, but the difference in QOL from pre- to-postintervention was not statistically different between the 2 arms. The response rate to the QOL outcome measure among parents in both arms was low, but according to prespecified power calculations, we still had an appropriate number of participants for analysis. The responding groups in both arms were still equal and did not have any statistical differences in clinical variables or baseline demographics, suggesting that the randomization was preserved despite the low response rates. Overall, the intervention components were feasible to deliver, acceptable to parents, and did not have adverse effects on parents’ perceptions of their child’s health care services.

Comparison of Study Arms

The RHO trial was designed with the hypothesis that transmitting RHO data between monthly clinic visits would accelerate weaning from HOT relative to relying solely on measurements made during monthly clinic visits alone. Our findings supported this hypothesis, and we found that the effect was statistically significantly dose dependent. There are several potential reasons. Theoretically, with no confirmatory data available, patients are being weaned too early, too late, or at exactly the right pace. Because the use of physiologic data shortened the duration of HOT, one possibility is that patients truly are receiving HOT longer than necessary, and the availability of physiologic RHO data allowed providers to note that patients were ready to wean sooner. Second, the use of RHO may have led to more interactions between the family and clinical care team, so that decrease in HOT duration was not solely attributed to the transmission of data. Parents randomly assigned to use RHO were instructed to record and transmit data to the data coordinating center (research coordinator) every 4 to 7 days as feasible. The research coordinator would then analyze the data and share the
recommendation based on the weaning algorithm (wean, maintain, or increase the O\textsubscript{2} flow rate) with the infant’s pulmonologist. The results were communicated to the parents by either the research coordinator or pulmonary team, depending on the site. Although communication increased between the pulmonary team and the family, there is no indication that additional clinical discussions other than the relay of recommendations (wean, maintain, or increase the O\textsubscript{2} flow rate) were communicated with the family.

**Study Results in Context**

The mean duration of HOT in our population was shorter than what has been otherwise reported in some studies. In our comparison group of monthly follow-up only, we implemented a standardized weaning protocol for in-clinic weaning. Previous reports did not describe a standardized protocol, so it is possible that standardization of in-clinic protocols itself substantially decreases HOT duration. This trial found that the mean duration of HOT for the standard-of-care arm (monthly clinic visits alone) was much shorter than our original hypothesis of 144 ± 66 days.

In addition to duration of HOT, this study examined family-centered outcomes of importance to parents and children, whose content was informed by input from a PAB. We did not find a significant between-study arm difference in parent-reported QOL, so it is hard to measure what type of HOT management protocol would increase parental satisfaction. It is encouraging that in both arms, families were happy with their infant’s health and health care at baseline and after discontinuing HOT. It is also difficult to distinguish what incremental decrease in HOT duration is clinically significant to parents’ well-being and not just statistically significant. Having an infant on HOT creates substantial restrictions on travel and on interactions with families and friends.\textsuperscript{6,8,10,13} Per our PAB, the levels of decrease in HOT duration seen in our study of several weeks and months are absolutely significant and meaningful.

Both the intervention and standard of care had very favorable safety outcomes. This suggests that whether or not providers and families choose to use RHO as part of their weaning regimen, use of HOT and either of the structured weaning protocols described in this study are safe and effective, and may allow earlier discharge from the NICU for some infants whose only
discharge-delaying factor is an O₂ requirement. Length of stay varied between institutions, and some NICUs were more likely to incorporate HOT than others. This was seen among the sites participating in the RHO trial. Length of stay for infants whose only discharge-delaying factor is an O₂ requirement needs to be further investigated.

Growth issues and hypoxia are believed to be related in premature infants, especially those requiring O₂. Including growth as an outcome in our study was considered essential by provider stakeholders and families. We were reassured that after discontinuation of HOT, patients in both arms did not experience worsening growth. This finding is similar to that of the Boost Trial (2003), which showed similar results in the inpatient setting, suggesting that O₂ does not help or drive growth in premature infants.

**Limitations**

This study had several potential limitations. First, in the absence of any verified O₂ target saturation guidelines, we used a consensus guideline to determine when to wean, increase, or maintain HOT flow rates. It is possible that slight alterations in these HOT adjustment parameters would have altered the weaning schedule and therefore affected the duration of HOT. Our original protocol received feedback from reviewers that our predetermined thresholds were very strict and might actually prolong HOT in former premature infants. Instead, the implementation of this data-driven protocol, with our algorithm, proved to shorten the duration of HOT when compared with standard monthly in-clinic weaning attempts.

Second, in this trial we encountered families that reduced HOT flow rates and discontinued O₂ completely on their own against the advice of their providers. A total of 25 families self-weaned either against their provider’s advice or with no guidance at all. The frequency did not differ between arms (12 in the standard-of-care arm and 13 in the RHO arm). Previous studies also experienced this frustrating limitation. Educating parents further on the importance of HOT and the reasons why their infant requires support may prevent this in the future. If HOT is incorporated into more standard-of-care guidelines to best implement RHO or
standardized weaning practices, further predischarge education with families will need to be carried out.

Third, to fulfill the RHO protocol, this trial was a multicenter randomized unblinded trial. For RHO to be used, families were given a second oximeter so they could record and transmit oximetry data to study staff, making blinding impossible. Study staff also needed to know which participants were to be sending RHO data and which ones needed strict in-clinic weaning followed by a PSG to discontinue HOT. To limit potential bias, study staff followed the structured algorithm to determine whether to wean, maintain, or increase HOT flow rates.

Finally, the response rate for the postdiscontinuation PedsQL outcome was low (108 parents responded from the 196 infants in the final cohort). We were able to collect enough responses to be powered to detect statistically significant differences, and there were no significant differences between responders and nonresponders. Still, the low response rate may not allow full generalizability of the parental QOL findings to the entire parental cohort.

Generalizability

Our trial is one of the largest cohorts of premature infants on HOT, and unlike prior cohorts, it includes patients from multiple sites, including both urban and rural bases, and patients with a diverse range of illness severity. We excluded patients with confounding causes of prolonged hypoxia other than prematurity that could affect duration of HOT. The findings of our trial should be generalizable for infants with BPD on HOT throughout the United States.
CONCLUSIONS

RHO is a safe and effective protocol to assist in the management of HOT in former premature infants with BPD. We found that use of RHO between clinic visits can safely shorten the duration of HOT in this population. The greater the reporting frequency of RHO measurements, the shorter the duration of HOT. Use of RHO is safe, was associated with less adverse effects on growth, and did not have a significant positive or negative effect on parent-reported QOL. RHO is thus a reasonable alternative to PSG to determine safe timing of HOT discontinuation in former premature infants with BPD.
REFERENCES


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Disclaimer:
The [views, statements, opinions] presented in this report are solely the responsibility of the author(s) and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute® (PCORI®), its Board of Governors or Methodology Committee.

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