Title:	Safety and Efficacy of Aerosolized Albuterol in Mechanically Ventilated Infants with Bronchopulmonary Dysplasia
Short Title	Aerosolized Albuterol in BPD
Drug or Device Name(s):	Albuterol Sulfate
eIRB Number:	15-012264
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Amendment 2 Date:	Amendment 4 Date:

Kevin Dysart, MD
The Children's Hospital of Philadelphia
2nd Floor, Main Building, Division of Neonatology
3401 Civic Center Blvd
Philadelphia, PA, 19104
Phone 215-590-1656
email: dysartk@email.chop.edu

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ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
SAE	Severe Adverse Event
BPD	Bronchopulmonary Dysplasia
N/IICU	Neonatal & Infant Intensive Care Unit
CHOP	The Children's Hospital of Philadelphia
CLD	Chronic Lung Disease
Crs	Compliance
Rrs	Resistance
cmH2O	Centimeter of water
mg	Milligram
ml	Milliliter
CLDP	Chronic Lung Disease Program
Hrs	Hours
MMAD	Mass Median Aerodynamic Diameter
µm	Micrometer
ETT	Endotracheal tube
SCG	Sodium Cromoglycate
MDI	Metered Dose Inhaler
µg	Micrograms
Vt	Tidal Volume
RR	Respiratory Rate
PEEP	Positive End Expiratory Pressure
PIP	Peak Inspiratory Pressure
MAP	Mean Airway Pressure
FiO2	Fractured inspired oxygen
CRF	Case Report Form
SpO2	Oxygen Saturation Percent
HR	Heart Rate
BP	Blood Pressure
FEF75	Forced Expiratory Flow at 75% of Forced Vital Capacity

ABSTRACT

Context:
Currently several dose schedules of Albuterol are administered via nebulization to infants in the neonatal and infant intensive care unit (N/IICU). As Albuterol is not FDA approved for this population (under 2 years) there is no standard recommended dose. Aerosolized Albuterol is one of the most widely used therapies that are utilized for infants with chronic lung disease. The common practice in the N/IICU is weight base dosing of all medications. This contradicts the aerosol science recommendations, which advise not to titrate doses by weight as the patient naturally self-regulates their dose according to the change in minute ventilation with age. In addition, the wide use of aerosolized Albuterol in the infant with Bronchopulmonary Dysplasia (BPD) has little current evidence of efficacy in this disease. Understanding the appropriate dose for effective treatment as well as the indication for use in the BPD population would provide the clinician with useful guidelines.

We propose to analyze the safety and efficacy of aerosolized albuterol in infants with BPD comparing the recommended dose per aerosolization literature with the common dosing practices at The Children's Hospital of Philadelphia (CHOP) as well as placebo.

Objectives:

Primary – To evaluate the efficacy of aerosolized albuterol to improve pulmonary dynamics in mechanically ventilated infants with BPD.

Secondary – To evaluate the safety of aerosolized albuterol in mechanically ventilated infants with BPD.

Study Design:
Prospective, blinded, randomized cross-over trial

Setting/Participants:
Mechanically ventilated infants with BPD in the N/IICU at CHOP. Twenty-Five infants with a diagnosis of BPD requiring mechanical ventilation will be recruited into this trial.

Study Interventions and Measures:
This is a randomized cross-over study. Participants will receive 3 sets of treatment (2.5mg Albuterol, 1.25mg Albuterol, 3ml normal saline placebo), in random order. Each treatment will be administered every 4 hours for 24 hours. After a 6 hour washout phase, the next group of interventions will be applied. Following another wash-out phase, the final group of intervention will be applied. Pulmonary mechanics from the ventilator (e.g. airway compliance, airway resistance, tidal volume, peak inspiratory pressure, Forced Expiratory Flow at 75% of forced vital capacity, etc.) and the patient short term response to therapy (heart rate, blood pressure, heart rhythm) will be assessed for the duration of the treatment period.

PROTOCOL SYNOPSIS

Study Title	Safety and Efficacy of Aerosolized Albuterol in Mechanically Ventilated Infants with Bronchopulmonary Dysplasia
Funder	Respiratory Therapy Departmental Funds
Study Rationale	Currently several dose schedules of Albuterol are administered via nebulization to infants in the neonatal and infant intensive care unit (N/IICU). As Albuterol is not FDA approved for this population (under 2 years) there is no standard recommended dose. Aerosolized Albuterol is one of the most widely used therapies that are utilized for infants with chronic lung disease. The common practice in the N/IICU is weight base dosing of all medications. This contradicts the aerosol science recommendations, which advise not to titrate doses by weight as the patient naturally self-regulates their dose according to the change in minute ventilation with age. In addition, the wide use of aerosolized Albuterol in the infant with Bronchopulmonary Dysplasia (BPD) has little current evidence of efficacy in this disease. Understanding the appropriate dose for effective treatment as well as the indication for use in the BPD population would provide the clinician with useful guidelines. We propose to analyze the safety and efficacy of aerosolized albuterol in infants with BPD comparing the recommended dose per aerosolization literature with the common dosing practices at The Children's Hospital of Philadelphia (CHOP) as well as placebo.
Study Objective(s)	**Primary** • To evaluate the efficacy of aerosolized albuterol to improve pulmonary dynamics in mechanically ventilated infants with BPD. **Secondary** • To evaluate the safety of two doses of aerosolized albuterol in mechanically ventilated infants with BPD.
Test Article(s)	• Two doses of Albuterol as well as a placebo to be administered according to standard nebulization practices for infants in the N/IICU on mechanical ventilation. • Collection of pulmonary mechanics through the ventilator as done in standard practice • Collection of vital signs, heart rate and heart rhythm to determine abnormalities related to the delivery of the

	medication. This can be collected from the full disclosure of information from the monitors routinely used in the N/IICU.
Study Design	Prospective, Blinded, Randomized controlled crossover trial. Each patient will serve as their own control and will receive 3 treatment groups (2.5 mg Albuterol, 1.25 mg Albuterol, 3ml normal saline) in random order every 4 hours for 24 hours with a 6 hour washout period in between each treatment group.
Subject Population key criteria for Inclusion and Exclusion:	**Inclusion Criteria** 1. Infants ≥ 36weeks corrected gestational age to one year of age 2. Diagnosis of BPD in accordance with NICHD definition 3. May have a current order for short acting bronchodilator, not required 4. May have congenital Anomalies unless one or more of the exclusion criteria are met, not required 5. Receiving Conventional Mechanical Ventilation via an artificial airway (endotracheal tube or tracheostomy) via Draeger V500 Ventilator 6. Parental/guardian permission (informed consent) **Exclusion Criteria** 1. Airway leak greater than 10% 2. Unilateral lung disease 3. Current order for inhaled anticholinergic (i.e. ipratropium bromide) 4. Active pulmonary or systemic infection 5. Scheduled order for other medication that cause bronchodilation (i.e. Atrovent, magnesium sulfate, ketamine, etc.)
Number Of Subjects	25 infants mechanically ventilated for BPD at the N/IICU at CHOP
Study Duration	Each subject's participation will last 84 hours.
Study Phases **Screening**	Study participants will be identified by the Chronic Lung Disease service team. Enrollment will be discussed with the infant's primary physician before parents are approached for consent.
Study Treatment	If therapy has already begun the infant will go through a 6 hour washout period prior to the delivery of the therapy in the first treatment group. The randomization and blinding of the treatment groups will be done by the research pharmacy and neither the research team nor the primary medical team will know which

Monitoring	treatment group the subject will be receiving at any given time. Since each subject is serving as their own control they will all receive both active treatment and placebo. Each subject will be continuously monitored for changed in pulmonary and hemodynamic changes in correlation with each dose of therapy during each treatment group.
Efficacy Evaluations	Increase in forced expiratory flow rate at 75% of forced vital capacity, increase in lung compliance, decrease in lung resistance, increase in tidal volume, and/or decrease in peak inspiratory pressure.
Safety Evaluations	Hemodynamic response: sustained increase in heart rate, change in cardiac rhythm, and/or sustained increase in blood pressure.
Statistical And Analytic Plan	Primary outcome of comparing pre and post FEF75 measures will be analyzed using either a paired t-test or Wilcoxon Sign depending on the quality of the data. The secondary outcomes of comparing each treatment group with mean change in FEF75 will be analyzed using linear mixed effects modeling.
DATA AND SAFETY MONITORING PLAN	Clinical adverse events will be monitored throughout the study period. There will be a monthly meeting among the study investigators and the Chronic Lung Disease Program team to discuss and monitor data and safety. All data will be kept confidential in accordance with HIPPA and CHOP policies.

TABLE 1: SCHEDULE OF STUDY PROCEDURES

Study Phase	Screening	Treatment/Intervention					
		1st Treatment Group	Washout Phase	2nd Treatment Group	Washout Phase	3rd Treatment Group	Final Monitoring Phase
Time in hours	3	4 - 27	28 - 34	35 - 59	60 - 66	67 - 91	92 - 98
Cumulative days	0	1		2		3	4
Informed Consent/Assent	X						
Review Inclusion/Exclusion Criteria	X						
Demographics/Medical History	X						
Physical Examination	X						
Vital Signs: BP, HR, RR (as part of clinical care)	X	X	X	X	X	X	X
Pulmonary Mechanics/ Ventilator Evaluation (as part of clinical care)	X	X	X	X	X	X	X
Height and Weight	X						
Prior/Concomitant Medications	X						
Randomization	X						
Dispense Study Drug		X		X		X	
Pulmonary Dynamics Monitoring		X	X	X	X	X	X
Adverse Event Monitoring		X	X	X	X	X	X

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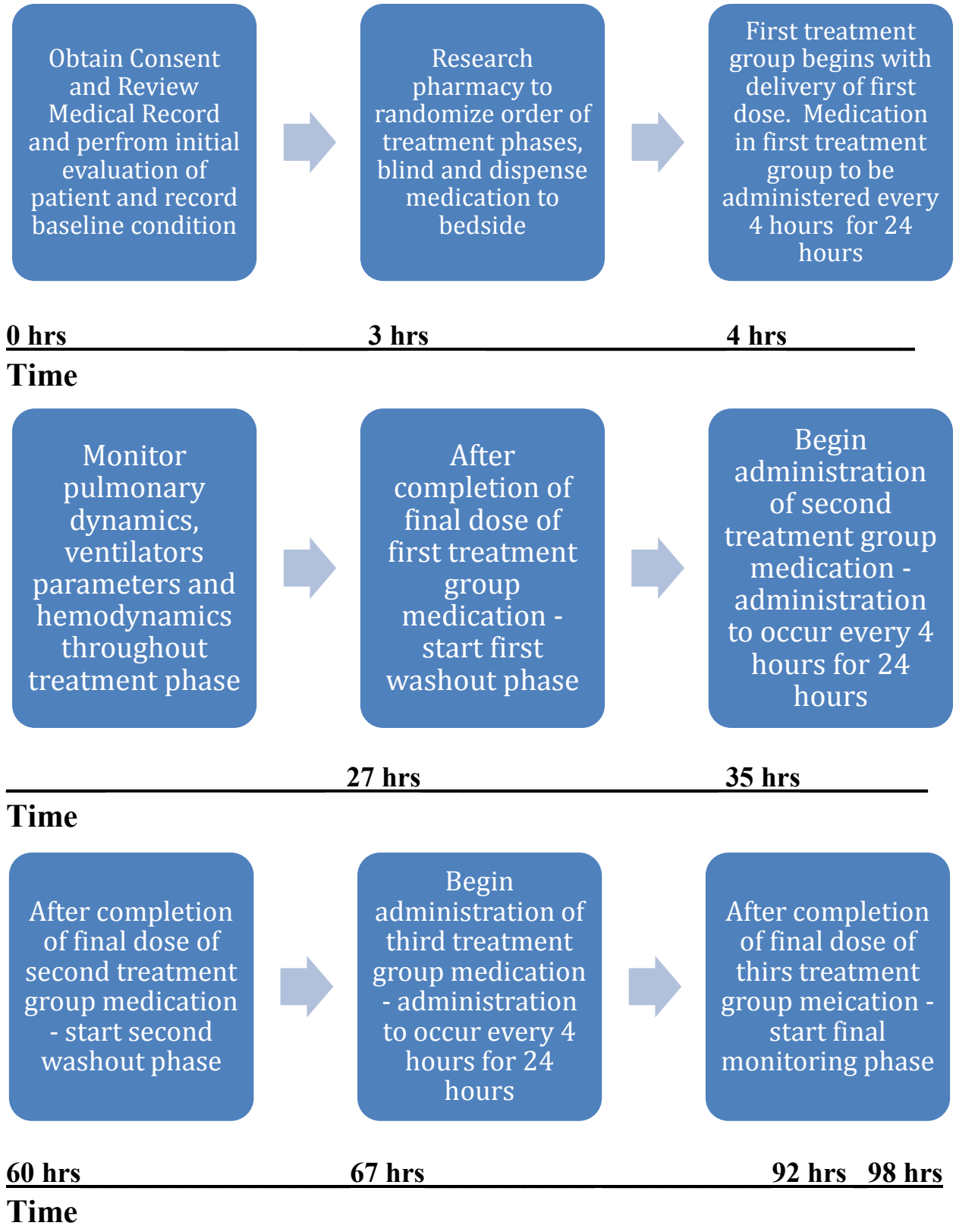
FIGURE 1: STUDY DIAGRAM



1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

The utilization of aerosolized Albuterol as a treatment approach for infants with bronchopulmonary dysplasia (BPD) has become commonplace in most Neonatal and Infant Intensive Care Units (N/IICU) around the country. Guaman et al published a recent point prevalence study of eight N/IICUs with established BPD programs that reported inhaled bronchodilator use in 32% of the pulled population (0-67% reported from individual centers).[1] In a retrospective review utilizing the Children's Hospital Association Pediatric Health Information System database that included 15 N/IICU's nationally, there was a 33% treatment rate of infants with BPD with bronchodilators.[2] The frequency of its use in daily practice at the Children's Hospital of Philadelphia (CHOP) is great with 33 of the 40 infants enrolled in the Chronic Lung Disease Program (CLDP) with a diagnosis of BPD received aerosolized albuterol in 2013 (unpublished data). This practice has evolved throughout the years without sufficient efficacy or safety information on the use of aerosolized albuterol in the infant population.

Aerosolization of different medications is complex and involves several biophysical considerations: stability of particle size, deposition and absorption with the various methods of aerosolization available. In addition several patient specific factors further complicate the matter: ventilatory pattern and anatomical differences, effect aerosol deposition to the lungs.[3-5] High respiratory rates and small tidal volumes effect deposition because less of the medication is drawn in to the lungs.[3-5] As infants grow the dose of inhaled medication is "self-regulated" as there is an increase in tidal volume and reduction of respiratory rate. The smaller the particle size the greater the chance of getting past the upper airway of infants and depositing in the lungs. The recommended Mass Median Aerodynamic Diameter (MMAD) for infants should be 1-3 μm.[3-4] Amirav, et al further concludes that for preterm infants and those with chronic lung disease the particle size should be small enough to get past the upper airway but large enough to provide efficient deposition during the short residence time the particles have in the airway before exhalation with the high respiratory rate of this population.[4] Since extra fine particles (~ 1-2 μm) deposit by sedimentation they are likely exhaled.[3-4] Therefore, it is probable that the perfect MMAD is 2-3μm for infants.

Through review of decades of aerosol deposition literature, Fink concludes that the pulmonary deposition of jet nebulized aerosols in neonates is < 1% of the nominal dose compared to 8-22% for adults.[5] He states that "the low efficacy of deposition in infants compensates for the fact that a standard adult dose would be too large…the low deposition in infants and children provides a comparable safety and efficacy profile to that of adults…the rationales to reduce doses for infants and small children have not been well substantiated in the literature".[5]

1.2 Name and Description of Investigational Product or Intervention

a. Albuterol Sulfate is a Beta2 bronchodilator medication that is aerosolized and breathed in to dilate the bronchial muscles that are constricted and make it easier to take a deep breath.

b. Normal saline is a diluent that is used with albuterol and other nebulized medication to ensure enough volume for delivery via nebulization. It is also used as a placebo in blinded aerosolized studies. In the N/IICU it is routinely used to assist with suctioning of the airways of intubated infants.

1.3 Findings from Non-Clinical and Clinical Studies

1.3.1 Deposition Rates from Non-Clinical Studies

Bench models are commonly used to estimate aerosol delivery to infants is estimated from bench. However in-vivo models include animal studies.

Dubus, et al aimed to assess the hypothesis that the Aeroneb vibrating mesh nebulizer was superior to the traditional jet nebulizer for delivery of aerosolized medications to the intubated and mechanically ventilated infant.[6] They performed a radiolabeled animal study with four macaque monkeys weighing 2.5-2.8kg. Each monkey was intubated with a 3.0 endotracheal tube (ETT) and medication was delivered with the following nebulizers to achieve the corresponding deposition:

- Jet nebulizer – airlife mistyneb (MMAD 4.8 μm): 0.5%
- Aeroneb Pro synchronized nebulization (MMAD 2.8 μm): 14.0%
- Aeroneb Pro continuous nebulization (MMAD 4.6 μm): 12.6%

1.3.2 Clinical Studies of Deposition Rates in Newborns

There are very few human newborn studies as dosing of radionuclides are involved mandating extra cautions. Kohler, et al compared pulmonary deposition with three different nebulizers in the preterm infant. The study was a randomized, 3-period, cross-over design.[7] They measured lung deposition by inhalation of 20 mg of sodium cromoglycate (SCG) and the measurement of SCG excreted in the urine. Urine was collected and analyzed for 12 hours post inhalation. Three types of nebulizers were utilized in all 17 spontaneously breathing preterm infants without chronic lung disease. The lung deposition of all three nebulizers was less than 1%.

Fok, et al aimed to compare the radio-aerosol deposition of salbutamol of a jet nebulizer and Metered Dose Inhaler (MDI) with vented and non-vented infants with BPD.[8] Ten ventilated infants and 13 non-ventilated infants were studied with both MDI and nebulizer. With spontaneously breathing infants the maximum aerosol deposition with MDI and holding chamber was 2.26% compared to 3.43% with the jet nebulizer. With ventilated infants with maximum aerosol deposition was 2.12% with MDI and 2.62% with nebulizer. The authors concluded that the use of the MDI and Jet are equivalent in aerosol delivery for preterm infants with BPD.

Both of these studies only examined deposition rates. They do not provide data on potential efficacy.

1.4 Selection of Drugs and Dosages

There is no standard dose recommendation for use of albuterol under the age of 2 years. Widespread usage of albuterol in infants with BPD has been shown in prior publications as

well as a review of our own CHOP data.[1,2] However in these publications there was no documentation of dosage used. In our review of CHOP data the most common dosages used were 1.25mg and 2.5mg. In light of the aerosolized medicine science publications that recommend dosing should not be reduced for age as the change in breathing mechanics (respiratory rate, tidal volume, and minute ventilation) self-regulate the drug dosage with lung deposition as well as the documentation that infants on mechanical ventilators receive <1% of the nominal dose of the medication, we determined the need to test 2 doses of the medication.[3-5] The recommended dose regardless of age (2.5mg) and a half dose (1.25mg) recommended by Lexicomp that do not have publications to support their dosing recommendations. Two doses of albuterol will be used (2.5mg and 1.25mg) diluted in normal saline. The placebo solution will be normal saline with no active medication.

1.5 Relevant Literature

1.5.1 Data on Efficacy of Varying Devices

The use of inhaled bronchodilators in infants with BPD has not been proven to be an effective treatment option to date. Ng et al, performed a review of the relevant literature to determine the utility of bronchodilators in the prevention of as well as treatment of BPD.[9] They found very little available information and thus concluded there was not enough evidence to show any effect the treatment of bronchodilators will have on BPD. The studies to date are based on varying dosage regimens and utilize older nebulization equipment and thus cannot be compared and translated into current practice.

Gappa, et al compared the clinical effectiveness of salbutamol delivered from an MDI with holding chamber to that of a jet nebulizer in very preterm infants with chronic lung disease.[10] Dynamic lung compliance and resistance were measured on 13 spontaneously breathing preterm infants with chronic lung disease (CLD). The dose of the medication delivered was 600 μg diluted in 2 ml normal saline for nebulization and 2 puffs of MDI was delivered per dose with 100 μg/puff. Measurements were performed prior to administration of medication and 20 minutes after administration showing significant fall in the resistance with a similar reduction between the 2 delivery methods. Compliance was not significantly changed after administration of medication with no significant side effects.

Denjean, et al sought to determine the dose-related response to aerosolized salbutamol in ventilator-dependent premature infants utilizing a placebo-controlled standard protocol with 10 ventilator-dependent preterm infants.[11] Passive respiratory system resistance and compliance collected at baseline and 10 min after administration of placebo and cumulative doses of salbutamol (100, 200, 400 μg) via MDI and a specially modified spacer. The authors showed a significant improvement in resistance and compliance with 200 μg dose having the greatest response.

1.5.2 Data on Safety

The greatest concern with the use of albuterol, a beta agonist, is the chronotropic effect that presents as sustained tachycardia with a >20% change in heart rate, sustained increase in cardiac output or arrhythmias. There are only a few studies specifically looking at the safety of the use of aerosolized albuterol in children under the age of two years. Hendrick et al[12], performed a multicenter trial to determine the safety with MDI albuterol in 2 doses and

placebo in children less than 24 months. They showed a tachycardia rate of 17% with 180 mcg, 7% with 90 mcg and 7% with placebo. Only one patient had a sinus arrhythmia. Kaashmiri et al[13], performed a randomized, blinded trial of 2 doses of albuterol MDI in infants less than 2 years of age. Their results showed only 1 patient having drug related tachycardia (>20% increase in HR from baseline).

Of the 14 clinical studies analyzed that used aerosolized albuterol in the infant population, 3 did not mention side effects, 8 made simple statements such as "no significant side effects" or "non-significant increase in heart rate". Fok et al[14], studied the use of salbutamol in infants with BPD using 3 different delivery methods. The authors stated all infants had clinically significant tachycardia after the medication ($p<0.05$). Denjean et al[11], also showed a statistically significant increase in the heart rate ($p<0.001$). Subject of this study were premature infants with an average corrected gestation age at the time of study at 32wk. This significant increase in heart rate came with >200µg dose of albuterol. Rotschild et al[15], sought to determine if infants with developing BPD would respond with improved pulmonary mechanics with the treatment of 2.5 mg salbutamol. Authors showed a statistically significant increase in heart rate (<0.001) with no significant difference in systolic blood pressure ($p=0.48$), diastolic blood pressure ($p=0.66$), no dysrhythmias and no sustained increase in heart rate after 30 min ($p=0.59$)

At CHOP the use of albuterol under the age of 2 is very liberal owing to the unique referral based population of infants with severe airway and lung disease. In NICUs nationally, the rate of albuterol administration in the BPD population is approximately 33% as shown in two point prevalence studies[1,2] The utilization rate in the CHOP NICU's own BPD population is approximately 80%. The respiratory therapists at CHOP monitor each patient and per policy stop the therapy and notify the doctor if the heart rate increases by more than 20%. Per the adverse drug reaction policy (TY-7-07), if therapy requires permanent discontinuation or a significant modification to the dose it is reported to pharmacy. A report from the adverse drug reaction team shows no adverse drug reactions related to albuterol in the NICU for the past 3 years.

With the frequent utilization in NICUs and the low rate of adverse reaction seen in the literature, as well as in our hospital, this study does not significantly increase the risk to these patients.

1.6 Compliance Statement

This study will be conducted in full accordance all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, 21 CFR Parts 50, 56 and 312 and the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation (ICH). All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent, and will report unanticipated problems involving risks to subjects or others in accordance with The Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

The overall objective of this study is to determine if nebulized albuterol is safe and effective for the treatment of ventilated infants with BPD.

2.1 Primary Objective

The primary objective of this study is to determine if Albuterol Sulfate improves the pulmonary dynamics of mechanically ventilated infants with BPD, specifically by an improvement in forced expiratory flow at 75% of forced vital capacity (FEF75) post medication.

2.2 Secondary Objectives

The secondary objectives are to:

- Determine if administration of albuterol is safe in the infant population with BPD by measure of hemodynamic side effects.
- Determine which dose of albuterol is most effective with the least amount of side effects seen by comparison of change in pulmonary mechanics and observation of hemodynamics changes.

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

3.1.1 Screening Phase

Subjects will be identified from daily bed census data by CLDP. Potential subjects will be screened by the study investigators using the protocol inclusion and exclusion criteria. All study investigators are clinical members of the CLDP and care for infants with CLD on a daily basis. During their daily medical care they will notify the PI and lead investigator of infants that may be appropriate for the study. In addition, the CLDP team have multidisciplinary sit down rounds weekly and screening for potential studies occur at this time as well. The infant's parent/guardian will be approached by the study investigators in person and permission (in the form of written informed consent) will be obtained, prior to any study related procedures being performed

3.1.2 Study Treatment Phase (start of the study intervention)

After informed consent is obtained the infant will be assessed by a study team member and baseline data will be collected on the ventilator settings and pulmonary dynamic measures as well as hemodynamics including cardiac rhythm. The research pharmacy will be informed of the enrollment of the subject and they will randomize and blind the treatment phases and deliver the medication to be used in the first treatment group. Each subject will be randomly assigned to each treatment group in random order and receive each medication every 4 hours for 24 hours with a 6 hour washout phase in between each treatment group.

3.2 Allocation to Treatment Groups and Blinding

The contents of the study medications (placebo and 2 albuterol doses) for administration will be blinded by a research pharmacist in the investigational pharmacy. Each medication will be delivered to the bedside in the same packaging and placed in the medication room in the patient medication bin so the bedside clinical respiratory therapists will not know which dose of medication or placebo is being delivered. Each treatment dose will be drawn up in a syringe with 3cc of volume. All doses will be placed in a brown light protected bag with only the patient information and the study number and treatment group number labeling. Treatment group labeling is only to indicate group 1, 2, or 3 so the bedside staff is aware where the patient is in the timeline of the study and will reliably know when to return the patient back to usual care of ordered aerosolized medication after the final treatment group and washout period. No medication name or dosage will be on the syringe or packaging.

Randomization will be done as follows. Study participants will be randomly assigned to 1 of 6 treatment sequences (A-F) using block randomization (block size = 6) in a 1:1:1 ratio (see table below). The randomization sequence will be obtained using the "ralloc" – random allocation of treatments in controlled trials function in Stata version 13.1. Randomization envelopes, log and labels will be created by the study team and provided to the research pharmacy. The randomization envelopes will consist of one envelope for each randomization block. Inside the envelope will have a slip of paper for each of the 6 sequences labeled as A-F. Each letter corresponds to the randomization sequence as listed in the table below. Only the investigational pharmacist will know what letter they select from the envelope and which sequence it will refer to for each patient at the time of randomization. The investigational pharmacist will record which randomization scheme was assigned to subject ID for unblinding after study completion. The randomization log will be held with the investigational pharmacy until study completion.

Treatment: X=Placebo; Y=1.25mg Albuterol; Z=2.50 mg Albuterol	
Treatment Sequence ID	Treatment Sequence
A	XYZ
B	XZY
C	YXZ
D	YZX
E	ZXY
F	ZYX

3.3 Study Duration, Enrollment and Number of Sites

3.3.1 Duration of Study Participation

The study duration per subject will be approximately 98 hours or 4 days with no follow-up.

3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

This study will enroll 25 infants from the N/IICU at CHOP.

3.4 Study Population

3.4.1 Inclusion Criteria

1) Infants $\geq$ 36 weeks corrected gestational age to 1 year of age
2) Diagnosis of BPD in accordance with the NICHD definition
3) May have a current order for short acting bronchodilator, not required
4) Mat have congenital Anomalies unless one or more of the exclusion criteria are met, not required
5) Receiving conventional mechanical ventilation via an artificial airway (endotracheal tube or tracheostomy) via Draeger V500 ventilator
6) Parental/guardian permission (informed consent).

3.4.2 Exclusion Criteria

1) Airway leak > 10%
2) Unilateral lung disease
3) Current order for inhaled anticholinergic (i.e. ipratropium bromide)
4) Active pulmonary or systemic infection
5) Scheduled order for other medication that cause bronchodilation (i.e. Atrovent, magnesium sulfate, ketamine, etc.)

Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

4 STUDY PROCEDURES

4.1 Screening Visit and Commencement of Study

The following evaluation will be done prior to the study:

- Informed Consent
- Physical Exam
- Vital Signs including cardiac rhythm (those routinely recorded as part of clinical care)

- Ventilatory parameters and pulmonary mechanics measures from the ventilator (as recorded as part of clinical care)
- Medical Record Review
- 6 hour washout phase (for subjects with an active scheduled albuterol order)

4.2 Study Treatment Phase

After initial assessments have been performed, the research pharmacy will randomize the medications for each treatment phase and blind the medications. Once the medication is delivered to the bedside the Respiratory Therapist assigned to the patient will administer the study drug in accordance with department procedure. Each subject will rotate through each treatment group in random order. Each treatment group will last 24 hours from the time of the delivery of the first dose of the medication to the time of delivery of the last dose of medication. Each dose of medication will be delivered every 4 hours. There will be a 6 hour washout phase in between each treatment group and a 6 hour monitoring period after the last dose of medication in the last treatment group is given. If any subject has the following assessment qualities observed by both RT and attending physician a dose of albuterol can be ordered off protocol: (1) new onset of lower airway wheeze or diminished breath sounds with no other causes, (2) reduction in exhaled tidal volume on ventiltor if in pressure ventilation or increase in pressure if in volume ventilation. If a dose of albuterol is given by the medical team than the washout phase clock will restart to ensure a 6 hour washout time inbetween each phase. If an infant requries 2 doses they will be withdrawn from the study.

4.2.1 Equipment Used in the Study

4.2.1.1 Ventilator

The ventilator that if preferred to be used for all BPD infants on the unit is the Draeger V500. We will not change the ventilator for the purposes of this study. If an infant is not on a V500 ventilator they will not be eligible for inclusion into the study.

4.2.1.2 Nebulizer

The nebulizer used for all infants in the N/IICU on a ventilator at CHOP is the Aeroneb Solo. This is a vibrating mesh nebulizer that does not add any additional flow into the ventilator circuit. The use of this nebulizer is standard practice in the N/IICU at CHOP.

4.2.2 Measurements

The following baseline measures will be collected prior to the delivery of the first treatment group (unless otherwise stated) and trended throughout the end of the study:

- Vital Signs: (heart rate (HR), blood pressure (BP) and oxygen saturation (SpO2)) that are recorded as part of clinical care will be documented and trended for the study
- Cardiac Rhythm

- Ventilator parameters (tidal volume (Vt), total respiratory rate (RR), Positive End Expiratory Pressure (PEEP), peak inspiratory pressure (PIP), compliance (Crs), resistance (Rrs), mean airway pressure (MAP), Peak Expiratory Flow (PEF), FEF75 and FiO_2. All parameters except the FEF75 are routinely documented as part of clinical care and will be recorded and trended for the study. The FEF75 will be performed by the study team by performing measurements of the flow/volume loop from a screenshot picture of the ventilator screen (a function the ventilator can perform).

4.3 Subject Completion/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 for adverse events (AEs) or if the infant is unable to complete a 6 hour washout phase without the medical team ordering a dose of albuterol to be given. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, it will be recorded in the source documents and on the case report form (CRF).

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Screening and Monitoring Evaluations and Measurements

5.1.1 Medical Record Review

Include a listing of the variables that will be abstracted from the medical chart (paper or electronic).

- Date of birth and gestational age at birth
- Weight at birth and at the time of study
- Primary and secondary diagnoses, including evidence of pulmonary hypertension, if present
- Medication history particularly in regard to post-natal steroid use, inotropic support, sedatives and use of inhaled nitric oxide.
- Demographic characteristics including race, gender and age will be recorded from the electronic patient record (EPIC) and parental interview.

5.1.2 Physical Examination

Baseline physical examination will be performed including pulmonary assessment. Examinations performed and charted in EPIC before and after medication delivery by the clinical respiratory therapist will be tracked.

5.1.3 Vital Signs

Vital signs for the study will be recorded form those documented for clinical care. Any vital signs seen outside the ranges considered clinically normal for each subject will be reported to the medical team as standard practice. All bedside care team members will be aware that the subject is enrolled in the study. BP will be monitored using the standard automated device and cuff that is being used in the ward currently. A limb that is free of vascular access and other contraindications for BP measurement will be used. The BP measurements that are performed as standard of care for this patient will be utilized and trended for the duration of the study.

HR and Pulse oximetry will be monitored continuously as is the standard of care for ventilated infants in the N/IICU. FiO2 will be titrated to achieve the SpO2 targets set for the infant by the care team. RR will be recorded from the ventilator.

5.1.4 Ventilatory Parameters

The following parameters will be collected and trended from the ventilator:

- RR
- Vt
- MAP
- PIP
- PEEP
- Crs
- Rrs
- PEF
- Screen shot of flow volume loop for measurement of PEF and FEF75

5.2 Efficacy Evaluations

5.2.1 Measures

Differences in premedication and post medication parameters Crs, Rrs, PIP, Vt, PEF and FEF75 will be compared for each medication administration, in each treatment group. Each treatment group will also be compared with each other in each subject to determine not only the efficacy of each treatment but also if one is more effective than the other.

5.3 Safety Evaluation

Subject safety will be monitored for adverse events. All patients will be on continuous monitoring of heart rate and SpO2 throughout the study. All subjects will be monitored for the following known side effects of the medication:

- Tachycardia
- Hypertension
- Arrhythmia

6 STATISTICAL CONSIDERATIONS

6.1 Primary Endpoint

The primary endpoint is to collect flow volume loop graphic and measure FEF75 on 25 infants' pre and post each treatment throughout each of the 3 treatment groups.

6.2 Secondary Endpoints

Secondary endpoints will include the following:

- Measurement in PIP, Vt, PEF, Rrs and Crs values before and after each treatment throughout each of the 3 treatment groups.
- Measurement in HR, BP and cardiac rhythm before and after each treatment and throughout each of the 3 treatment groups.

6.3 Statistical Methods

6.3.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender).

6.3.2 Efficacy Analysis

For the Primary Objective of this study, paired t-test or Wilcoxon sign will be utilized for the assessment of improvement in FEF75 of 0.6 ml/sec by independently comparing pre and post treatment measures for each dose delivered for all three treatment groups.

For the Secondary Objective of the study, we will compare the mean change in FEF75 pre- and post-treatment between the 3 treatment arms. More specifically, we are proposing a 3 X 3 cross-over study design to compare 3 treatments. Treatment doses be randomly assigned to participants at baseline line (treatment 1), then following a washout period, participants will be randomly assignment to receive one of the two remaining treatments (treatment 2), and then finally after an additional washout period will receive the remaining treatment (treatment 3). For this analysis we will use a random effects model inclusive of treatment dose and treatment order to account for potential correlation of FEF75 measurements between treatment doses (despite use of a hypothesize sufficient washout period). Will apply the mixed effects methodology for data analysis using the Mixed command in STATA.

6.3.3 Safety Analysis

All subjects enrolled in the study will be included in the safety analysis. The frequencies of AEs by type, body system, severity and relationship to intervention will be summarized. SAEs (if any) will be described in detail. Additionally, AE's and SAE's will be reported to the IRB as described in sections 4.3 and 8.0 of this protocol.

6.4 Sample Size and Power

Since FEF75 has not been used as an outcome measure in ventilated infants with BPD prior, we collected pre and post treatment data from 7 patients that would meet our inclusion criteria. We observed a mean change in FEF75 of 1.3 ml/sec with a standard deviation of 0.8 ml/sec. Based on these preliminary data, we performed our sample size calculation in two ways. We first calculated the necessary number of participants to detect a mean difference of 0.6ml/sec (a conservative estimate of approximately half of effect size measured in our pilot data) using a paired t-test for two correlated means (analogous to the statistical analysis that will be performed for our primary objective). Based on an alpha of 0.05, a sample of approximately 25 infants will provide 90% power to detect a difference of 0.6mL from a baseline mean of 2.6mL/sec and a post-treatment mean of 3.2

Next, we performed a sample size calculation for our second objective. We used simulation with 200 replications to model the necessary number of subjects for a generalized linear model based on an estimated correlation of 0.5 between each of the mean FEF75 change values for the 3 treatment doses. The power provided by several sample sizes is shown for 3 different effect sizes in the table below. Based on this calculation, a sample size of 25 subjects with provide greater than 80% to detect a mean difference of 0.6ml/sec between the 3 treatment doses, accounting for likely correlation between each measure. Therefore, we plan to enroll 25 subjects in this study.

Sample Size	Power to detect a specified mean change in FEF75		
	0.5ml/sec	0.6ml/sec	0.7ml/sec
20	0.56	0.71	0.78
25	0.70	**0.82**	0.87
30	0.80	0.86	0.93

6.5 Interim Analysis

Adverse events will be monitored throughout the study. The Chronic Lung Diseases Program team will review the AE data monthly. If any safety issues are identified upon review, further study will be discontinued.

7 STUDY MEDICATION (STUDY DEVICE OR OTHER STUDY INTERVENTION)

7.1 Description

7.1.1 Packaging

Albuterol is routinely dispensed in multidose light protective bottles or individual unit of use in a foil packaging labeled with percentage solution (0.5%), milligram dosage and milliliters of fluid (ex, 5mg/ml or 2.5mg/0.5ml). Sterile Saline (0.9%) for inhalation will be used for the placebo and is packaged in individual 3cc pink ampules or in multiuse bottles. For this

study as we are randomizing and blinding the dosage. To do this the treatment doses will be prepared by a research pharmacist in the investigational pharmacy. Each treatment dose will be drawn up in a syringe with 3cc of volume. All doses will be placed in a brown light protected bag with only the patient information and the study number and treatment group number labeling as outlined in section 3.2. No medication name or dosage will be on the syringe or packaging. As this medication is routinely used at CHOP we will utilize mediation that is stocked by the pharmacy. There will be no special delivery of mediation for this study.

7.1.2 Labeling

Albuterol Sulfate (salbutamol) is a relatively selective beta2-adrenergic bronchodilator. The primary action is to stimulate adenyl cyclase, the enzyme that catalyzes the formation of cyclic-3',5'-adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP) in beta0adrenergic cells. The increased AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells. Controlled clinical trials have shown that inhaled albuterol can produce a cardiovascular effect in some patients, as measured by HR, BP and ECG changes such as flattening of T wave, prolonged QTc interval and ST segment depression. Most patients exhibited an onset of improvement in pulmonary function within 5 min and remained close to peak for 2 hours with continued improvement in lung function for 3-4 hours.

7.1.3 Dosing

Dosing will be 2.5 mg and 1.25 mg of Albuterol and 3ml of sterile saline as randomized by the research pharmacy. Each participant will receive each dose. There is no recommended dosing by the manufacturer as Albuterol is not FDA approved for this population.

7.1.4 Treatment Compliance and Adherence

The blinded medication will be administered according to the research protocol by the clinical respiratory therapist assigned to the patient in accordance with departmental protocol.

8 SAFETY MANAGEMENT

8.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

8.2 Adverse Event Reporting

Unanticipated problems related to the research involving risks to subjects or others that occur during the course of this study (including SAEs) will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

8.3 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a subject who has received an intervention (drug, biologic, or other intervention). The occurrence does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All AEs (including serious AEs) will be noted in the study records and on the case report form with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event.

8.4 Definition of a Serious Adverse Event (SAE)

A SAE is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- death,
- a life-threatening event (at risk of death at the time of the event),
- requires prolongation of existing hospitalization, or
- a persistent or significant disability/incapacity

Important medical events that may not result in death or be life-threatening may be considered a serious adverse drug event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A distinction should be drawn between serious and severe AEs. A severe AE is a major event of its type. A severe AE does not necessarily need to be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but would not be an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

8.4.1 Relationship of SAE to study drug or other intervention

The relationship of each SAE to the study intervention should be characterized using one of the following terms in accordance with CHOP IRB Guidelines: definitely, probably, possibly, unlikely or unrelated.

8.5 IRB/IEC Notification of SAEs and Other Unanticipated Problems

The Investigator will promptly notify the IRB of all on-site unanticipated, serious Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed using the eIRB system and in accordance with the timeline below. External SAEs that are both unexpected and related to the study intervention will be reported promptly after the investigator receives the report.

Type of Unanticipated Problem	Initial Notification (Phone, Email, Fax)	Written Report
Internal (on-site) SAEs Death or Life Threatening	24 hours	Within 2 calendar days
Internal (on-site) SAEs All other SAEs	7 days	Within 7 business days
Unanticipated Problems Related to Research	7 days	Within 7 business days
All other AEs	N/A	Brief Summary of important AEs may be reported at time of continuing review

8.5.1 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 (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

8.6 Investigator Reporting of a Serious Adverse Event to Sponsor

Reporting must be consistent with regulatory, sponsor or GCRC requirements (if applicable)

8.7 Medical Emergencies

Any medical emergency that may arise will be treated by the N/IICU bedside team in accordance with standard practice and protocols. Emergency unblinding may occur in order to assist in clinical treatment decisions when an unexpected adverse event occurs. The clinical team will confer with the PI and the PI will make the request to the investigational pharmacy,

9 STUDY ADMINISTRATION

9.1 Treatment Assignment Methods

9.1.1 Randomization

Randomization will occur as detailed in section 3.2.

9.1.2 Blinding

Blinding will occur as outlined in section 3.2.

9.2 Data Collection and Management

The information collected will be entered into a password protected computerized database using RedCap. Confidentiality will be ensured from abstraction through analysis by utilizing the HIPPA functions in RedCap. To ensure security, a copy of the data collected will be

saved on a password-protected file in the Division of Neonatology Chronic Lung Disease HIPPA protected @CHOP community. Only members of the study team will have access to the @CHOP Community. Data will be unblinded after the study to ensure uniformity and continuity of all data for inclusion in analysis. It will then be de-identified for data analysis and dissemination in abstract and manuscript form. All Identified data will be destroyed 6 years.

9.3 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy and that the investigator and other site personnel will not use such data and records for any purpose other than conducting the study.

No identifiable data will be used for future study without first obtaining IRB approval. The investigator will obtain a data use agreement between the provider (the PI) of the data and any recipient researchers (including others at CHOP) before sharing a limited dataset.

9.4 Regulatory and Ethical Considerations

9.4.1 Data and Safety Monitoring Plan

There will be a monthly meeting among the study investigators and the Chronic Lung Disease Program team to discuss and monitor data and safety. Data will be unblinded after the study to ensure uniformity and continuity of all data for inclusion in analysis. It will then be de-identified for data analysis and dissemination in abstract and manuscript form. PI will monitor and oversee the study progress, accuracy and security of the data.

9.4.2 Risk Assessment

The risk of this study is associated with side effects of albuterol sulfate for subjects that have not been ordered this therapy as part of standard care. For subjects that have been ordered for schedule therapy by their medical team the risks are different. The risk of change of efficacy and toxicity from the ordered dose as well as the placebo and washout phases where no medication at all will be received.

Medication packaging for albuterol states warning of use as paradoxical bronchospasm, deterioration of asthma, cardiovascular effects and hypersensitivity reactions. General Precautions include use with individuals that have cardiovascular disease (specifically coronary insufficiency, cardiac arrhythmias and hypertension), patients with convulsive disorders, hyperthyroidism or diabetes mellitus. Clinically significant changes in systolic and diastolic blood pressure have been seen after use of bronchodilators. These cautions for use from the manufacturers are intended for individuals within the targeted range of approval receiving therapy with minimal monitoring, including those at home on no monitoring. The subjects enrolled in this study will all be in the intensive care unit on continuous monitoring as a baseline for clinical care for their underlying disease. This increased monitoring allows the bedside providers to respond and notify the medical and study teams with any change or abnormality related to the study treatments.

The participants in this study will be more closely monitored for side effects in relation to albuterol as well as efficacy that currently is not routinely done in standard practice. Clinical assessment will be performed pre and post treatment as per respiratory therapy standard. Systolic and diastolic blood pressure will be documented as part of the study for trend with treatment.

9.4.3 Potential Benefits of Trial Participation

There are no direct benefits to the subject for participating in the study as we will not know the most effective dose for the patient until the conclusion of the study. The benefits are for future patients with BPD to assist with determining the most effective dose of Albuterol Sulfate with the lowest possible side effects.

9.4.4 Risk-Benefit Assessment

The risk of participation in the study is a minor increase over minimal risk as the risks are reasonably proportional to those these infants experience with their current medical condition and the participants will be closely monitored for any potential side effects of the medication. The infants will not receive any direct benefit, however this study will assist us in gaining a better understanding of what role, if any, albuterol can play in the treatment of severe BPD.

For subjects that currently do not have albuterol as part of their treatment regime, the risks are those of the side effects of the medication listed in section 9.4.2 (i.e. increased heart rate, increased blood pressure, etc.). For subjects that have an order for scheduled albuterol, the risk is that they will receive at least one dose of albuterol that is different than what was prescribed by the medical team as well as absence of a prescribed medication during the washout phases. The subjects will be monitored not only during the treatment phases but also during the washout phases. If a subject is assessed by the medical team and deemed in need of a bronchodilator during the washout phase than they are able to order a one-time treatment. There are recommendations as to which clinical symptoms will respond to a bronchodilator such as albuterol as well as when subjects will be withdrawn from the study because of the need for these medications in section 4.2. Documentation of the number of these as needed therapies for each patient will be tracked as well as the pre and post FEF75 and ventilator mechanics that are collected during each treatment phase. Therefore, the overall risk-benefit assessment is favorable.

9.5 Recruitment Strategy

Subjects fulfilling the inclusion criteria of the study and staying in the N/IICU of The Children's Hospital of Philadelphia will be recruited. Advertising will not be used to recruit subjects. Prospective subjects will be identified from bed census data by members of the Chronic Lung Diseases Program. All study investigators are clinical members of the CLDP and care for infants with CLD on a daily basis. During their daily medical care they will notify the PI and lead investigator of infants that may be appropriate for the study. In addition, the CLDP team have multidisciplinary sit down rounds weekly and screening for potential studies occur at this time as well. A study investigator will approach the parent/guardian of the subject in person if the inclusion criteria are met.

9.6 Informed Consent/Assent and HIPAA Authorization

Parents of the subjects will be approached by either the members of the Chronic Lung Disease Program or study investigators to obtain informed consent/ HIPAA Authorization. The subjects will be permitted to take as much time as they need to make a decision. The investigators will be available to answer any questions or concerns about the study and to ensure that the parent/guardian signing the consent document comprehends the nature of the study, the study procedures and the risks and benefits of participation. Entry into the study will not be coerced. Study procedures will not proceed without documentation of consent. Also, HIPAA Authorization will be included as a combined consent-authorization document.

9.6.1 Waiver of Assent

Assent is to be waived under 45 CFR 46.408, as the capability of all of the infants is so limited that they cannot reasonably be consulted.

9.7 Payment to Subjects/Families

There will be no payments made to subjects or parents/guardians for participation in the study.

10 PUBLICATION

The study investigators plan to publish the findings of this study in a peer-reviewed journal. Any results shared at conferences or in papers will not contain identifiable patient information.

11 REFERENCES

1. Guaman MC, Gien J, Baker CD, Zhang H, Austin ED, Collaco JM. Point Prevalence, Clinical Characteristics, and Treatment Variation for Infants with Severe Bronchopulmonary Dysplasia. Am J Perinatol 2015 Mar4; epub ahead of print.

2. Slaughter JL, Stenger MR, Reagan PB, Jadcherla SR. Inhaled bronchodilator use for infants with bronchopulmonary dysplasia. Journal of Perinatology 2015;35:61-65.

3. Schuepp KG, Straub D, Moller A, Wildhaber JH. Deposition of aerosols in infants and children. Journal of Aerosol Medicine 2004;17(2):153-156.

4. Amirav I, Newhouse MT. Deposition of small particles in the developing lung. Pediatric Respiratory Reviews 2012;13:73-78.

5. Fink JB. Aerosol delivery to ventilated infant and pediatric patients. Respiratory Care 2004;49(6):653-665.

6. Dubus JC, Vecellio L, De Monte M, Fink JB, Grimbert D, Montharu J, Valat C, Behan N, Diot P. Aerosol deposition in neonatal ventilation. Pediatric Research 2005;58(1):10-14.

7. Kolher E, Jilg G, Avenarius S, Jorch G. Lung Deposition after inhalation with various nebulizers in preterm infants. Arch Dis Child Fetal Neonatal Ed 2008;93:F275-F279.

8. Fok TA, Monkman S, Dolovich M, Gray S, Coates G, Paes B, Rashid F, Newhouse M, Kirpalani H. Efficiency of aerosol medication delivery from a metered dose inhaler versus jet nebulizer in infants with bronchopulmonary dysplasia. Pediatric Pulmonology 1996;21:301-309.

9. Ng G, da Silva O, Ohlsson A. Bronchodilators for the prevention and treatment of chronic lung disease in preterm infants (Review). The Cochrane Library 2012;6:1-21.

10. Gappa M, Gartner M, Poets CF, von der Hardt, H. Effects of salbutamol delivery from a metered dose inhaler versus jet nebulizer on dynamic lung mechanics in very preterm infants with chronic lung disease. Pediatric Pulmonary 1997;23:442-448.

11. Denjean A, Guimaraes H, Migdal M, Miramand JL, Dehan M, Gaultier C. Dose-related bronchodilator response to aerosolized salbutamol (albuterol) in ventilator dependent premature infants. J Pediatr 1992;120:974-9.

12. Hendrick JA, Baker JW, Atlas AB, Naz AA, Lincourt WR, Trivedi R, Ellworth A, Davis AM. Safety of daily albuterol in infants with a history of bronchospasm: A multi-center placebo controlled trial. The open respiratory medicine journal 2009;3:100-106.

13. Kaashmiri M, Shepard J, Goodman B, Lincourt WR, Trivedi R, Ellsworth A, Davis AM. Repeated dosing of albuterol via metered-dose inhaler with acute obstructive airway disease. Pediatric Emergency Care 2010;26(3):197-202.

14. Fok TF, Lam K, Ng PC, So HK, Cheung KL, Wong W, So KW. Randomized crossover trail of salbutamol aerosol delivered by metered dose inhaler, jet nebulizer, and ultrasonic nebulizer in chronic lung disease. Arch Dis Child Fetal Neonatal Ed 1998;79:F100-F104.

15. Rotschild A, Solimano A, Puterman M, Smyth J, Sharma A, Albersheim S. Increased compliance in response to salbutamol in premature infants with developing bronchopumonary dysplasia. J Pediatr 1989;115:984-91.