# *Comparison of Aerosol Delivery of Infasurf to Usual Care in Spontaneously Breathing RDS Patients*.

**Executive Summary:**

Rationale: Surfactant replacement therapy can be life saving for newborn infants born with symptomatic lung surfactant deficiency causing Respiratory Distress Syndrome (RDS). Currently such therapy requires instillation of a liquid suspension into the trachea through an endotracheal tube. Prolonged endotracheal intubation or repeated re-intubations have undesirable adverse effects on fragile premature infants. Instilling surfactant as liquid suspension into the lung is associated with adverse events due to interruption of breathing in patients who already have respiratory insufficiency. Effective aerosol delivery of Infasurf to such patients could decrease the incidence and length of endotracheal intubation and decrease the incidence and severity of adverse events during surfactant administration.
Design: This prospective, randomized, multicenter, unblinded clinical trial will compare "usual care" to aerosolized Infasurf. The study objective is to document that aerosolized Infasurf is superior to "usual care" and provides for some patients effective surfactant therapy with less need for endotracheal intubation and instillation of a surfactant suspension into the airway. Two cohorts will be recruited: (a) patients who did not receive surfactant at birth who develop RDS in the first hours of life and (b) patients who received instillation of surfactant for RDS in the first hour of life, were extubated, and have continuing RDS.

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## 1. GENERAL INFORMATION

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**1.1 Study Title** *Comparison of Aerosol Infasurf to Usual Care for Respiratory Distress Syndrome (RDS)*

**1.2 Protocol Number** Aero-02

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Chair Data Monitoring and Safety Committee: Douglas Willson, MD,
Professor of Pediatrics (critical care) Medical College of Richmond

**1.6 Principal Investigators:** To be selected

**1.7 Description**

This is a pivotal clinical trial to determine whether Infasurf aerosolized into the oropharynx using a Solarys® aerosol generator adapted for neonatal use is superior to "usual care" for non-intubated, spontaneously breathing patients with mild RDS. This alternative method of delivery may benefit some patients by supplying sufficient Infasurf to avoid endotracheal intubation and intratracheal instillation of a surfactant suspension. Patients who have not received surfactant in the first hour of age and patients who received intratracheal surfactant in the first hour after birth but were subsequently extubated will be eligible to participate. Treatment will not be masked. All data will be extracted from the medical record for the first 28 days of life or until hospital discharge, whichever occurs first.

## 2. BACKGROUND INFORMATION

### 2.1 Test Drug & Test Device

Infasurf® (calfactant) Intratracheal Suspension for intratracheal use only is an FDA approved drug for the prevention and treatment of the Respiratory Distress Syndrome (RDS). It has no contraindications. It has no identified toxicity. Administration of Infasurf is associated with occasional complications of cyanosis, alterations in heart rate and blood pressure, airway obstruction and reflux of the surfactant. Currently, administration of Infasurf requires endotracheal intubation for intratracheal instillation.

The Solarys® aerosol generator is an FDA approved medical device for delivery of aerosolized drugs to the lungs of intubated patients. The proximal tip of the device has been imbedded in a pacifier shaped adaptation so the Infasurf aerosol can be delivered into the oropharynx and not into the respiratory support air flow at the nares.

### 2.2 Preclinical

Studies have been conducted in surfactant deficient premature lambs in which Infasurf has been aerosolized, rather than instilled, into the lung through the endotracheal tube. In some lambs, those with moderate respiratory dysfunction, the aerosolized Infasurf was able to significantly improve respiratory function. Premature lambs with RDS do not spontaneously breathe.

Additional studies have been done in full term, healthy newborn lambs in which the aerosolized Infasurf was delivered into the upper airway above the larynx. No physiologic benefit was observed (the animals were healthy) but a sufficient fraction of the Infasurf was inhaled into the lung to predict a positive beneficial effect in symptomatic individuals. These animal studies have not yet been presented at scientific meetings or published.

### 2.3 Potential Risks

It is possible that some patients will have their respiratory status worsen when aerosolized Infasurf is administered because of physical interference with ventilation. Constant, direct monitoring of the patients by health care professionals during the aerosolization is included in the protocol so that such events will be immediately recognized, the aerosolization discontinued and appropriate interventions immediately implemented to restore optimal breathing. Pilot studies of over 30 patients resulted in no patient developing interference with breathing that required discontinuation of the aerosolization.

Infasurf is unchanged in any way by aerosolization. Aerosolized Infasurf deposits only in the lung (the site of its activity) or in the stomach. There are no additional risks from Infasurf delivered as an aerosol than there are from Infasurf when instilled into the lung.

**2.4 Potential Benefits**

Successful administration of Infasurf by aerosolization will provide two important benefits for patients. (1) Endotracheal intubation (or endotracheal re-intubation) may be able to be avoided in some patients, and (2) the adverse events at instillation due to filling the airway with liquid and interrupting breathing may be diminished or abolished.

**2.5 Justification**

The dose aerosolized will be up to twice the dose currently instilled which is 3 ml/kg body weight (105 mg phospholipid/kg body weight). Liquid Instillation delivers to the interior lung an amount of Infasurf that is approximately twice the amount of lung surfactant normally present in healthy newborn animals and 12 times the amount in healthy adults.[1] Thus, if at least 10% of the dose of 210 mg/kg body weight aerosolized Infasurf migrates to the deep lung it is expected the patient will become surfactant sufficient.

Repeat dosing will be administered if a positive effect was observed followed by subsequent deterioration of respiratory status. If a patient does not respond with sufficient benefit to the aerosolized Infasurf the attending physician can remove the patient from the aerosol trial and administer instilled Infasurf or other approved surfactant.

**2.6 Compliance**

The study will be conducted in compliance with Good Clinical Practices.

**2.7 Study Population**

Patients will be recruited who:

(a) have a clinical diagnosis of RDS,
(b) are receiving respiratory support: supplemental oxygen plus (a) nasal continuous positive airway pressure (NCPAP), or high flow nasal cannula (HFNC) or non-invasive ventilation (NIV) to assist breathing
(c) are not intubated and receiving mechanical ventilation for respiratory failure.

## 3. OBJECTIVES AND PURPOSES OF THE TRIAL

For newborn infants born with a deficiency in lung surfactant because of prematurity or other causes of delayed lung maturation lung surfactant replacement therapy is life saving.[2,3,4] The objective of this trial is to demonstrate that there is a group of patients who can benefit from surfactant replacement therapy with lower risk of administration complications and less discomfort by utilizing an alternative, safer administration technique – aerosolization.

Currently surfactant replacement therapy requires instillation of a liquid suspension into the airways. In order to instill into the airways it is necessary that an endotracheal tube be inserted and the surfactant administered through the endotracheal tube. A single dose may not be sufficient therapy and, if repeat dosing is likely or inevitable, a decision has to be made to either prolong the time of intubation or to remove the tube and possibly subject the patient to re-

intubation. One purpose of this trial is to determine if aerosolizing Infasurf provides an effective alternative for some patients that enable delivery of surfactant replacement therapy without subjecting them to the pain, discomfort and risk of endotracheal intubation or re-intubation.

The volume of the liquid instillation of the currently approved surfactants (2.5 to 4.0 mL/kg body weight) is larger than the total volume of the airways below the trachea which is 1 ml/kg body weight. Complications at administration are the physiologic consequences of two processes: (a) liquid obstruction of some airways, and (b) stimulation of irritant receptors in the lung. Liquid obstruction can produce transient low blood oxygen and high blood carbon dioxide, which together with neurally mediated irritant reflexes result in transient cardiopulmonary dysfunctions: cyanosis, tachycardia, bradycardia, hypotension, hypertension, airway obstruction and reflux of surfactant. Aerosolized delivery has the potential of minimizing both airway obstruction by liquid and the stimulation of irritant receptors in the lung.

Specifically the Objectives of the Trial are:

(a) Document superiority of aerosolized of Infasurf to usual care in early RDS in preventing the need to intubate and instill a liquid surfactant suspension into the patient.

(b) Show acute improvement in respiratory function by aerosolized Infasurf.

(c) Document that aerosolized Infasurf is as safe as "usual care" for RDS patients.

## 4. TRIAL DESIGN

### 4.1 Efficacy endpoints

The primary efficacy endpoint will be the incidence of the requirement for endotracheal intubation and instillation surfactant to "usual care" over 72 hours, the time course for acute RDS.

Secondary efficacy endpoints will measure other clinical parameters that are indicative of lung surfactant sufficiency:

(a) Incidence of death and/or bronchopulmonary dysplasia (defined as an oxygen requirement to maintain acceptable blood oxygen saturations) at 28 days or discharge, whichever comes first.

(a) Severity of acute RDS measured by quantitation of oxygen supplementation and respiratory support from randomization to 72 hours of age or intubation and surfactant instillation, whichever comes first.

b) Duration of acute RDS measured by duration of supplemental oxygen.

c) Protection from acute lung injury as measured by the incidence of lung air leaks or pulmonary hemorrhage from randomization to 72 hours of age or intubation and surfactant instillation.

### 4.2 Trial Design

This will be a prospective, randomized unmasked study comparing Infasurf aerosolization to "usual care." There will be a 1:1 patient assignment to each group.

### 4.3 Bias avoidance

Randomization codes predetermined using small, but variable, blocks to assure that each site will have approximately a 1:1 ratio of aerosolized and usual care participants. The study will be unblinded because it is impossible to blind staff to aerosolization of Infasurf. Visual evidence of Infasurf administration is obvious to all care givers both during and after the therapy. Also it is not ethically justified to subject the "usual care" group of fragile NICU patients with RDS to aerosolization with a saline placebo when there is only the potential for complications and none for benefit.

**4.4 Trial Product**

Infasurf (calfactant) is an FDA approved surfactant replacement drug. Repeated testing documents that aerosolization produces no change in its composition, biophysical or biologic activity.[5] Aerosolization utilizes a Solarys® disposable nebulizer FDA approved for human use in patients on mechanical ventilation. The device has been modified so that the distal end is imbedded in a "pacifier like" modification that insures the tip cannot be obstructed by oral tissues and protects the oral tissues from abrasion by the tip of the device. The Infasurf is aerosolized into the oropharynx in micro-droplets of 3 to 100 microns diameter rather than into the bias flow at the nose.

**4.5 Duration**

Patients are eligible for randomization to aerosolized Infasurf therapy or "usual care" to 12 hours of age if not treated with instilled surfactant in the first hour of life; or to 24 hours of age if treated with instilled surfactant at birth (≤1 hour of age). Aerosolized patients may receive up to 3 aerosol treatments. For the "Usual Care" there is no "participation" in any intervention only extraction of data from medical record.

Data will be extracted from the medical record until day 28 of life or discharge from the hospital, whichever occurs first.

No long term follow-up is planned for this study. No long term harm has been identified in the pivotal studies used for regulatory approval of any surfactant.[2, 3, 4]

**4.6 Stopping Rules**

**Individuals:** Aerosolization will require the usual bedside monitoring by NICU devices and personnel appropriate for all patients in the first hours of life with significant respiratory difficulty. Any patient, who in the judgment of the clinical care team, is experiencing an adverse event due to the aerosolization will have it stopped and not restarted. Taking appropriate remedial steps to resolve an adverse event will be the responsibility of the patient's clinical care team. The patient will not receive additional aerosol therapy if dosing is discontinued due to an adverse event.

**Sites**. Following an adverse event resulting in discontinuation of aerosol therapy, recruitment by that site will automatically be suspended.

The Principal Investigator (or a co-investigator) will notify the sponsor within 24 hours of the adverse event. The Sponsor will notify the Study Chair and the Chair of the Data Monitoring and Safety Committee (DMSC) within 24 hours of receiving notification.

The site will not re-start recruiting to the study until the site P.I., the Study Chair and the Sponsor decide that appropriate remediation, if necessary, has been achieved.

Any adverse event during aerosolization will be reviewed by the NICU Medical Director at the site within 24 hours of occurrence. S(he) shall contact and consult with the Study Site P.I. and after that review either allow the study to continue recruiting or suspend the study. In either case the local IRB and the Medical Director of the Sponsor will be notified within 24 hours. If the study is suspended it will not be restarted until the NICU medical director, the site P.I., the local IRB, and the Sponsor have all approved the decision to restart the trial at that site.

In addition, if the study is suspended at any one site the Sponsor will notify the P.I. at all other participating sites and the national and all local IRBs. Any local IRB, site P.I. or the Sponsor can suspend the study at any or all of the other participating sites. If suspended at other sites restarting will require prior approval by the local IRB and P.I. and the Sponsor.

**Entire Trial:** The Study Chairman, the DSMB chair and the Sponsor will confer upon receiving notification of any adverse event resulting in discontinuation of aerosol therapy with 24 hours. If any one of the three judges that the welfare of patients is best served by suspending recruitment to the trial the Sponsor shall immediately notify all the sites that recruitment for the study has been suspended and the reason for the suspension.

Within 5 days the Principal Investigator of the site where the adverse event occurred will submit a full description of the adverse event along with relevant data from the patient's medical record. The PI will provide an assessment and recommendations with the summary and the data.

Upon receipt of report from the site PI the Study Chair and the DMSC shall separately review the communication from the site P.I. The Study Chair and the Chair of the DMSC will hold a teleconference to reach a consensus to advise the Sponsor to:
(a) Stop the trial for the safety of patients.
(b) Suspend the trial until the cause of the adverse event is identified and remedied.
(c) Suspend the trial at the site of the adverse event only until a cause is remedied.
(d) Restart the trial at the site and continue the trial at the other sites.

**4.7 Infasurf + Solarys Accounting**

Infasurf used in this trial will be identical to current FDA approved Infasurf but provided in a larger vial. Storage of the product will require refrigeration but not masking of product identity. The vials will have a label that allows the study number of the patient (determined by the randomization assignment) and the data of administration to be entered at use.

The Solarys aerosolization device modified for delivery to non-intubated premature infants will be provided packaged with the Infasurf. Each unit will have a label on it packaging with a unique ID number and a space for entering the date and patient ID number when used.

Used vials and devices will be retained after administration by each site and returned to the Sponsor. Unused vial-device units will be returned to the Sponsor at the end of the trial. Reconciliation of vial-device units will be done by the Sponsor.

**4.8 Randomization Codes**

Each participating site will be provided a separate sequential randomization code in opaque envelopes. The blocks will be small but the size of the blocks will be confidential so investigators cannot predict assignment. Patient assignment will be to the study arm indicated by the next envelope in sequence opened after consent is obtained. The study sponsor will generate the randomization code for each site using the Moses-Oakford algorithm.[6]

**4.9 Data Sources**

All data will be extracted from the medical record. At the time of administration an entry will be made into the progress notes of all patients who received aerosol that includes the information required to complete the form in Appendix A. This protocol requires no study specific evaluation, testing or monitoring of the patients.

## 5. SELECTION AND WITHDRAWAL OF SUBJECTS

**5.1 Inclusion criteria**

Cohort 1: RDS Patients Who Did Not Have Early Surfactant Instillation
1) NICU patient, ≥1hour of age and <12 hours of age.
2) Clinical diagnosis of RDS, with or without chest X-ray data.
3) Inspired oxygen ≥25% and ≤40% to maintain adequate oxygen saturation.
4) Not intubated
5) Requiring: (a) nasal continuous positive airway pressure (nCPAP), or
(b) high flow nasal cannula (≥2L/kg/min) (HFNC), or
(c) non-invasive ventilation**.**

Cohort 2: RDS Patients Post Early Surfactant Instillation

1) NICU patient <24 hours of age.
2) Intubated, given instilled surfactant at ≤ 1hours of age, then extubated within 6 hours.
3) Inspired oxygen ≥25 and ≤40 % to maintain adequate oxygen saturation.
4) Not intubated.
5) Requiring: (a) nasal continuous positive airway pressure (nCPAP),or
   (b) high flow nasal cannula (≥2 L/kg/min) (HFNC), or
   (c) non-invasive ventilation.
6) Increasing in $FiO_2$ and/or respiratory support for ≥ 1 hour.

**5.2 Exclusion criteria**

1) Congenital anomaly limiting care options or requiring early surgery.
2) Cardiopulmonary decompensation.
   a) hypotension with metabolic acidosis (base excess < -10 meq/l).
   b) Oxygen saturations < 88% at start of aerosolization.
   c) $PaCO_2$ ≥ 60 mmHg at start of aerosolization.
3) Grade 3 or Grade 4 intraventricular hemorrhage by cranial ultrasound, if known.
4) Acute hypoxic encephalopathy with or without seizures.

**5.3 Subject withdrawal**

1) A patient's attending physician can withdraw the patient at any time if (s)he decides that continuation in the study poses a risk for the patient.
2) If a parent rescinds permission a patient's participation in aerosol therapy ceases.
3) If there is an adverse event requiring discontinuation of the aerosolization administration the patient will be withdrawn from further study interventions.

Patients withdrawn by physicians or because of an adverse event will continue to have all data extracted from the medical records and included in safety evaluations.

Patients withdrawn by parent request will have all data collected from the medical record both before and after withdrawal from active participation in the trial. The provision for continued data collection is explicit in the informed consent and that data is necessary to have inclusive data on safety.

**6. TREATMENT OF SUBJECTS**

**6.1 Aerosolization of Infasurf**

The aerosol is generated using a Solarys® Aerosol Delivery system adapted for premature newborns. The distal tip of a catheter is fixed to a proprietary adapter for premature and term infants with RDS. The adapter has a shape similar to a neonatal pacifier. The nipple tip is actually an inverted dome that prevents the cannula tip from being obstructed by oral or pharyngeal tissues and protects delicate tissues from abrasion by the tip of the cannula. The distal tip exits just a few millimeters from the end of inverted tip of the "nipple" and delivers the aerosol into oropharynx. A fine aerosol mist is produced at the end of the catheter. A schematic of the set-up is in Appendix C.

Newborns are obligate nose breathers. Typically, non-intubated RDS patients have a ≥3 liter/kg/minute flow of gas passing by the nose under a positive pressure. The baby inhales from, and exhales into, that flow. Newborn babies with RDS have tachypnea, ~ 60 breaths/minute, and have low tidal volumes, ~ 5 mL/kg/ breath. Less than 10% of the nasally delivered respiratory support is inhaled. The aerosol is generated in the oropharynx so when the baby inhales aerosol is drawn into the lung. When the baby exhales, some of the aerosol is exhaled, but some remains in the lungs and supplements the surfactant already there.

The Solarys aerosol works by slowly propelling the Infasurf suspension down a small central tube in the Solarys system at a rate of approximately 0.19 ml/minute. Simultaneously an air-oxygen mixture (set by the baby's respiratory needs) is propelled down 5 tiny tubules surrounding the liquid filled tube at a rate of ~0.9 liter/minute. As the liquid exits the distal end of the central tube the gas exiting from the surrounding tubules generates the aerosol mist.

Dose: A dose equal to twice the current instilled dose 210 mg/kg body weight (6 ml/kg body weight) will be aerosolized. That will require approximately 32 minutes/kg body weight. Lung deposition of aerosol is small, usually less than 25% of the dose so even an aerosol of 6 ml/kg body weight will result in a much lower lung delivered dose than the current practice of instillation of 105 mg/kg/dose.

Re-dosing: Up to 2 re-dosings are allowed once 4 hours has passed since the start of the last dose. The indication for re-dosing will be:
1) a positive response to the previous dose, defined as improvement in respiratory function, and
2) a subsequent deterioration in respiratory function, and
3) no adverse event during the initial dose.

Usual Care: There will be no protocol driven interventions in the usual care group. Use of pacifiers as tolerated in these patients is encouraged to decrease the incidence of loss of continuous airway pressure through the mouth.

Sham therapy has not been included because it cannot produce an effective masking of treatment assignment to care givers because of both the presence of residual Infasurf in the mouth and stomach and there is a reliable decrease in inspired oxygen requirement by the end of aerosolized Infasurf therapy.

Separation of the effect of additional gas infusion derived from aerosolized Infasurf effect by sham treatment is unnecessary. Pressure in the airway is set by the nasal therapy and that therapy will be adjusted, if necessary, to maintain the airway pressure ordered by the supervising provider. The tidal volume of spontaneous breathing participants is affected only by the airway pressure not by the volume of bias flow. Usual care patients will have the positive airway pressure set and adjusted as their respiratory status requires by their supervising provider.

The decision not include a sham procedure was also based on the concern of interrupting and/or modifying ongoing respiratory support in fragile newborns with RDS to implement the sham. Such an intervention has no reasonable expectation of benefit for the subject but does have some potential for adverse consequences. There will be no protocol driven interventions in the usual care group.

**6.2 Other treatments**

Participation in this trial will not restrict participating patients from any other medication or therapeutic intervention deemed appropriate by their care givers.

**6.3 Subject Compliance** No compliance concerns for NICU patients

## 7. ASSESSMENT OF EFFICACY OF AEROSOLIZED INFASURF

**7.1 Parameters**

1) Comparison of requirement for instilled surfactant to "usual care" over 72 hours.
2) Comparison of severity of RDS to "usual care" over 72 hours.
3) Comparison of duration of respiratory support for RDS to "usual care" up to 7 days.
4) Comparison of incidence of pulmonary complications of RDS to "usual care" to 7 days.

**7.2 Efficacy methods**

All data will be extracted from each patient's medical record and entered into a case report form. No specific testing is defined. Data to be extracted to assess efficacy is:

1) Requirement for Instilled Surfactant to 72 hours of age.

- Number of patients requiring surfactant instillation from randomization to 72 hours of age. Intubation and instillation is indicated if there is a continuing, > 1hour, requirement for >40% inspired oxygen plus continuing positive pressure support to maintain acceptable blood oxygen saturations.

2) Measures of Severity of RDS from Randomization to Surfactant Instillation or 72 hours of age.
(a) Supplemental oxygen measured as the increase and/or decrease over time.
(b) Duration of positive pressure respiratory support over time.

3) Duration of RDS to 7 days of age :
(a) Time from birth to when patient last required >25% oxygen.
(b) Requiring >25% oxygen for ≥7 days (168 hours) from birth shall be defined as "unresolved RDS".

4) Incidence of pulmonary complications to 7 days of age
(a) Occurrence(s) of radiologically or clinically diagnosed pneumothorax, pneumomediastinum, pulmonary interstitial emphysema, subcutaneous emphysema or pneumopericardium.
(b) Pulmonary hemorrhage defined as gross bleeding from the airway, changes in a chest X-ray consistent with pulmonary hemorrhage and acute deterioration of respiratory function.
(c) Acute pneumonia defined as acute deterioration of respiratory function accompanied by clinical and chest X-ray findings consistent with bacterial pneumonia and a clinical decision to institute appropriate antibiotic therapy for acute pneumonia**.**

## 8. ASSESSMENT OF SAFETY

### 8.1 Parameters

Adverse Events During Aerosolization.

1) Discontinuation of aerosolization before the full dose is given for any reason
2) Incidence, magnitude and duration of adverse cardiopulmonary effects:
   (A) Hypoxemia defined as $O_2$ saturation of < 80 % for >1 minute despite interventions.
- (B) Airway obstruction defined as blockage of ventilation for >1 minute producing hypoxemia and bradycardia and requiring endotracheal suctioning and/or re-intubation.
   (a) during Infasurf aerosolization(s)
   (b) during instillation(s**)**
   (C) Other.

Other safety parameters: These data will be extracted from the medical record of each patient from birth to 28 days of life, death or discharge (whichever is first).
1) Incidence of pneumonia, sepsis or other major infection to 28 days
2) Incidence and severity of seizures, brain hemorrhages or other brain injuries
3) Incidence and severity of necrotizing enterocolitis
4) incidence and severity of bronchopulmonary dysplasia.
5) Incidence and severity of any other severe unexpected adverse events**.**

**8.2 Methods** Identification of all safety outcomes will be by review of the patient's medical record**.**

**8.3 Analysis** Severe, unexpected adverse events. Any severe, unexpected adverse event occurring to aerosolized assigned patients will be immediately reported to the medical director of a participating site. The medical director will review the adverse event and determine if it is related, or possibly related, to the administration of aerosolized Infasurf. If the event is considered "related" or "possibly related" the sponsor will be immediately notified and will be responsible for filing the appropriate notification to FDA. The sponsor will provide the same information to the study chair and to the other study sites. The local site P.I. will be responsible for providing the local IRB with the information about the event.

Non-serious adverse events By regulation an "adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related." (21 CFR 312.32(a).

## 9. STATISTICS

### 9.1 Statistical Methods

ONY, Inc., or its designee, will be responsible for (a) data management, (b) reviewing and validating all information in the clinical report forms, (c) statistical analysis, and (d) generation of the clinical study report. A Statistical Analysis Plan (SAP) providing details of statistical analyses performed after completion of the study will be developed. Prior to locking the database, all data editing will be completed and decisions regarding the evaluability of subject data for inclusion in statistical analyses will be made. The rationale for excluding any data from statistical analyses will be prospectively defined, and classification of all or part of a subject's data as non-evaluable will be documented before the database is locked and the statistical analysis is begun. ONY, Inc., or designee will perform the statistical analysis of the data derived from this study. All analyses will be carried out using SAS version 9.4 (or higher) statistical software (Cary, NC).

Statistical design**:** This study is a randomized, multiple-center clinical trial designed to assess the superiority of the experimental intervention (aerosolized Infasurf) relative to active control ("usual care") with regards to the incidence of intubation and instillation of liquid surfactant suspension. A total of up to 200 subjects who received instillation of surfactant for RDS in the first hour of life ("the post-instilled cohort") and up to 458 subjects who did not receive surfactant at birth who develop RDS in the first hours of life ("the uninstalled cohort") will be enrolled. Treatment assessment will be done for each cohort separately, that is, this study may be thought of as two individual trials under one protocol.

Stratification**:** The randomization will be stratified by center and patient cohort and significance tests applied in the analyses will be stratified by center.

Randomization: Subjects will be randomized to the intervention or active control arm in a 1:1 fashion using a stratified permuted block randomization scheme with variable block sizes of 2 and 4. Randomization lists will be generated by the study biostatistician which will then be used to create an envelope-based system to be used at the individual study sites. Subjects will be included in primary data analyses according to their randomized assignment irrespective of the treatment actually received (intent-to-treat). Exceptions would include those who withdraw their consent to use any of their data prior to subject evaluation.

Accrual. Subjects will be accrued to the study on a first-come basis. The projected accrual is approximately 80 per month, and therefore recruitment is expected to be complete at most 365 days following the study starting point. Subjects will be followed to hospital discharge or 28 days whichever is shorter so total study duration will be approximately 13 months.

Descriptive analyses. Measured outcome variables will be summarized overall and by relevant demographic and baseline variables. Descriptive statistics such as frequencies and relative frequencies will be computed for all categorical variables. Numeric variables will be summarized using simple descriptive statistics such as the mean, standard deviation and range. A variety of graphical techniques will also be used to display data, ex. histograms, boxplots, scatterplots, etc.

Primary efficacy analyses. The primary efficacy analysis will be performed within each cohort separately and is based on a test for superiority of the experimental treatment relative to active control with regards to intubation rate. An overall assessment of the probability of intubation differences across study sites will be done using the Cochran-Mantel-Haenszel test. A one-sided nominal significance level of 5% will be utilized. Additional analyses will be performed utilizing both cohorts of subjects in order to assess differential treatment effects.

Primary safety analyses. All adverse events will be recorded during the study period and then tabulated at the end of the study.

Secondary analyses. Secondary efficacy outcomes representing measures of severity of RDS (oxygen supplementation and respiratory support measures from randomization to Surfactant Instillation or 72 hours of age, whichever comes first) will be summarized using standard descriptive statistics and compared between treatment groups using the stratified Wilcoxon rank sum test. In the case of outcomes measuring the duration of acute RDS (duration of supplemental oxygen), so to accommodate the potential censoring involved, distributional estimates will be based on the Kaplan-Meier method and groups differences statistically assessed using the stratified log-rank test. For the comparison of measures of protection from acute lung injury (incidence of lung air leaks or pulmonary hemorrhage from randomization to 72 hours or intubation and surfactant instillation), the Cochran-Mantel-Haenszel test will be used. All statistical tests will be one-sided and tested at a 5% nominal significance level.

Interim analysis. A group sequential approach will be utilized in the statistical evaluation of data, with a two interim analyses and the final analysis planned. The interim analyses, which will assist in making the decision of whether or not to stop the trial early for futility, will take place after the study outcome variables are observed in approximately the first 1/3 of evaluable subjects and after approximately 2/3 of evaluable subjects. Assuming increasing recruitment during the months and allowing for data clean up and statistical analysis, we anticipate the interim analysis will be performed at approximately 4 months after enrollment of the first patient. The principal interim analyses will involve the computation of the conditional power pertaining to the test of the primary efficacy outcome, that is, we will compute the probability of rejecting the primary null hypothesis at the end of study given the data observed thus far. In the event of unfavorable trends in the data, the conditional power of achieving a final conclusion of superiority will be much less than the initial planned power of the study for a given point in the alternative parameter space, thus making conditional power a quantitative tool for use in interim decision making. Monte Carlo simulations based on 10,000 iterations will be utilized to compute the conditional power under two difference scenarios: 1) assuming the parameter values utilized for sample size derivation, and 2) assuming the true parameter values are equal to the sample estimates computed from the interim data. Given the uncertainty in the actual values of the parameters, the conditional power associated with the second scenario should be viewed as that which is most informative in decision making. Additionally, 95% confidence intervals will be obtained and used to assess if the values assumed in the planning of the study are much different than those suggested by the data. The conditional power for selected values within the computed confidence intervals may be calculated if deemed potentially informative. Results of interim analyses will be reviewed by the Data and Safety Monitoring Board. After the second interim analysis, sample size may be modified using the method discussed in Gould (1992),[7] performed in conjunction with an effect size of a 20% decrease in intubation rate.

**9.2 Sample size justification**

In order to gauge the adequacy of the proposed sample size, the statistical power based on the proposed superiority analyses described above was determined. Power in this context is defined as the probability of deeming the experimental treatment superior to active control after performing the test for superiority on the study data at the conclusion of the study, done in conjunction with a 5% nominal significance level. For the sake of simplicity, calculations corresponding to the test based on the proposed approach are approximated by those of a simple two-sample binomial test. We assume the intubation probability corresponding to the active control group to be 60%. This is based on an abstract presented at the Pediatric Academic Societies meeting of 2016 in which the incidence of intubation and instillation of surfactant among infants with early RDS requiring 30 - 40% oxygen was 32 of 50, 64%. A clinical meaningful effect in the uninstalled cohort is defined as a 20% decrease (in percentage points) in the intubation rate which equates to a 48% intubation rate. Calculations show a sample size of 229 per group (458 total) in this cohort will result in a test procedure which is associated with power of approximately 80.1%. In the post-instilled cohort, 200 subjects will be enrolled. This will provide approximately 80% power is detecting a 30% decrease in the intubation rate (60% versus 42%).

**9.3 Criteria for trial termination**

There will be no termination of the trial for early efficacy. Criteria for termination for futility are presented in 9.1 in interim analysis. The data monitoring and safety committee will review the adverse events and will recommend to the study chair and the sponsor that the trial be suspended or discontinued for safety. Since this is a study of an alternative

method of administration of Infasurf which is FDA approved as safe and effective termination for adverse events unrelated to administration of the aerosol is not included.

**9.4 Missing data**

The amount and nature of missing data will be characterized and no method of imputation will be used for missing data. A summary of missing data will be provided according to the number of subjects, the time points where the data are missing, and clinical center. For each clinical center, the number and percent of subjects with no missing data will be presented in tabular form.

**9.5 Procedure for revising the analysis plan**

If the study biostatistician determines the analysis plan is in need of revision after the study starts, the biostatistician and study chairman will discuss the validity and influence of revision in the evaluation of study data and will then determine if the revision can be conducted. The details of any revisions will be described in the clinical study report for this protocol.

## 10. ACCESS TO DATA

**10.1 Study Sites**

Participating sites will agree to providing access to the patient medical records of study participants. They will also agree to allowing true copies of those parts of the patient's medical record that support the data in the case report forms to be retained by the Principal Investigator at the site and by the Sponsor.

**10.2 Access to Data post study closure**

Participating sites will agree to provide access to the patient medical records of study participants should additional data need to be obtained following approval of a revised protocol that is approved by the sponsors national IRB or hospital IRB. They will also agree to allowing true copies of the patient medical record that support the requested data in the case report forms to be retained by the Principal Investigator at the site and by the sponsor.

**10.3 Families**

The informed consent specifically includes the agreement by the family that the Principal Investigator and the Sponsor may keep true copies of those parts of the medical record that support data entered into the case report forms. In addition, the family agrees to allow the Institutional Review Board of the participating site and Food and Drug Administration reviewers full access to data in the medical records.

## 11. QUALITY ASSURANCE & QUALITY CONTROL

**11.1 Quality Control**

All information about interventions in this study will be included in the patient's medical record. All sites are approved Level III Neonatal Intensive Care Units in licensed acute care hospitals. Data in the medical record shall be controlled by the quality control procedures at each participating institution. Any data considered spurious by study monitors will be evaluated by the site P.I. who will attest to its accuracy or inaccuracy.

All principal investigators and co-investigators will have credentials to practice as direct care providers in the Neonatal Intensive Care Units of the hospitals.

**11. Quality Assurance**

Study monitors will extract data from the medical record and enter it into an electronic case report form. The Case report form will have a 200% verification of agreement with the medical record. Completed and verified case report

forms will be accrued into the study data set which will meet all Good Clinical Practices criteria for integrity, security, traceability and privacy.

## 12. ETHICS

### 12.1 Patient Safety

Insuring that both the "usual care" group and the aerosolized Infasurf groups have unfettered access to optimal medical care is the major consideration in development of this protocol.

For the "usual care" group the only requirement is that the family consents to our accessing its child's medical record. Full confidentiality will be maintained and there should be no downside for participation.

The aerosolized Infasurf group may benefit if the therapy decreases the incidence of endotracheal intubation and instillation of surfactant. However, all members of that cohort retain full access to surfactant instillation therapy, if needed. To protect the welfare of these patients no study specific assessments or tests are mandated by the protocol. Documentation of the patient's status in the medical record contains sufficient information to evaluate the efficacy and safety of aerosolized Infasurf

### 12.2 Consent

No patient can participate in the study without the consent of parent(s) or guardian.

### 12.3 Confidentiality

All participating patients will be assigned a unique study number. The principal investigator at each site and the sponsor will each retain a log matching the patient's name and hospital number to the study number. Also the case report form for each subject retained by both the local P.I. and the Sponsor will have both the subject's study Identification number and the hospital identification information. This is to allow the Principal Investigator, the Sponsor or FDA to audit the study data or expand the data extraction from the patient's medical record if necessary for efficacy or safety evaluations.

All study results will be presented as either group results or, if individual responses are reported for illustration, identified only by the study number.

## 13. DATA HANDLING AND RECORD KEEPING

### 13.1 Case report form

A copy of the case report form is in Appendix B. It includes demographic data, respiratory support data from randomization to 3 days and data from the patient's chart relevant to efficacy and safety outcomes to 28 days, death or discharge (whichever occurs first). Parent(s) or guardian will give permission for the Principal Investigator and the Sponsor to retain (and keep confidential) true copies of those parts of the participant's medical record from which the case report data is extracted.

### 13.2 Record keeping

Duplicate files of every patient will be maintained by the Principal Investigator and the Sponsor. Each patient's file will contain a true copy of the relevant parts of the patient's medical record supporting the case report form data and a hard copy of the completed case report form and data that links the patient's hospital identification to the study identification. A true copy of the signed consent form will be retained by both the PI and the Sponsor for each participant.

**14. PUBLICATIONS**

The Study Chair will be the lead author. ONY will retain the right to review and comment on a manuscript for 30 days before submission or re-submission to a peer refereed journal but will have no right to restrict submission or require editing.

ONY has the rights to the data completed data and the right and responsibility for submitting study reports to regulatory agencies.

## *15 APPENDICES*

### *APPENDIX A* **Intervention Notes Formats**

Initial Aerosol Procedure Note

Date Time: Patient was randomized to the Aerosolization Group in the Aerosolized Infasurf Trial in the {never treated} {previously instilled} cohort. The initial aerosolization was started at __ __:__ __ hours and was completed at __ __:__ __ hours. A total of __ __ mL of Infasurf was aerosolized. The Inspired $O_2$ prior to starting the aerosol was __ __%. The aerosolization {was} {was not} completed. There {was no} {was an} adverse event during the aerosol delivery. {If present describe in detail}.

Repeat Aerosol Procedure Note

Date Time: A repeat aerosolization was started at __ __:__ __ hours and was completed at __ __:__ __ hours. A total of __ __ mL of Infasurf was aerosolized. The Inspired $O_2$ prior to starting the aerosol was __ __%. The aerosolization {was} {was not} completed. There {was no} {was an} adverse event during the aerosol delivery. {If present describe in detail}.

Usual Care Procedure Note

Date Time: Patient was randomized to the Usual Care Group in the Aerosolized Infasurf Trial in the {never treated} {previously instilled} cohort. The Inspired $O_2$ at the time of randomization was __ __%.

**Appendix B. Case Report Form**

# Aerosolized Infasurf Trial Case Report

**1. Identity Data**

**Last Name** _____

**Date of Birth** __ __/__ __/__ __ __ __

**Time of Birth** __ __:__ __

**Hospital #** _____

**Study #** __ __ __ __ __

**Consent #** __ __ __ __ __

**Strata** __A ___B

**Rx Group** __Usual Care __Aerosolized

**2. Demographic Data**

**Sex** __M __F

__Single __MultA __ MultB __MultC

**Birth Wt** ___ ___ ___ __grams

**Gestational Age** __ __wks __days

**Maternal Steroids** __N __<12 hrs __>12 hrs

**Delivery:** __ Vaginal ___C-Section

**APGAR** __ __ 1min __ __ 5 min

**Intubated in DR** __Y __N

**Surfactant in DR** __Y __N

**3 A. 1st Aerosolization Procedure Data**

| | | |
|---|---|---|
| Date | | |
| Start time | | |
| End time | | |
| Patient Age (hrs) | | |
| Dose (mL) | | |
| Aerosol duration (min) | | |
| Mode of Support | | |
| FiO2 | Pre | |
| | 30 min | |
| | 60 min | |
| | 90 min | |
| | 120 min | |
| | 180 min | |
| | 240 min | |
| Aersolization interrupted | | |

**3 B. 2nd Aerosolization Procedure Data**

| | | |
|---|---|---|
| Date | | |
| Start time | | |
| End time | | |
| Patient Age (hrs) | | |
| Dose (mL) | | |
| Aerosol duration (min) | | |
| Mode of Support | | |
| FiO2 | Pre l | |
| | 30 min | |
| | 60 min | |
| | 90 min | |
| | 120 mins | |
| | 180 min | |
| | 240 min | |
| Aersolization interrupted | | |
| Full dose given | | |

**3 C. 3rd Aerosolization Procedure Data**

| | | |
|---|---|---|
| Date | | |
| Start time | | |
| End time | | |
| Patient Age (hrs) | | |
| Dose (mL) | | |
| Aerosol duration (min) | | |
| Mode of Support | | |
| FiO2 | Pre l | |
| | 30 min | |
| | 60 min | |
| | 90 min | |
| | 120 mins | |
| | 180 min | |
| | 240 min | |
| Aersolization interrupted | | |
| Full dose given | | |

**4. Respiratory Status Randomization From Birth to 72 Hours of Age for All Patients (source respiratory and nursing sheets or charts)**

| Date | Time | Age (hrs) | FIO2 | CPAP | HFNC >2/kg/min | Non-invasive ventilation | Mechanical ventilation/ oscillation |
|---|---|---|---|---|---|---|---|
| | | **6** | | | | | |
| | | **12** | | | | | |
| | | **18** | | | | | |
| | | **24** | | | | | |
| | | **36** | | | | | |
| | | **42** | | | | | |
| | | **48** | | | | | |
| | | **54** | | | | | |
| | | **60** | | | | | |
| | | **66** | | | | | |
| | | **72** | | | | | |

**5. Endotracheal Intubations +/- Surfactant Instillation (source procedure note)**

| # previous intubations | Age (hrs) | $FiO_2$ | Surfactant (Inf,Curo,Surv) | Surfactant Dose (ml/kg) | Complications of Surfactant Instillation* (all that apply) |
|---|---|---|---|---|---|
| 0 | | | | | |
| 1 | | | | | |
| 2 | | | | | |
| * 1=cyanosis; 2=bradycardia, 3=reflux, 4=airway obstruction 5= hypotension 6= re-intubated 7=required CPR | | | | | |

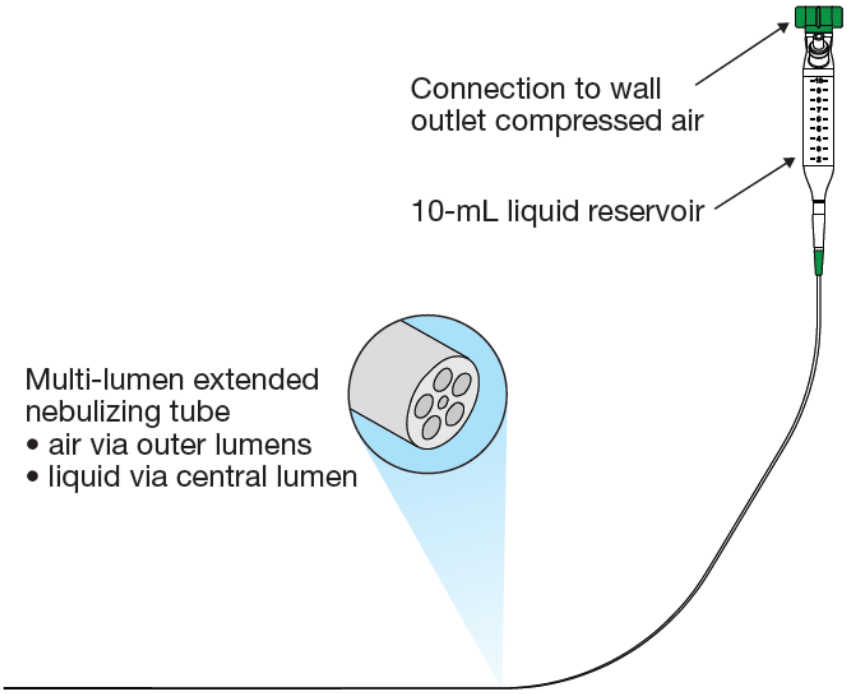
**6. Imaging Results Days 1-4 (source report of radiologist interpreting the image(s))**

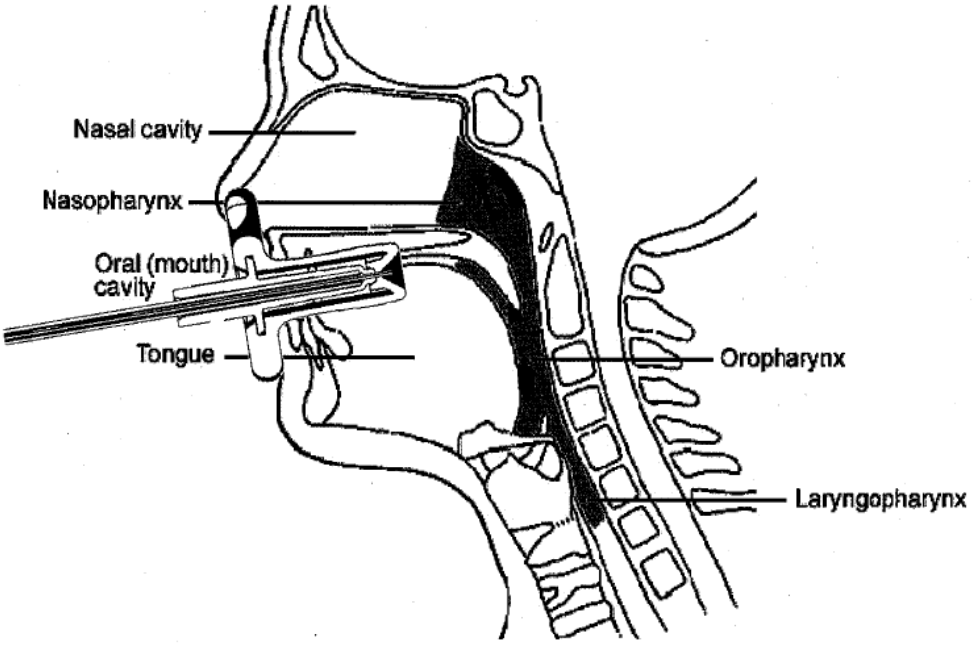
| | Day 1 | | Day 2 | | Day3 | | Day 4 | |
|---|---|---|---|---|---|---|---|---|
| Imaging | Normal | Abnormal | Normal | Abnormal | Normal | Abnormal | Normal | Abnormal |
| Chest X-ray(s) | | | | | | | | |
| Head ultrasound(s) | | | | | | | | |
| Other ultrasound(s) | | | | | | | | |
| Other X-ray(s) | | | | | | | | |
| CT scan(s) | | | | | | | | |
| MRI (s) | | | | | | | | |
| Chest X-Ray abnormality is defined as a diagnosis, not just a description (1)RDS; (2)pneumothorax (3)PIE (4) pneumomediastinum (5) pneumonia (5) interstitial edema (6) pulmonary hemorrhage (7) other<br><br>Head ultrasound abnormality (1)IVH grade 1or 2 (2) IVH grade 3 or 4 (3) PVL (4) HIE (5) cerebral edema (6) other | | | | | | | | |

**7. Patient Outcomes on Days 4, 8, and 29 of Life and Discharge Summary**
**(source progress notes on days 5, 9, and 29or discharge (D/C)**

| Organ System | Diagnoses | Day 4 | Day 8 | Day 29 or D/C |
|---|---|---|---|---|
| Status | (1)Alive (2)Deceased (3)Ventilated (4)On CPAP/HFNC/NIV (5)On $O_2$ for RDS (6)On $O_2$ for apnea (7)Other | | | |
| | | | | |
| CNS | (1)IVH-1/2 (2)IVH-3/4 (3)HIE (4)PVL (5)Seizures (6)Apnea (7)Cerebral edema (8)Other | | | |
| | | | | |
| Respiratory | (1)RDS (2)Pneumothorax (3)PIE (4)Pneumonia (5)Pulmonary hemorrhage (6)Peneumomediastinum (7)BPD (7) Other | | | |
| | | | | |
| Cardiovascular | (1)CHF (2)Hypotension (3)Hypertension (4)PDA (5)PDA Rx drugs (6)PDA Rx surgery (7)Arrhythmia (8)Other | | | |
| | | | | |
| GI | (1)NEC stage 1 (2)NEC stage 2 (3)NEC stage 3 (4)GI bleeding (5)diarrhea (6) GE reflux (7)other | | | |
| | | | | |
| Renal | (1)Oliguria/anuria (2)Uremia (3)Hypernatremia (4)Hyponatremia (5)Hyperkalemia (6)Hypokalemia (7)Other | | | |
| | | | | |
| Metabolic | (1)Hypoglycemia (2)Full parenteral feedings (3)Partial parenteral feedings (4)Full oral feedings (5)Other | | | |
| | | | | |
| Hematologic | (1)Neutropenia (2)Thrombocytopenia (3)Coagulopathy (4)Other | | | |
| | | | | |
| Infection | (1)Sepsis (2)Meningitis (3)Cellulitis (4)Other | | | |
| | | | | |
| Hepatic | (1)Hyperbilirubinema (2)Other | | | |

**APPENDIX –C – SCHEMATIC OF AEROSOL DELIVERY SYSTEM**



*Appendix D.*

# Aero-02 Respiratory Support Data Sheet

**Patient ID: _____ Site # _____ Usual Care / Aerosol (circle)**

| Date | Time (1) | Mode of Support (2) | Mode of Ventilation (3) | Fio2 | Flow (l/min) | Peak ($cmH_20$) | Peep ($cmH_20$) | RR | Set Vt. (4) | Mean Airway Pressure ($cmH_20$) | I time (Sec) | PS ($cmH_20$) | Hz. | Amplitude |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
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1. ***Please log Initial respiratory support data and also any respiratory support data for all time points where settings were changed including mode of support up to 96 hours from birth.***
2. ***Mode of Support: Mech. Ventilation (MV), HFOV, HFJV, NIPPV, SNIPPV, Cpap, Bubble Cpap, Bi-Pap, HFNC, LFNC***

3. ***Mode of Ventilation: PRVC, SIMV, VG etc. Please be specific.***
4. ***Input Vt. If Volume mode of ventilation is used (VG, PRVC, VAPS, Volume Limit).***

# Aero-02 Respiratory Support Data Sheet Day 8, 28, Discharge

Patient ID: _____ Site # _____ Usual Care / Aerosol (circle)

| Date | Time (1) | Mode of Support (2) | Mode of Ventilation (3) | $Fio_2$ | Flow (l/min) | Peak ($cmH_20$) | Peep ($cmH_20$) | RR | Set Vt. (4) | Mean Airway Pressure ($cmH_20$) | I time (Sec) | PS ($cmH_20$) | Hz. | Amplitude |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Day 8** | | | | | | | | | | | | | |
| | **Day 28** | | | | | | | | | | | | | |
| | **Disch.** | | | | | | | | | | | | | |

1. ***Please log initial respiratory support data and also any respiratory support data for all time points where settings were changed including mode of support up to 96 hours from birth.***
2. ***Mode of Support: Mech. Ventilation (MV), HFOV, HFJV, NIPPV, SNIPPV, Cpap, Bubble Cpap, Bi-Pap, HFNC, LFNC***
3. ***Mode of Ventilation: PRVC, SIMV, VG etc. Please be specific.***
4. ***Input Vt. If Volume mode of ventilation is used (VG, PRVC, VAPS, Volume Limit)***

Please find and log Respiratory Settings for each day. If less than 28 days' use discharge.

**On Resp. support:** **Date: ____/____/____** **Time: __/__**

**Off Resp. support for RDS:** **Date: ____/____/____** **Time: __/__**

**Off all Resp. support (includes LFNC):** **Date: ____/____/____** **Time: __/__**

**Adverse Event- Day end Progress Note**

□ Days 1- 28 or Discharge collected and uploaded

**Directions:**

1. Start by entering the respiratory support data at the time the patient was placed on support.
2. Create a row any time there is a change in either the mode, the $FiO_2$ or the settings on the mode of ventilation. Enter all variables associated with any change in respiratory support.
3. For $FiO_2$ do not record every minor, short term adjustment during procedures by the nursing staff, include changes ordered by the care provider or a change that appears on the respiratory flow sheet as a continuing adjustment of target $FiO_2$.

4. Upload data collected from the above respiratory flow sheet and the daily progress notes into the secure portal provided.

**Data Collector:_____** **Date:____/____/____**

**Data Source:_____**

**16. References**


[1] Notter RH. Lung Surfactants, Marcel Dekkar, NY, 2000, page 141.
[2] Infasurf (calfactant) package insert
[3] Survanta (beractant) package insert
[4] Curosurf (poractant alfa) package insert-
[5] Data on file at ONY, Inc.
[6] Moses LE, Oxford RY. Tables of Random permutations, Stanford University Press, Stanford, CA, 1963
[7] Gould, A.L. Interim analyses for monitoring clinical trials that do not materially affect the Type I error rate. Statistics in Medicine, 1992;11: 55-66