INVESTIGATOR STUDY PLAN

1. TITLE
Implementation of Effective Home Oxygen Weaning Strategies in Premature Infants

2. EXTERNAL IRB REVIEW HISTORY*
N/A

3. PRIOR APPROVALS:

Conflict of Interest (COI): *N/A*
Clinical Engineering Department: *N/A*
Biohazardous Agents: *N/A*
Radiation*: N/A*

4. OBJECTIVES*

Specific Aims include:

a) Test the implementation of successful implementation of the recorded home oximetry (RHO) program in 14 diverse medical centers:
b) Test the hypothesis that implementation of RHO will be associated with:
    a. Increased number of sites offering RHO and number of patients utilizing RHO;
    b. Reductions in duration of home oxygen therapy (HOT) in infants utilizing RHO and decreased neonatal intensive care unit (NICU) length of stay;
    c. Increased number of neonatologists utilizing HOT and number of patients offered HOT;
c) Identify the recipient factors: Organizational characteristics, (i.e. cohorted NICU follow-up programs versus general pediatric pulmonary clinic), and Patient/family characteristics, (i.e. socio-demographic characteristics, disease burden of prematurity, and parental knowledge and beliefs) that predict variation in the adoption of RHO across sites, to inform iterative improvements and future widespread dissemination

5. BACKGROUND*

Improvements in neonatal care have led to increased survival of premature infants, although many continue to have significant lung disease following discharge from the neonatal intensive care unit (NICU).[1] Current estimates suggest a third of extremely preterm infants will require *home oxygen therapy* (HOT) after NICU discharge, including 60% of those born at gestational age of 23-24 weeks.[1-4] In infants requiring supplement oxygen (O_2), HOT provides a means of facilitating NICU discharge, but its use is highly variable, [5,6] ranging from 10% to 95% across the United States (U.S). Studies suggest that NICUs with higher rates of HOT utilization have shorter lengths of stay (LOS), even adjusting for birth gestational age. [5,7] To date, these have been observational studies without specific interventions for increasing HOT utilization.

Institutional variation in HOT appears to be related to provider preference, rather than patient severity of illness.[3,5,7] Longer NICU stays potentially put undue burden on families and contribute

to increased parental stress, while impairing neurodevelopment and family bonding. [5,8,9] A critical obstacle to increased HOT utilization has been a lack of evidence-based consensus guidelines for its safe management.[6] There is little data to guide weaning, and little evidence regarding its safe discontinuation. A survey of pediatric pulmonologists found some recorded oximetry was frequently utilized prior to permanently discontinuing HOT.[10] More recently, NICUs in Australia have reported using recorded overnight oximetry to guide O_2 weaning in the inpatient and outpatient setting.[6] Although similar practices exist in the U.S., they are not implemented consistently. Inefficient oxygen management strategies may lead to an inappropriate prolongation of HOT, potentially risking O_2 toxicities.[11-13]

Although many families prefer their infants to be discharged on HOT as opposed to prolonged NICU stays, prior research has also shown that HOT may increase family anxiety.[5,9] Families also report that prolonged HOT can result in excessive parental stress and social isolation.[9,14] Discussions with our parent advisory board (PAB) validates these reports that parental tension is increased not only with longer NICU LOS, but also with prolonged HOT duration. Decreasing HOT duration is therefore highly desirable but will require successful dissemination of an evidence-based weaning strategy.

Recoded home oximetry (RHO) provides objective data on oxygenation status but has only been utilized in research and standard clinical practice in limited settings. The DECAF trial (Rhein et al.) utilized RHO to determine effects of extended caffeine on intermittent hypoxia in infants in infants born prematurely. Increased availability of RHO could provide data to support O_2 weaning protocols, but efficacy and safety of HOT weaning strategies, with or without RHO, has not been reported. Recently, we completed a 4-year prospective multi-center randomized control trial (2014-2018) in 9 academic centers, of the effect of RHO on duration of HOT, patient safety, and family experience as compared to routine monthly clinic-based HOT management. The RHO trial was carried out in close collaboration with physicians and family members from across sites and focused on family engagement throughout the HOT management process. The intervention included transmission of RHO from parents to providers every 4-7 days and utilized a structured algorithm to determine whether to increase, decrease, or maintain O_2 flow rates (Appendix Table 1). The guidelines developed for the RHO trial were the first to set standard O_2 threshold targets for outpatient O_2 weaning in premature infants. Optimal targets remain controversial, but the protocol's consensus-based guidelines were consistent with all published statements. The RHO trials guidelines are easily generalizable and could potentially be utilized in a wide variety of clinical settings.

The RHO trial was the first prospective, multi-center randomized trial to evaluate any HOT weaning management strategy. Results of the RHO trial found time to discontinue HOT was 22% shorter in the RHO group infants (78.1 ± 6.4 days) versus the standard of care group (100.1 ± 8.0 days, p=0.03). Respective median times were 71 and 90 days. HOT duration was shorter for participants sending more frequent RHO data reports between monthly clinic visits (10.3% shorter duration for each additional report provided per month, 95% CI -5.2 to -5.3%, p=0.0001). Despite its focus on a medically fragile cohort, there were relatively few adverse events (AEs) in the study, with fewer events in those randomized to RHO. The RHO trial found that utilization of RHO is a safe and effective strategy for managing HOT in premature infants-shortening the duration of HOT, while increasing parent satisfaction.

We now propose to implement the RHO management program in 12 diverse medical centers. The proposed RHO program builds on earlier studies involving oximetry acquisition and analysis, family-caregiver partnerships in HOT management, and preliminary research regarding family engagement in HOT management processes through data transmission.

6. INCLUSION AND EXCLUSION CRITERIA*

RHO Program eligible infants will be identified prior to NICU discharge by each participating site, once the need for HOT is identified by the discharging neonatal clinical team. Per their standard of care management, this will include:

Inclusion Criteria:

(1) An infant with a birth gestational age < 37 0/7 weeks postmenstrual age (PMA) who has a requirement for O_2 past NICU discharge
(2) An infant diagnosed with pulmonary hypertension who is not currently on pulmonary hypertension specific medication therapy (phosphodiesterase-5 inhibitors or riociguat, endothelial receptor antagonists, prostacyclin or prostacyclin derivatives)

Exclusion Criteria:

(1) An infant with a syndrome or other diagnosis with known high risk for persistent hypoxia (cardiac disease, Trisomy 21, Pierre-Robin Sequence, etc.),
(2) Infant who has a requirement for O_2 flow rate > 1 L/min or tracheostomy
(3) Infants with conditions that may influence prolonged need for oxygen beyond lung disease of prematurity will be excluded

7. STUDY-WIDE NUMBER OF SUBJECTS*

This is a multi-center quality improvement initiative taking place at 14 academic medical centers across the United States, with Lawrence Rhein, MD, MPH serving as the Principal Investigator. Each site will implement the same version of the RHO Program protocol. The PI and co-investigators estimate based off preliminary work that approximately 600 premature infants on HOT will be included annually, and a total of 1,800 infants will be included over the three-year implementation period.

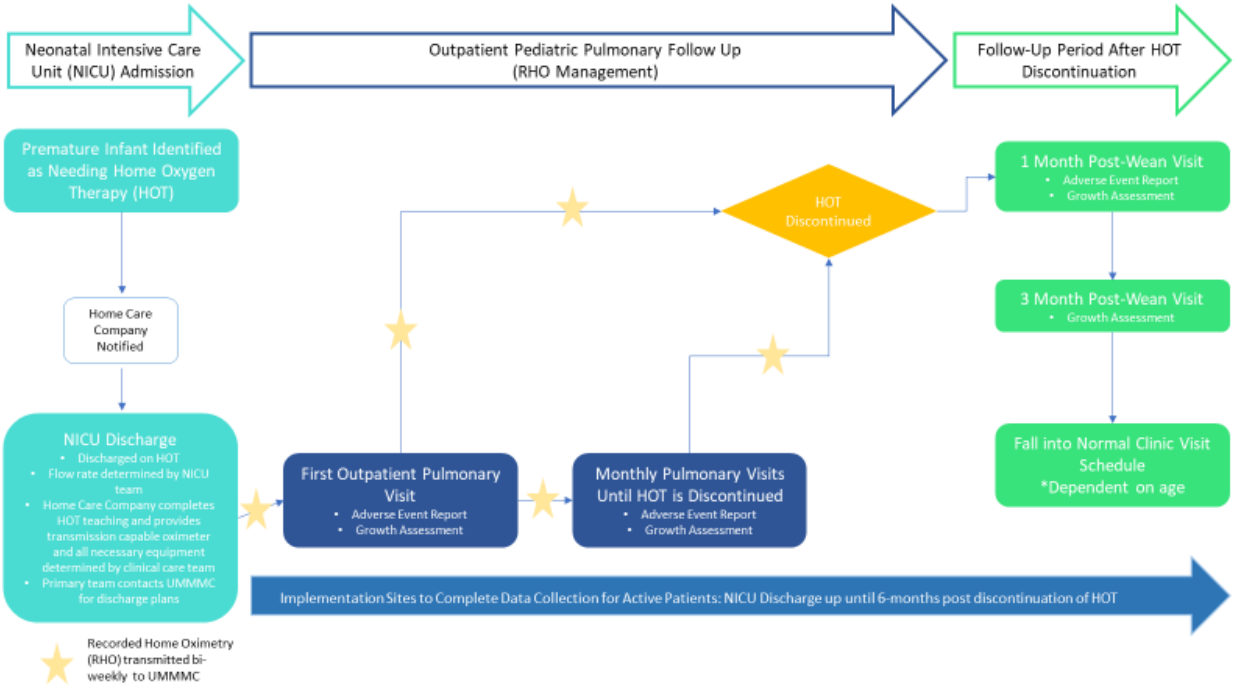
8. STUDY-WIDE RECRUITMENT METHODS*

All recruitment methods are local to individual implementation sites.

9. STUDY TIMELINES*

Each participating site will adopt the RHO program as their standard practice for weaning former preterm infants off HOT. Once the NICU's clinical team at a participating site has determined an infant's need for HOT by their units' guidelines they will join the program. The NICU staff and

pediatric pulmonologist caring for the patient outpatient will meet with the family to describe the process for weaning and answer any questions the parents have about the RHO program. The infant will continue to be followed by the RHO program until 6-months after successfully discontinuing HOT. The program's timeline is depicted in **Figure 1**.



The RHO Program's implementation trial will track implementation data for a three-year project period. Enrollment into the RHO program will begin in March 2021 and continue through February 2024.

Analysis of implementation specific data for the RHO program will be analyzed throughout the project's duration as this is a quality improvement study at the site level. Barriers and facilitators will be analyzed throughout so appropriate changes can be made to the program to optimize patient and family satisfaction and improve safety and duration outcomes for preterm infants on HOT. Any changes that directly affect patients will require a modification to the UMass Medical School IRB.

10. STUDY ENDPOINTS*

For the current implementation study of the RHO program, our specific aims are:

(1) Test the implementation of the RHO program in 14 diverse medical centers;
(2) Test the hypothesis that implementation of RHO will be associated with:
   a. REACH: increased number of sites offering RHO and number of patients utilizing RHO;
   b. EFFECTIVENESS: reductions in duration of HOT in infants utilizing RHO and decreased NIUC LOS;

c. ADOPTION: increased number of neonatologists utilizing HOT and number of patients offered HOT;
d. IMPLEMENTATION: Specific determinants will affect implementation; and
e. MAINTENANCE: sustained compliance, including increased providers and DME companies using RHO as standard care

(3) Identify the recipient factors: Organizational characteristics, (i.e. cohorted NICU follow-up program versus general pediatric pulmonary clinic), and Patient/family characteristics, (i.e. socio-demographic characteristics, disease burden of prematurity, and parental knowledge and beliefs) that predict variation in the adoption of RHO across sites, to inform iterative improvements and future widespread dissemination.

11. PROCEDURES INVOLVED*

Once an infant is identified as requiring HOT, they will be considered as part of the implementation site's cohort. Families will receive program information and their child's specific de-identified health information to be collected as part of the study. If a family decides they don't want to participate they can opt-out and their child's care will not be affected in any way. They will still be managed by the RHO program as this is the standard of care chosen by their physician but their data will not be collected as part of the implementation study.

Please refer to Figure 1 for a timeline of the procedures involved.

Implementation Study Procedures:

Implementation Baseline Demographic Information

We will obtain baseline demographic information from all site participants in the RHO program to establish the center's baseline rates for infants utilizing HOT and duration and safety data. Retrospective Vermont Oxford Network (VON) variables will be collected from the infants VON data form after NICU discharge. This data will be considered retrospective as VON data is obtained after the infant's final disposition to home. Please refer to the REDCap survey "VONData_RHOImplementation.pdf" for the list of variables to be collected as baseline data. Baseline data will be collected for all infants born and already discharged at each center from January 2018 to the start of their participating implementation wave (April 1, 2021 or July 1, 2021). Additionally, as part of establishing baseline HOT and adverse event rates for infants at each site we will also collect retrospective follow-up data from the pediatric pulmonary data available. Please refer to the REDCap form entitled "AdditionalBaselineData_RHOImplementation.pdf" for variables to be extracted from patient's electronic medical record.

NICU Demographic Information

NICU demographic information will be collected for each infant being followed by the RHO program. This data will be collected from their electronic medical record and VON data collection form collected after their initial NICU discharge. Data variables to be collected are outlined in the REDCap survey form "Demographics_RecordedHomeOximetry."

Home Pulse Oximeter Recording Procedures

The recording system we used for prior studies and plan to use for this study is the Masimo RAD-97 pulse oximeter. These monitors are provided by home care companies as standard of care to all infants going home on supplemental O_2. The oximeter will be placed in the neonatal mode which will have the set parameters for a 12-second averaging time display, low SpO2 of 92%, and heart rate alarms will be set at a high of 220bpm and a low of 90bpm. ***Infants will utilize their clinically-provided monitor as determined by their primary clinical team***.

The RAD 97 will be wirelessly connected to the Patient SafetyNET at UMMMC to allow for wireless transmission of oximetry recordings. Once a patient receives their clinically provided pulse oximeter the site lead at their site will proved the oximeters serial number to the data coordinating center so that the device can be "admitted" into the SafetyNET to allow for continuous data capture.

Remote oximetry will begin at time of NICU discharge once the oximeter is connected to the patient's home WIFI.

During the 3-4 day evaluation periods to determine readiness to wean or status post wean, parents will be instructed to use the oximeter as determined by their primary clinical team but continuously during nocturnal sleep periods. Sites will be assigned to a data downloading schedule of either Monday/Thursday or Tuesday/Friday. A minimum of 25 hours (1500 minutes) of data is to be analyzed and deemed interpretable before any change in supplemental oxygen is made. If the data is deemed inadequate or unreadable, the parent will be notified and no change in oxygen management will be made. The determination to wean, increase or maintain will be based off our consensus-based algorithm used in the original RHO trial (**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 25 hours (1500 minutes) of data, will be required for analysis to make any wean.		

For infants in the RHO program, O_2 weaning will proceed, when allowable per weaning criteria in the protocol, in 50% decrements to a minimum of 125cc/min. (For example, flow rate of 500cc/min will be decreased to 250cc/min, and 250cc/min will be decreased to 125cc/min), the next weaning step will be to room air during the day and nocturnal O_2 only at a flow rate of 125cc/min. The final step will be from nocturnal oxygen to off supplemental O_2 entirely.

Staff at the data coordinating center will send an email notification to the primary physician or designated study staff with the specific recommendation to wean, increase, or maintain with the flow rate included. Please see Email Script Below:

Hi _____,

Here is data of <u>Subject ID</u> on 250cc/min of continuous oxygen. His/her data today shows a maintain at their current flow rate of oxygen.

Minutes Valid SpO2	Mean SpO2	Minimum SpO2	Maximum SpO2	Second Below 96% SpO2	Minute Below 96% SpO2	% Time Below 96% SpO2	Second Below 93% SpO2	Minute Below 93% SpO2	% Time Below 93% SpO2	Second Below 90% SpO2	Minute Below 90% SpO2	% Time Below 90% SpO2
2589.45	96.4	76	100	43791	729.85	28.1	7222	120.3	4.6	1290	21.5	0.8

Best,

<u>Monthly Clinic Visits</u>

As part of the RHO program, infants will be seen in clinic monthly while on oxygen by their pediatric pulmonologist or neonatologist responsible for weaning their HOT. At these visits, their physician will ask them about any adverse events (hospitalizations, emergency department visits or respiratory illnesses). If any AE events did occur these will be captured in the REDCap form

"Adverse Event" in order to evaluate safety outcomes. With the more recent use of telemedicine, infants maybe seen remotely between clinic visits when a respiratory AE or flow increase occurs, but this will be left to the individual physician's discretion.

Adverse Event Criteria and Reporting Procedures

Information about all adverse events, whether volunteered by the infants family, discovered by the physician during a monthly visit, or detected through physical examination, or tother means, will be collected and recorded and followed as appropriate.

An adverse event is the appearance of worsening of any undesirable sign, symptom, or meical condition occurring after NICU discharge until 6-months post successful discontinuation from HOT. Events will be followed even if the event is not considered to be related to the program.

As far as possible, each adverse event should be evaluated to determine.

1. The severity grade (mild, moderate, or severe) or (grade 1-4)
2. Its relationship to the RHO program (related/not related)
3. Its duration (duration in days)
4. Whether it constitutes as a serious adverse event (SAE) (hospitalization or life-threatening)

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:
  - related to underlying prematurity and in the opinion of the site investigator not outside the normal course for a preterm infant diagnosed with BPD on HOT and associated equipment
  - routine treatment or monitoring of HOT and other associated diagnoses related to prematurity, 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 UMass Data Coordinating Center as soon as possible after learning of its occurrence.

Serious Adverse Events that are **serious**, **unexpected** and **related** to the study, including rehospitalizations 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).

Follow-up Data

Infants will remain in the RHO program until they have been off all supplemental oxygen for 6-months. During this time sites will monitor the infant for any AE or adverse outcomes related to weaning (i.e. poor growth, aspiration, or need to reinitiate HOT).

12. DATA AND SPECIMEN BANKING*

Recorded pulse oximetry will be banked for future analysis. All necessary steps to ensure confidentiality will be taken. Coded subject numbers will be assigned to each patient. The linked sheet will remain separate from the coded database, and within a UMass password protected computer. Oximetry data will be stored securely on a network share drive. Study staff will work with UMass Information Technology to ensure data is securely protected and storeed.

The REDCap database will also be archived after study closer to be used in future studies. All future studies proposing to use this data will require a new IRB submission and approval. No identifiable health information will be collected in the REDCap and names of individuals will not be linked to the coded identifiers.

13. Data Analysis and Management*

This is a quality improvement and implementation study of the RHO program which aims to study the effectiveness of a structured guideline to weaning home oxygen in premature infants. We will use the data collected to optimize implementation strategies and for further more widespread dissemination of the RHO program.

Data Management

At time of NICU discharge infants will be provided a unique ID code which will be shared with researchers at UMMMS. Individual sites will be the only individuals able to view the link between the participants' names and unique ID. The link to all codes will be maintained in a secure, HIPAA compliant database in the research space at each participating site. The unique patient number will be used on all documents and email correspondence between UMMS and the individual site.

Data will be collected by the research coordinators who have been trained in how to collect the specific clinical data from the medical record. All data will subsequently be entered into the

studies REDCap by the research coordinator. The database will be designed with rules to prevent entry of impossible values in relevant fields. Subjects will be identified only by a study identification number in the database. The database will be password protected with each individual having their own unique set password.

Individual sites will have access to their own sites data but will not have access to other centers data or information. Research staff at UMMS will oversee the management of the REDCAP and have access to all centers de-identified data. Each month the data team at UMMS will provide monthly data inquiry reports to clean and to provide missing data. Individual sites will be responsible for answering these monthly data cleaning reports by the following month and clearing up any discrepancies in the data.

14. PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS*

Although this is a quality improvement study at the site level a data safety 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 15 patients have been followed by the RHO program, and subsequently not less than twice yearly. The DSMB will include 2 neonatologists (not associated with the RHO program) and two pediatric pulmonologists (not associated with the RHO program) as well as one primary pediatrician from the community (also not associated with the RHO program). 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 DSMB meeting, Dr. Rhein and the primary program coordinator will be present to discuss the RHO program's implementation and any issues raised, and then they will leave the meeting so the DSMB can review any adverse events. If a child is noted to have more than 3 respiratory re-hospitalizations, the committee will come together and decide what, if any part of the program needs to be altered and/or stopped.

Stopping Rules:
The RHO program's implementation will be stopped, if there are at least 3 related respiratory related hospitalizations at one center and the majority of the DSMB votes that these are program related and cannot be remedied.

15. WITHDRAWAL OF SUBJECTS WITHOUT THEIR CONSENT*

Where this is a quality improvement initiative at the individual site level and the RHO program is being implemented as standard of care no infants will be enrolled to participate, rather they will receive RHO as part of their standard pulmonary follow-up. If families stop utilizing the oximeter or data is no longer available, the site pediatric pulmonologist caring for that infant will notify the UMass research staff that the baby is no longer an active participant in the RHO program. Withdrawal cases will be reviewed on a case by case basis and the IRB will be notified if any risks to the patients were the cause of the withdrawal from the program.

Data that we have already collected will stay in the study database and cannot be removed in order to maintain the integrity of the research.

16. RISKS TO SUBJECTS*

Patients participating in the RHO program are receiving the standard weaning strategy for home oxygen at their site. Therefore, there will be no additional risk aside from usual practice.

Patients on continuous oxygen are instructed to use the oximeter continuously. The oximeter probe must be rotated every 12-hours. Patients receive training and education from their clinical team on best practice and when to rotate or change the probe to prevent skin irritation. 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. Clinical staff will also instruct each family to use different sites for the probes to minimize risk.

Another risk is the loss of the infant's personal information. This is very unlikely to happen, and we will do everything we can to make sure personal health information is protected by only collecting de-identified data and data collected to a minimum of only information necessary to complete data analysis.

17. POTENTIAL DIRECT BENEFITS TO SUBJECTS*

Infants being followed by the RHO Program will likely experience shorter durations of home oxygen compared to other weaning strategies prior to implementation. The RHO trial (Rhein et al.) found that HOT duration was 22% shorter in infants randomized to utilize RHO compared to the at the time standard of care of monthly clinic visits.

The RHO trial also found that infants in the RHO group experienced fewer adverse events and improved growth outcomes compared to standard of care infants. Infants in the RHO program will benefit from the same telemedicine benefits as those in the trial with even more frequent check-ins from their clinical team which may potentially prevent emergency department visits and rehospitalizations.

18. VULNERABLE POPULATIONS*

- ***Infants****:* The RHO program will follow former premature infants on HOT. Infants will be followed by the RHO program as standard of care at their clinical institution responsible for their oxygen weaning management. Families will be notified that the program is ongoing as part of a large-scale implementation project. Families will have the option to opt-out of having their child's data included as part of the larger implementation trial.

19. MULTI-SITE RESEARCH*

Dr. Lawrence Rhein is the lead principal investigator for this implementation study.

As the coordinating site, UMass study staff led by Dr. Rhein, will conduct a monthly conference call with all other site PI's and research staff to review implementation progress and identify any site level barriers to implementation. During these calls, Dr. Rhein will review any updates to implementation and provide overall implementation progress updates utilizing QI Run Charts to demonstrate progress in real time.

The study staff at UMass will provide bi-weekly data interpretations to each identified study staff at each participating center. Additionally, site's will receive a data query and monthly data report from the data coordinating center at UMass to track internal progress and insure data quality.

20. COMMUNITY-BASED PARTICIPATORY RESEARCH*

Not applicable as this study is not community-based research.

21. SHARING OF RESEARCH RESULTS WITH SUBJECTS*

We do not intend to share research results with individual infants followed by the RHO program. Our study team does intend to publish the results of this implementation research study in a peer-reviewed journal and regional and national conferences to promote large scale dissemination of the RHO program. No individual patient level data will be shared and each center will be included using a de-identified site ID.

22. SETTING

The research will take place at UMass Memorial Medical Center and the UMass Medical School University Campus.

23. RESOURCES AVAILABLE

This study includes the PI, sub-investigators, research coordinator, and research assistants. Collectively the staff has over 35 years of clinical research, quality improvement, and implementation science experience. The roles of each research staff member is listed below:

Principal Investigator:

- This position requires advanced training in Pediatric Pulmonology and Neonatology, research design, and statistical analysis experience. The PI is responsible for ensuring that all team members have current CITI training, appropriate training for their respective roles, including knowledge of the study protocol and procedures for maintaining confidentiality. They will also be involved with overseeing implementation at each of the participating centers and working with co-investigators to optimize implementation of the RHO program.

Sub-Investigator:

- This position requires advanced training in Pediatrics, implementation science research, and quality improvement initiative design. Sub-investigators may be responsible for data

analysis and performing any other study related procedures that fall within their scope of practice only after receiving appropriate training and direction from the PI.

Research Coordinator:

- This position requires research experience directly related to IRB submissions, program design and implementation, statistical analysis, and data reporting. The research coordinator for this implementation trial will oversee the regulatory IRB submissions for each site and be the direct contact between UMMS IRB and other participating centers. They will be responsible for overseeing data quality and reporting. Additionally, they will be responsible for any study related procedures that fall within their scope of practice only after receiving the appropriate training required to perform the procedures.

Research Assistant/Research Nurse:

- This position requires a specialized research professional working with and under the direction of the clinical PI. Research coordinators support, facilitate and coordinate the daily implementation trial activities and play a critical role in the conduct of the study Their responsibilities include: downloading, analyzing, and sending RHO interpretation results to patient's clinician overseeing their oxygen weaning. Additional responsibilities include: data management, handling IRB submissions, and performing any other study related procedures that fall within their scope of practice only after receiving the appropriate training required to perform the procedures.

A trained and experienced research coordinator/nurse/or assistant will perform various tasks required by the study at various time points. A trained and experienced research coordinator and or assistant/nurse will enter site level data into the REDCap database, and perform regulatory functions required by the study.

24. LOCAL RECRUITMENT METHODS

This project is a quality improvement initiative at the site level implementing a safe and effective way to wean home oxygen in the outpatient setting in infants with BPD. Therefore, all infants discharged home on oxygen will be eligible to have their data shared for the larger implementation study.

Site project staff will speak with the on-service NICU attending from UMass once per-week to identify infants who are approaching discharge and will require HOT. The primary pediatric pulmonologist who will care for the infant outpatient and manage their oxygen weaning they will share the information of the implementation study. At this time, all parents' questions about HOT, weaning, and other parental concerns will be discussed. For families, that don't feel comfortable having their infants de-identified data shared as part of the implementation study they will have the ability to opt-out of the research. Their child will still be followed by the RHO program as this will be the standard of care for their medical center for weaning HOT.

No compensation will be provided to families as they will be receiving the standard of care treatment for weaning HOT.

25. LOCAL NUMBER OF SUBJECTS

The UMass NICU admits approximately 100 very-low birth weight infants per year. Of these VLBW infants, roughly 25 infants will require home oxygen after NICU discharge per-year. Over the course of the 3-year study period we plan to capture limited de-identified data on 75 infants.

26. CONFIDENTIALITY

Local procedures for maintenance of confidentiality:
The patient's research records will be confidential to the extent possible. In all records, the subject will be identified by a unique code number and their name will be known only to the site research staff. A digital version of the "Master List" with these codes and subject identifiers will be kept in a folder on a locked, password protected shared drive. The subject's name will not be used in any reports or publications of this study. UMMS Institutional Review Board and/or their representatives may inspect the patient's medical records that pertain to this research study. The funder of this implementation trial will not have access to any patient names or information, even upon request.

Where and how will data be stored locally:
Any patient opt-out forms for UMass participants and all other source documents will be stored in the NICU Research Office at UMass Memorial. This office is secured with a lock and only study staff will have keys. The electronic data is protected in a REDCap database that is password protected and encrypted and, on a computer, shared drive which is only accessible by study staff.

Confidentiality for Multi-Site Research:
Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor. This confidentiality is extended to the clinical information relating to participants. We are only collecting the level of de-identified patient level data necessary to evaluate overall implementation across sites. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

All research activities will be conducted in as private a setting as possible.

Representatives of the clinical site IRB or DSMB may inspect all documents and records required to be maintained by the clinical site principal investigators, including but not limited to, medical records (office, clinic, or hospital) for any infant that has an adverse event that could possibly related to the RHO program. The clinical study site will permit access to such records.

RHO program participants oximetry data, for the purposes of interpretation with the RHO algorithm, will be transmitted to and stored at the Data Coordinating Center at UMass Medical School. These reports will not include any participant patient specific data or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical study sites and by the Data Coordinating Center research staff will be secured and password protected. Sites will not have access to all data entered into the studies REDCap

database, but will have access to their own site level data. Links with patient identifiers will be kept at individual sites and not shared with the Data Coordinating Center under any circumstances, they will store this information on password protected computers only accessible to study staff at their institutions.

At the end of the study, the study database will be archived for use in future studies which will require a new IRB submission and approval.

27. PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF SUBJECTS

This project is a quality improvement initiative at the individual site level. Each participating center will be implementing the RHO program as their standard of care for weaning infants off oxygen in the outpatient setting. Due to the design of this project, the only confidential information which will be collected is PHI at the site level. To minimize the risk of identification, there will be a separate master list on an Excel spreadsheet that will link the subject to a unique study identification number. Only research staff at an individual site will have access to this number. No PHI will be collected in the study REDCap database.

No patient identifiers will be shared with the data coordinating center at UMMS.

28. COMPENSATION FOR RESEARCH-RELATED INJURY

Where infants being followed by the RHO program are receiving standard of care guidelines at their institution for weaning HOT no funds have been put aside.

29. ECONOMIC BURDEN TO SUBJECTS

Where all clinical visits and oxygen equipment are part of routine care, they will be billed to the parent's or the baby's insurance. Routine care will involve charges being submitted to the insurance company, the parent will be responsible for any deductibles, co-payments, or co-insurance payments that their coverage normally requires.

30. CONSENT PROCESS

This research is a quality improvement initiative at the site level and does not involve no more than minimal risk to patients on HOT. All infants followed by the RHO program will receive the standard of care for weaning HOT at their home institutions. By sharing retrospective NICU variables and information on duration of HOT and adverse events the rights and welfare of patients is not altered in anyway.

This research could not practicably be carried out without the waiver of written informed consent where this is an implementation study on implementation barriers and facilitators across sites. In order to best describe the implementation and long-term generalizability of the RHO program all safety and efficacy data of patients need to be included. If we were to require informed consent this could add bias to the implementation trial's results, impacting the feasibility and generalizability of the program's further dissemination into clinical practice.

Families of infants who will be discharged home on supplemental oxygen will be provided the RHO program's brochure and all their questions regarding the program will be answered by the pediatric pulmonologist or physician responsible for the oxygen management. Additionally, families will be provided the trials fact sheet to review. If families feel that they don't want their infant's data shared as part of the implementation trial they will have the option to opt-out by speaking to the physician.

31. PROCESS TO DOCUMENT CONSENT IN WRITING

Since this study is minimal risk and involves the standard of care treatment there will be no process for documenting written consent.

32. DRUGS OR DEVICES

The Masimo RAD 97 oximeter and Masimo SafetyNET reporting system are cleared under a 510K (K180046 for Masimo RAD 97 and K071047 for Masimo SafetyNET).

Masimo RAD 97's will be distributed as standard of care to all patients by their home care companies. Each home care company will follow their own procedures for service and annual safety checks.

The SafeyNET has been approved and installed by UMass Biomedical Engineering and is regularly serviced and monitored by their department.