Study Title: A randomized controlled trial of respiratory function monitoring during stabilization of preterm infants at birth

Short Title: MONITOR Trial

NCT Number: NCT03256578

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MONITOR TRIAL
(Monitoring Neonatal Resuscitation Trial)

A multi-center randomized controlled trial of respiratory function monitoring during stabilization of preterm infants at birth

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Table of Contents

List of Abbreviations

BPD- Bronchopulmonary Dysplasia
CHOP- Children's Hospital of Philadelphia
CRF- Case Report Form
DR – Delivery Room
DSMB – Data Safety Monitoring Board
CPAP – Continuous Positive Airway Pressure
ET- Endotracheal
ETT – Endotracheal Tube
FiO2 – Fraction of Inspired Oxygen
HUP – Hospital of the University of Pennsylvania
IR- Infant Resuscitation Room
IRB- Institutional Review Board
IPPV- Intermittent Positive Pressure Ventilation
NICU- Neonatal Intensive Care Unit
PEEP – Positive End Expiratory Pressure
PHI – Personal Health Information
PIP – Positive Inspiratory Pressure
PPV – Positive Pressure Ventilation
RFM – Respiratory Function Monitor
SAE – Serious Adverse Event
SAIL – Sustained Aeration of Infant Lungs (Trial)
SI – Sustained Inflation
SpO2 – Saturation Pulse Oximeter Oxygen Saturation
Vte – Expired Tidal Volume
Vti – Inspired Tidal Volume

Study Summary

Title	A randomized controlled trial of respiratory function monitoring during stabilization of preterm infants at birth
Short Title	Monitor Trial (Monitoring Neonatal Resuscitation Trial)
IRB Number	Pending
Protocol Number	Protocol 12.295 v4 21-09-2013
Methodology	Multi-center, non-blinded, randomized controlled trial
Study Duration	Study enrollment is expected to take 3 years, with an additional 6 months for data analysis and manuscript preparation
Study Center(s)	Hospital of the University of Pennsylvania, Philadelphia, United States Children's Hospital of Philadelphia, Philadelphia, United States Leiden University Medical Center, Leiden, the Netherlands Department of Newborn Research, Royal Women's Hospital, Melbourne, Australia Maternal & Children's University Hospital La Fe, Valencia, Spain Neonatal Intensive Care Unit, V.Buzzi Children's Hospital, Milan, Italy Karolinska University Hospital Huddinge, Stockholm, Sweden
Objectives	Primary: To determine whether a visible respiratory function monitor display increases the proportion of PPV inflations performed within a predefined exhaled target tidal volume range of 4 – 8 mls/kg. Secondary: To determine whether visible data and waveforms displayed on an RFM impact other clinical, physiological, and biochemical indicators of ineffective lung aeration.
Number of Subjects	286 infants across 6 sites
Main Inclusion and Exclusion Criteria	Infants will be included in this study if they are (1) between 24 and 27 $^{6/7}$ weeks gestation (2) receiving PPV for resuscitation at birth. Exclusion criteria include (1) a congenital abnormality which might interfere with breathing, (2) RFM not available.
Intervention	In the RFM-visible group, the RFM will record respiratory parameters of all PPV inflations, and the RFM display will be visible to the clinical resuscitation team in addition to routine clinical monitoring.
Reference Group	In the RFM-masked group, the RFM will record respiratory parameters of all PPV inflations, but the RFM display will not be visible to the clinical resuscitation team. Routine clinical monitoring alone will be used during PPV.
Statistical Methodology	The Primary outcome will be analyzed as a comparison of proportion of exhaled tidal volumes 4-8 mls/kg between the RFM-visible and RFM-masked groups. Secondary outcome measures of ineffective lung aeration will be analyzed through mean and proportion comparisons between the RFM-visible and RFM-masked groups.
Safety Evaluations	DSMB data monitoring of the trial will occur over the first month and every 6 months. If the DSMB finds a difference between groups of at least 10% in mortality in the first week of life, the trial will be stopped.
Data and Safety Monitoring Plan	An external DSMB is comprised of three members: a trained neonatologist, a biostatistician, and pediatric oncologist, all with extensive experience in conducting trials. The DSMB will be updated in the progress of the trial every 6 months, or more frequently if necessary.

1. Background and Study Rationale

This study will be conducted in full accordance all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46 and 21 CFR Parts 50, 54, 56.

1.1 Introduction

The transition from the fluid-filled fetal lung to the aerated lung is essential for successful adaptation after birth. Extremely preterm infants have an immature respiratory system and struggle to successfully aerate the lung. Most extremely premature newborns require respiratory support with positive pressure ventilation (PPV) during this transition. However, non-invasive (facemask) PPV is technically challenging to perform. Inadequate (too little) PPV inflation leads to ineffective ventilation and hypoxia, manifested by a lack of prompt rise in heart rate and progression to need for tracheal intubation. Excessive (too large) PPV inflations damage the newborn lung from stretch and pressure injury. Providers have few tools to identify inadequate or excessive PPV inflations. *Current delivery room technology is inadequate to guide PPV inflations delivered to preterm infants.*

This is a randomized trial to determine if a visible respiratory function monitor (RFM) displaying real-time measurements of delivered inflations improves clinical providers' ability to perform PPV within a pre-defined target tidal volume in preterm infants after birth.

1.2 Background and Relevant Literature

Extremely preterm infants often fail to establish efficient gas exchange independently in the delivery room (DR) [1,2] and many receive mask ventilation or tracheal intubation and mechanical ventilation.[3] However, immediately after birth the immature lung is highly vulnerable to injury. [4] As there is increasing evidence that gentle ventilation may reduce lung injury, short- and long-term morbidity, [4-13] more effective non-invasive resuscitation strategies[14] in the DR are required.

Caregivers are guided by international and national neonatal resuscitation guidelines and a face mask is commonly recommended and widely used for initial ventilation after birth.[15,16] A tight seal between mask and face creating a leak free ventilation circuit is important to provide positive end expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) to the transitioning preterm infant.[17] Leak at the mask may contribute to inadequate ventilation or even failure of the resuscitation.[17,17-22] Achieving effective manual ventilation can be difficult [18-22] because most clinicians are not aware when mask leak or airway obstruction occur.[19,23,24] With variable leaks, variable tidal volumes are delivered that may be either inadequate or excessive causing lung injury. This has been described as atelectotrauma, rheotrauma and barotrauma. Moreover, inadequate ventilation may lead to persistently lower oxygen saturations (SpO2) prompting clinicians to increase FiO2. The newly born infant's lung is

susceptible to pro-oxidant mediated inflammation[25] and administration of supplemental oxygen during neonatal resuscitation has recently been revised to reflect this.

Traditionally, adequacy of ventilation during positive pressure ventilation (PPV) in the DR is assessed by adequate chest rise and an increase in heart rate.[26] This contrasts with the assessment of optimal ventilation in the neonatal intensive care unit. Best practice guidelines from experts state that mechanical ventilation should be guided by a continuous display of airway pressure, gas flow, tidal volume (VT) and gas leak at the endotracheal tube (ETT).[20-22]

1.3 Respiratory Function Monitor (RFM)

Recently, it has been demonstrated that the use of a respiratory function monitor (RFM) can guide PPV in the DR.[23,27] In this study, the New Life Box, (Advanced Life Diagnostics, Weener, Germany) a neonatal Respiratory Monitor (RFM), will be used to measure and calculate inflation pressures, flow, and tidal volumes in all enrolled infants. The New Life Box uses a small (dead space 0.7 mL) variable orifice anemometer to measure gas flow in and out of a face-mask or endotracheal tube. This signal is automatically integrated to provide inspired (Vti) and expired (Vte) tidal volume. The difference equals the leak from the facemask or endotracheal tube. Complete airway obstruction occurs when no flow of gas into or away from the infant is seen during a positive pressure inflation. The RFM can also calculate and measure respiratory rate and minute volume, inflations and spontaneous inspirations, and all ventilation pressures. Using customized software heart rate, oxygen saturation and expired carbon dioxide can be integrated into the RFM.

The NewLife Box monitor presents graphical information for pressure, flow, and volume. In addition, the monitor displays numeric data for pressure (PIP and PEEP), tidal volume (Vti, Vte), flow, respiratory rate and percent leak. The monitor integrates and displays physiologic data streaming from the patient (heart rate and oxygen saturation) as well as FiO2 from an oxygen analyzer in the inspiratory limb of the respiratory circuit. If enabled, the monitor can incorporate video captured from an external camera. The video serves as a helpful aid in the interpretation of the events during the RFM waveform recordings.

1.4 Preliminary Clinical Studies of RFM

Kattwinkel et al, showed using a mechanical model of an infant's lung during a simulation of neonatal resuscitation, operators had a faster response to compliance changes if tidal volumes were displayed.[28] Manikin and observational studies have shown that a RFM enabled the clinical team to quickly recognize mask leak, inadequate expired V_t, or airway obstruction. [23,27] In addition, spontaneous breathing in newly born preterm infants is difficult to observe and quantitate and often missed by the clinician leading to unnecessary respiratory support or even intubation.[29] An RFM is very useful for observing and measuring spontaneous breathing.[30]

However, thus far data from large randomized studies on the use of an RFM during neonatal resuscitation are lacking. Schmölzer et al, observed a reduction in mask leak, less excessive tidal volumes and less intubations in a small randomized feasibility trial of RFM versus no RFM during mask ventilation in preterm infants at birth.[31] This study stressed that increasing training and experience in using an RFM may lead to greater benefits. Schilleman et al reported that clinicians in the DR did not use all the information available from RFM, but relied more on traditional clinical parameters.[29]

The use of an RFM in the DR has the potential to improve neonatal respiratory support and reduce lung injury. To prove this, a large randomized trial is needed.

2. Study Objectives

Our hypotheses are that using a RFM during PPV resuscitation of infants at birth will lead to: 1) a lower incidence of large mask leaks, 2) less frequent airway obstruction, 3) more rapid and frequent evaluation and adjustment of mask hold and position, 4) faster recognition of spontaneous breathing, 5) faster recognition of potentially injurious tidal volumes, and 6) more prompt and appropriate adjustment of applied airway pressures. All these effects we speculate will contribute to a more adequate and less injurious delivery of PPV (proportion of tidal volumes within the target range of safe tidal ventilation) and therefore potentially better resuscitation and outcome for the infants.

2.1 Primary Objective

To test the hypothesis that observing the data and waveforms displayed on an RFM during the provision of PPV to preterm infants (24-27 $^{6/7}$ weeks gestation) after birth will increase the proportion of inflations performed with a predefined VTe "safe range" of 4 – 8 mls/kg.

2.2 Secondary Objectives

To determine whether observing the data and waveforms displayed on an RFM impact other longitudinal clinical, physiological, and biochemical indicators of ineffective lung aeration.

3. Investigational Plan

3.1 General Design

This is a multi-center, non-blinded, randomized controlled trial to evaluate whether a visible RFM display increases the proportion of inflations performed with VTe within target range of 4-8 mls/kg in infants born between 24 and 27 $^{6/7}$ weeks gestation receiving PPV for resuscitation after birth.

The New Life Box RFM will be used to record the parameters of all inflations delivered during resuscitation of all enrolled infants. In the RFM-visible group, the information on the RFM display will be visible to clinical providers, while in the RFM-masked group, the RFM display will be masked.

3.2 Screening Phase

The study PI and research coordinator will evaluate maternal admissions to the Labor and Delivery Unit at the Hospital of the University of Pennsylvania (HUP) to preliminarily assess eligibility based on estimated gestational age and maternal labor status. Women with threatened delivery between 24-$27^{6/7}$ weeks gestation will be screened for eligibility. Following the prenatal consult performed by the clinical neonatology team, a member of the study team will approach the mother to offer study participation for the infant and obtain antenatal informed consent (See Ethics, below). This conversation will be coordinated with other ongoing studies of preterm infants (See, Concurrent Enrollment).

3.3 Study Intervention Phase

At time of resuscitation, following birth and randomization, a neonatal Respiratory Monitor (RFM) will be used to measure, calculate and display inflation pressures, flow and tidal volumes. It is standard practice in the HUP NICU to record resuscitations with the RFM masked as part of an ongoing departmental Quality Improvement project.
In infants randomized to the intervention, the clinical team will be able to directly observe the monitor. Those randomized to the RFM-masked display arm will only see a black screen, though the RFM will be collecting data in the background.

Oxygenation and heart rate will be measured with the Philips Intelliview vitals monitor via a pulse oximeter and electrocardiogram monitoring. A pulse oximetry probe will be placed on each infant's right upper extremity. The concentration of inspired oxygen (FiO_2) will be measured with a Teledyne oxygen analyzer inserted into the inspiratory limb of the Neopuff circuit. In centers where it is allowed, a digital video recording of each resuscitation will be made. The video recording will only show the infant and the hands of staff. It will not show the mother, father, obstetrical staff, or obstetric procedures.

All signals measured will be digitized and recorded at 200Hz using the Bicore physiological recording program (a customized neonatal respiratory physiology program) or Spectra physiological recording program (a customized neonatal respiratory physiology program).

3.3.1 Allocation to Interventional Group

Eligible infants born between 24 and $27^{6/7}$ weeks gestation will be randomized to either have the RFM visible or covered. Randomization will occur directly before delivery, so the RFM display can be visible or masked, according to group allocation. Allocation will be stratified by

center and gestational age (24-25 and 26-27 weeks) using variable block (4-8) sizes. Generation of the randomization envelopes will be done centrally for the trial. Concealment of the allocation will be ensured by using opaque sealed envelopes.

In case of multiple births: if two monitors are available each infant will be randomized separately. If only 1 monitor is available and time does not allow using the monitor for both, only the first born will be randomized. If time allows to use the monitor for the first and the following one, both/all infants will be randomized.

Envelopes for each gestational age strata will be stored and available in the infant resuscitation room. The envelope will be opened before birth of the infant by the Neonatal Fellow or Neonatal Attending in charge of the resuscitation, or a member of the study team.

3.4 Primary Endpoint

The **primary endpoint** is the proportion of PPV inflations with VTe between 4-8mL/kg.

3.5 Secondary Endpoints

The **secondary endpoints** include the following:

RFM Outcomes:

- Oximetry data on SpO2 and heart rate in the first 10 minutes from birth.
- Duration of significant mask leak (defined as > 60 %) as a proportion of time face mask was used for PPV.
- Significant airway obstruction (defined as a reduction in flow and volume (< 25th percentile of measured VTe with minimal leak during the inflation and typical flattening of the flow waves and the PIP was unchanged) as a proportion of the time face mask is used for PPV.
- Occurrence of inadequate tidal volume (defined as <4 ml/kg) as a proportion of PPV is given (face mask and intubated).
- Oxygen saturation (SpO2) levels between 3 and 10 minutes.
- FiO2 changes in the first 10 minutes.
- Total amount of pure oxygen given to the patient (oxygen load) in first 10 minutes will be calculated taking into consideration birth weight, tidal volume, respiratory rate, FiO2 and timing of stabilization.

Clinical Outcomes:

- Rates of endotracheal intubation in the first 24 hours after birth.
- The need for circulatory support over first 24 hours (inotropes and fluid boluses).

- Incidence of air leak (pneumothorax, pulmonary interstitial emphysema, or pneumomediastinum) in the first 72 hours, reported by a radiologist masked to the intervention.
- Incidence of abnormal cranial ultrasound findings (i) all intraventricular hemorrhage, (ii) severe – ie. Papile grade III and IV intraventricular hemorrhage, (iii) cystic periventricular leukomalacia before discharge from hospital.
- Duration of endotracheal (ET) ventilation (hours) before discharge from hospital.
- Duration of nasal CPAP (hours) before discharge from hospital.
- Duration of supplemental oxygen therapy (hours) before discharge from hospital.
- Total duration of assisted ventilation (ET, CPAP) in hours before discharge from hospital.
- Incidence of bronchopulmonary dysplasia (BPD) at 36 weeks corrected gestational age defined as the need for supplementary oxygen and/or any form respiratory support. The severity of BPD will be assessed as proposed by Jobe et al.[32] and oxygen reduction test will be performed in case of moderate BPD as described by Walsh et al. [33]
- Neonatal mortality – death in the DR, within a week after birth, before discharge from hospital.
- Composite outcome of death or BPD.
- Retinopathy of prematurity needing treatment.
- Necrotizing enterocolitis grade 2 or more.

4. Study Population and Duration of Participation

4.1 Inclusion Criteria

- Gestational age (GA) 24 – 27 $^{6/7}$ weeks at birth, by best obstetrical estimate
- Receive positive pressure ventilation during delivery room resuscitation

4.2 Exclusion Criteria

- Known major anomalies including that may affect measured cardiorespiratory parameters: congenital diaphragmatic hernia, trachea-oesophageal fistula, cyanotic heart disease, pulmonary hypoplasia
- RFM not available during resuscitation.

4.3 Subject Recruitment

Parents of potentially eligible infants will be approached on an inpatient basis, once admitted to the Labor and Delivery service at HUP. The study team will be made aware of potential parents through communication with the inpatient clinical neonatology team, who perform clinical consults on all admitted pregnant women with threatened preterm delivery.

4.4 Duration of Participation

The intervention will involve monitoring the infant in the resuscitation room following delivery until determined by the clinical team as stable or for the first 15 minutes of resuscitation. The remaining information for this study will be extracted from the participant medical record. There is no follow up involvement after hospital discharge.

4.5 Total Number of Subjects and Sites

There are 6 clinical sites. Recruitment will end when approximately 286 evaluable infants are recruited. At UPenn, we anticipate enrolling 80 infants over 3 years in order to produce 50 evaluable subjects.

The 6 sites include:

1. Hospital of the University of Pennsylvania, Philadelphia, United States
2. Leiden University Medical Center, Leiden, the Netherlands
3. Department of Newborn Research, Royal Women's Hospital, Melbourne, Australia
4. Maternal & Children's University Hospital La Fe, Valencia, Spain
5. Neonatal Intensive Care Unit, V.Buzzi Children's Hospital, Milan, Italy
6. Karolinska University Hospital Huddinge, Stockholm, Sweden

Infant's transferred from HUP to Children's Hospital of Philadelphia (CHOP) for continued medical care before 36 weeks corrected gestational age will have their medical records reviewed for long term outcome data.

4.6 Vulnerable Populations:

This study will enroll neonates, in accordance with HHS regulations 45CFR 46.

5. Study Intervention

5.1 Description

All enrolled infants will have RFM recording performed during delivery room resuscitation. For infants in the RFM-visible group, the RFM display will be visible. For infants in the RFM-masked group, the RFM display will not be visible.

5.2 Subject Encounter: Delivery Room

There is only one subject encounter in this study design: the respiratory function monitoring performed during delivery room stabilization. Data collected to ascertain the secondary outcomes will be obtained from review of the medical record.

The study PI will train the resuscitation team in the use of all equipment. The respiratory therapists specifically will be responsible for ensuring the equipment is correctly set up prior to

use. The RFM (NewLife Box, Advanced Life Diagnostics) will be calibrated and set up prior to delivery. A disposable neonatal flow transducer (Avea neonatal flow sensor, Carefusion, Yorba Linda CA) will be placed in line between the facemask and respiratory device. Resuscitation team members will follow a standard protocol to set up the RFM and initiate recording, which does not require technical expertise. Data files will be labeled with a unique study-specific identifier that does not contain protected information. The monitor itself is user-friendly, and requires only pressing a button to initiate recording.

The RFM has a button that will cause the screen to be black, although the monitor is still recording respiratory function data. Once the randomization envelope is opened, the screen will be either left visible or "blacked out" according to the assigned group allocation.

5.3 Training

Training and increasing experience in RFM may lead to greater benefits.[29,31] To ensure all resuscitators will use a RFM with confidence, adequate training of all personnel involved must precede the trial. The training will take place in each participating center, led by the experts in delivery room recording and use of the RFM monitor.
At HUP, all neonatal providers who perform the "leader" role during infant resuscitation will receive standardized training in RFM waveform and output interpretation.

5.4 Blinding

It is impossible to blind the caregivers to the intervention as the display will be clearly either visible or masked. However, we plan to centralize waveform, data and video analysis from the monitor whereby the individual (PhD student in Leiden) is blinded to the allocation.

5.5 Technique of Resuscitation

Other than allocation of the visible or masked RFM, all other resuscitative measures (e.g. intubation, external cardiac massage, administration of oxygen and other drugs) will be at the discretion of the staff involved, following local standard of care protocols.

The primary equipment used to provide resuscitation will be a T-piece device.

When performing a delivery room trial in multiple centers, different local resuscitation guidelines are inevitable. However, this can be considered as strength of the trial as this could show that using a monitor is useful independent of practiced resuscitation guidelines.

5.6 Discontinuation of Monitoring

The sensors will be removed from the circuit at the following events, whichever occurs first:

- The infant is stabilized on non-invasive support and is transitioned to nasal prong CPAP
- Disconnection of the endotracheal tube for administration of surfactant delivery or connection to the ventilator
- 15 minutes of recording have elapsed
- At the discretion of the resuscitation team leader

After the sensors are removed from the circuit, the New Life Box will recording will be discontinued. The program will automatically save the data file under the study-specific identifier that was entered during the set-up process.

6. Study Procedures

All encounters will take place during the hospitalization. Screening will occur on an antenatal basis, and the study encounter will take place during delivery room resuscitation after birth. All subsequent data will be collected from the patient medical record.

6.1 Screening

Screening will take place on an antenatal basis. Women admitted to the Labor and Delivery floor with threatened preterm delivery between 24-27 $^{6/7}$ weeks will be screened for eligibility. Parents of potentially eligible infants will be approached to offer study participation and obtain informed consent.

6.2 Study Intervention Phase

As noted in Section 5.2, the only study-related intervention is use of the RFM (either blinded or visible) during delivery room resuscitation.

6.3 Data Collection Phase

Secondary outcomes will be collected from the clinical medical record. In the case the infant is transferred to CHOP for care before 36 weeks corrected gestational age, the CHOP medical record will be reviewed for long term data.

6.4 Subject Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator due to changes in clinical status that make them ineligible for the study (ie, congenital anomaly diagnosed, or PPV not given during resuscitation). The Investigator may also withdraw subjects after enrollment if data is found to be incomplete or poor quality after the delivery room encounter.

If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the CRF.

Statistics on the number of subjects who are withdrawn and the reason for withdrawal will be maintained to account for all enrolled subjects.

6.5 Safety Evaluations

In accordance with University of Pennsylvania Research Policies and Procedures, Federal and State Laws and Regulations, and section 10, subsection 1, of the Dutch WMO, the investigator will inform the subjects' parents or caregivers and the reviewing accredited IRB if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited IRB, except insofar as suspension would jeopardize the subjects' health. The investigator will ensure that all subjects' parents or caregivers are kept informed.

7. Statistical Plan

7.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive statistics (including mean and standard deviation for continuous variables, such as birth weight and standard percentages for dichotomous variables such as sex)

7.2 Primary and Secondary Outcomes

The Primary outcome will be analyzed as a comparison of proportion of tidal volumes within the predefined safe range (4-8 mls/kg) between the RFM exposed and RFM masked groups using Chi square test.

Secondary outcome measures of ineffective lung aeration will be analyzed through mean and proportion comparisons between the RFM exposed and RFM masked groups.

7.3 Sample Size and Power Determination

There are few data available to estimate possible improvements when a RFM is used. Only one small feasibility study (from Melbourne, one of the participating centers) is available where median mask leak decreased from 54 (37-82) % to 37 (21-54) % when a monitor was used, PIP was adjusted more often (42 % vs 9%), mask was repositioned more often (73 vs 26%) and less infants had Vte > 8 mL/kg (20% reduction). It is likely that less mask leak and pressure adjustment led to more efficient respiratory support and this explains why less infants < 32

weeks of gestation needed intubation in the delivery room in the group where the RFM was visible (21 % vs 57 %; p = 0.035).[31] In addition, Wood et al, showed, in a manikin study, that mask leak was halved when a RFM was used during mask ventilation. [23]

The primary outcome will be the proportion of tidal volumes within the target range (4 - 8 ml/kg). This will be calculated as the proportion of adequate tidal volume of the total amount of inflations per infant. The duration of PPV provided will vary between infants and this may be a source of bias. To minimize this, we will take the proportion of adequate tidal volume as a percentage of the total amount of inflations per infant.

About 60 infants <28 weeks of gestation are born a year in each neonatal center. Almost all infants receive PPV at birth. Currently the median (IQR) proportion of adequate tidal volumes given to infants during PPV at birth is 25% (5%-45%) (based on recordings in Leiden). Therefore, we calculated to detect an 40% absolute increase in proportion of adequate tidal volumes (corresponding to an increase from 25% to 35%) with a power of 80% and an α error of 5% (two tailed test), 143 infants are required for each arm.

With 6 centers participating and on average 50 infants < 28 weeks gestation per year per center and taking into account (based on previous delivery room trials using waiver of consent) an estimated 20% of denials for consent, missed eligible patients, problems with equipment, we will be able to recruit 286 infants in 18-36 months. We expect that the data entry, analysis and writing of the manuscript will take another 6-12 months.

The incidence of intubation is not an appropriate outcome for calculating sample power in this trial because the decision is often based on local protocols rather than clinical need. The need for intubation in the group blinded to the RFM in the Schmoelzer study was unusually high in that small trial and does not reflect the experience in other centers who may have a higher threshold for intubation. In addition, it will be difficult to reach consensus between the participating centers as different intubation criteria are currently used.

8. Safety and Adverse Events

8.1 Definitions

8.1.1 Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. All adverse events observed by the investigator or his staff will be recorded.

8.1.2 Serious Adverse Event

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events.

8.2 Recording of Adverse Events

Adverse events and their relationship to study, severity, time of experience, expectation, actions taken to resolve the event and final outcome will be recorded as documented in the medical record, or if reported by the NICU team even before documentation.
Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF).

All adverse events occurring in the infant resuscitation room will be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study participation is not the cause

8.3 Relationship of AE to Study

The extremely preterm subjects in this study will each experience expected and unexpected adverse events. Many extremely preterm infants experience serious adverse events, such as death or life-threatening events, based on their underlying prematurity.

However, because of the high acuity of subjects during delivery room stabilization, adverse events will be monitored during the study to ensure timely detection of events that may affect safety. Specifically, all adverse events (serious or non-serious) that occur in the delivery room setting will be assessed and recorded. The local study investigator will determine the relationship between study procedure and adverse events that occur in the delivery room (definitely related, probably related, possibly related, unlikely or unrelated).

Of note: because need for positive pressure after birth is an inclusion criteria for this study, respiratory failure requiring PPV or endotracheal intubation after birth will not be considered an adverse event.

Events that occur once the baby is transferred to the NICU are unlikely to have resulted from the use of the RFM during delivery room stabilization. Adverse outcomes related to extreme prematurity may occur during the NICU hospital stay and are pre-defined secondary outcomes in this study (see Secondary Endpoints, Section 3.2.2). These outcomes will not be reported on

an individual basis, but they will be analyzed by the DSMB every 6 months to assess whether there are significant imbalances between study groups with regards to these outcomes.

8.4 Reporting of Adverse Events, Adverse Device Effects and Unanticipated Problems

Investigators will submit reports of the following problems within 24 hours from the time the investigator becomes aware of the event: Any serious adverse event that occurs any time during or after the research study, which in the opinion of the principal investigator is: Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information) AND Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

Reporting Process

Unanticipated problems posing risks to subjects or others as noted above will be reported to the Penn IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file as well as forwarded to the Coordinating site in Leiden.

8.4.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information will be submitted to the IRB.

8.4.2 Investigator Reporting: Notifying the Penn IRB

The UPenn site PI will report all reportable adverse events to the Penn IRB in accordance with the Penn IRB definition of reportable events and reporting timelines. Documentation of all reported events and any associated decisions made by the IRB will be forwarded to the lead clinical site and coordinating PI in Leiden.
Investigators at other sites will be responsible for safety reporting to their local IRBs.

8.5 Data and Safety Monitoring Plan

The trial has an external Data Safety and Monitoring Board, chaired by Dr. Anton van Kaam. The DSMB charter details the frequency of DSMB meetings, specified analyses and stopping rules, and specific roles of the DSMB.

Interim analysis September-October 2017

A pre-planned interim analysis of the Monitor trial was performed after 50% of inclusions with primary outcome data were available. The investigator and the statistician involved in the trial collected and performed the analysis blinded for the groups. The results were submitted to the DSMB on the 25th of October 2017. The results showed no safety concerns, but also no difference in primary outcome (proportion of tidal volume delivered between 4-8 mL/kg) with a p value of 0.96. Since this met the criterion of the pre-defined stopping rule in futility (p-value > 0.90), the DSMB recommended to stop the trial on November 14, 2017.

The recommendation was immediately communicated with all principal investigators of the sites participating in the trial and the recruitment was temporarily halted. A Steering Committee conference call was held to discuss the recommendation on November 28, 2017. All investigators agreed to continue the trial and reach full recruitment, based on the following:

- At the time the recommendation of the DSMB became available, the recruitment rate was already at 75%. Collecting the data for the primary outcome was a time-consuming process as the analysis of the respiratory function needed to be performed manually.
- The presence of a learning curve in using the monitor was proposed and continuing recruitment will increase the chance of observing chances in performance as centers gain experience.
- There is no evidence of safety concerns

Given this, all members of the Steering Committee agreed continue enrollment to reach the original goal enrollment, anticipated by the end of 2018.

This decision was endorsed by the DSMB.

9. Study Administration, Data Handling, and Record Keeping

9.1 Confidentiality

All research team members at UPenn are CITI Human Subject Protection and Good Clinical Practice certified, as a requirement of their participation in any study. The basic rights of study participants will be respected and maintained by the investigators and by all who are involved in the collection or processing of individually identified data. All data collection and processing procedures are designed to protect individual rights and to comply with all applicable laws and ethical principles including confidentiality. Among the rights that must be protected are:

- the right to informed consent, which requires that prospective participants in a research project and, if needed, their family members, be provided adequate information about the potential risks, benefits, and requirements of participation so that each can make an informed decision about participation
- the right to decline, which requires that prospective participants be fully informed that their participation is completely voluntary, that they may withdraw at any time, that access to adequate health care will be provided whether or not they participate in the research, and that they may refuse to answer any question
- the right to privacy, which requires guarantees of confidentiality of information and other specific protection as specified in the Privacy Act of 1974.

The basic rights of study participants will be respected and maintained by the investigators and by all who are involved in the collection or processing of individually identified data. Our data collection and processing procedures are designed to protect individual rights and to comply with all applicable laws and ethical principles.

The data collection forms will include unique study ID numbers only and basic demographic data as participant identifiers. Thus, the files maintained will contain limited identifying information and protect subject confidentiality. Safeguards are in place to greatly decrease the chances that characteristics of a case can be linked to the individual participating in the study. Access to direct identifiers will be limited to staff who meet all relevant training requirements and are assigned to (or support) this project, and who must have access to these identifiers for purposes of quality control and monitoring. All other persons, including statisticians and investigators will be blinded to identifiers until such time as for reasons of safety or clinical care, those identifiers must be shared. All data with identifiers will be stored on firewall-protected secure servers.

9.2 Data and Device Collection, Storage, and Management

9.2.1 Storage of the RFM

The RFM is locked and secured in the restricted-access infant resuscitation room (IR). The RFM is clearly labeled for 'RESEARCH USE ONLY' and contact information for the PI and study team are provided. The RFM is routinely checked by clinical engineering and ongoing updates and software checks are performed by the study team and the developers in Leiden, Netherlands.

9.2.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays,

subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.2.3 Video Recordings

Video recordings are standardly made during newborn resuscitations for quality improvement and audit, educational, and research purposes. Video recordings are used as quality assurance during the data processing for the RFM. The video recordings are used and viewed by the Neonatology Department for QI purposes, and according to hospital policy, must be deleted after 30 days unless a release is provided. In this study, video files provide a method to clearly identify actions such as mask repositioning or spontaneous breathing, and they improve interpretation of respiratory waveforms under these conditions. Parents of enrolled participants will be provided the option to give their permission for the use of the video recording of their infant's resuscitation for research purposes. If permission is obtained, the videos will be labeled with the study identifier and the video recordings will be securely transferred onto the computer of the PI. They will be maintained on a password protected computer on the secure HUP server in a locked office. Following 30 days, only study staff at HUP and at Leiden will have the ability to access and view the video recordings. The videos will be securely transferred with the RFM files to the coordinating site in Leiden through a secure file transfer protocol. Once all the RFM data records have been reviewed and analyzed, the video recordings will be deleted.

9.2.4 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. Each study subject will be assigned a unique study identifier. The study coordinator will keep a master list that links the identifiable information (MRN) with the study identifier. All case report forms will only contain the unique study ID.

The master list will be securely stored on a password protected file on a secure server in the locked office of the study coordinator.

9.2.5 Data Management

Data concerning eligibility, randomization, basic characteristics, delivery room management, parameters from the recordings and outcome parameters will be collected according to the CRF forms. The coordinating site will use a secured web based database (proMISe) to manage the collaborative data.

When infants are eligible, but not randomized or excluded afterwards, only the screening CRF concerning eligibility and randomization will be completed.

Individual patient RFM data will be stored on a secure server on a password protected computer accessible to the HUP study team. The data will be centrally managed at the University of Leiden. At regular intervals the collected RFM data, with identifiers removed, will be securely sent to the PhD candidate in Leiden for analysis. The analysis will be supervised by Arjan te Pas. Support for data management and statistical analysis will be provided by the study statistician.

9.3 Records Retention

The study team will retain study essential documents for at least 3 years after publication of study findings.

10. Ethical Considerations

This study is to be conducted accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

10.1 Risks

This is a minimal risk study. It is standard practice in the HUP NICU to record infant data with the RFM masked for all infants less than 32 weeks with the RFM monitor. This is part of a department quality improvement initiative (IRB reviewed INTRO QI initiative).

The Avea neonatal flow sensors (Carefusion) added in line are FDA-approved for clinical use. The potential risks include minimal added dead space to the respiratory circuit with the sensors in place (approximately 0.7mL of dead space). This is not considered to be a significant addition to potential dead space in the circuit, after considering the existing respiratory tubing and facemask. Previous published studies of RFM have not reported adverse events due to the sensors' presence.

All other physiologic monitoring will be obtained using the current standard-of-care sensors (ie, heart rate, respiratory rate, and pulse oximetry). Data from all of these sensors will be collected and recorded by the New Life Box Respiratory Function Monitor. The New Life Box is

a research tool with FCC conformity that integrates and records data streaming from multiple data sources.

We do not yet know the optimal information that should be presented to clinicians to improve clinical care and therefore there is the potential that viewing the RFM could alter the care of the clinical team within the scope of standard care practices. Previous studies of RFM use in the clinical environment have not described adverse effects on the resuscitation team's performance from using the RFM. However, the resuscitation team leader can turn off the RFM display at any point during the resuscitation if s/he is concerned about the impact of the RFM on the resuscitation (See Section 5.6, Discontinuation of Monitoring).

Investigational devices that carry significant risk must have an investigational device exemption (IDE) filed prior to initiation of clinical studies. Research involving non-significant risk devices is subject to approval by appropriate IRBs but does not require an IDE prior to initiation of the research. Because the NewLifeBox is a non-significant risk device, we will not seek an IDE, based on The Federal Drug Administration Code of Federal Regulations: CFR Title 21, Section 812.3.

10.2 Risk Benefit Assessment

Potential direct benefits to the subjects with the RFM screen visible include the potential for higher proportion of PPV inflations delivered within a pre-specified "safe" VTe range. The indirect benefit of study participation is the contributing to the scientific knowledge for future preterm infants. The study outlined in this proposal will generate important knowledge about the respiratory characteristics associated with lung aeration in extremely preterm infants. Given that the risks of the study are minimal and the potential benefits to future infants, it is reasonable to proceed with the project.

10.3 Informed Consent Process / HIPAA Authorization

Prior to delivery, the PI or study coordinator will obtain antenatal consent and HIPAA authorization from the parents of potentially eligible infants. The consent process will take place in a private room. Following the consent discussion, a copy of the consent form will be provided to the parents, and they will have the opportunity to review the form before providing consent.

10.3.1 Co-Enrollment

There is potential for co-enrollment with other delivery room studies that require antenatal consent. The Monitor study team will communicate with other neonatal study teams to ensure that consent discussions are coordinated among all investigators, in order to reduce the parental burden.

Co-enrollment with other interventional trials, including Neonatal Network trials, will be reviewed and approved by the appropriate concurrent research committees and Monitor trial coordinating PI.

Of note, this study will co-enroll some infants who are enrolled in the ongoing SAIL (Sustained Aeration of Infant Lungs) trial. The SAIL trial Executive committee has approved co-enrollment for the SAIL and Monitor trials.

10.4 Waiver of assent

As the subjects are infants, assent will not be obtained.

10.5 Funding Source

There is no external funding source or study sponsor. Dr. Foglia currently has 75% of her time protected for research, has already obtained the RFM that will be used for this study, and has grant funds to cover the cost of RFM sensors and equipment. Thus, there are sufficient resources to start this study.

10.6 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

10.7 Subject Payments

No payments or gifts will be made to families or subjects for participation in this study.

10.8 Publication Plan

Research results will be made available to the scientific community and public in a timely manner. The primary method by which data are shared with the scientific community is through peer-reviewed publications and presentation at meetings.

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