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NYU Langone Health

EFFICACY OF COMBINED NEBULIZED HYPERTONIC SALINE AND CHEST PERCUSSION THERAPY IN ACUTE VIRAL BRONCHIOLITIS

A pilot, non-randomized, single-site clinical study investigating the efficacy of combined therapy of nebulized 3% hypertonic saline and chest percussion therapy in pediatric patients with acute viral bronchiolitis.

Principal Investigator:	Tuan Nguyen, D.O. Department of Pediatrics 259 First Street, Mineola, NY 11501 tuan.nguyen@nyulangone.org 516-663-3677, 405-535-7093
Research Mentor:	Arsenia Asuncion, M.D., FAAP, MACMD Department of Pediatrics 259 First Street, Mineola, NY 11501 Associate Professor of Pediatrics Assistant Dean, Clinical Education Associate Director, Pediatric Critical Care Medicine NYU Grossman Long Island School of Medicine NYU Langone Hospital - Long Island arsenia.asuncion@nyulangone.org 516-663-4742
Co-investigators:	Raphael Gildengorn, M.D. Diana Gonzalez-Golden, M.D. Jenika Mitchell, M.D. Zuhal Mojaddidi, M.D. Shanta Ramsaran, D.O.
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Study Product Provider:	Nephron

Initial version: 14 May 2024

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation (“ICH”) Guideline for Good Clinical Practice (“GCP”) (sometimes referred to as “ICH-GCP” or “E6”) will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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List of Abbreviations

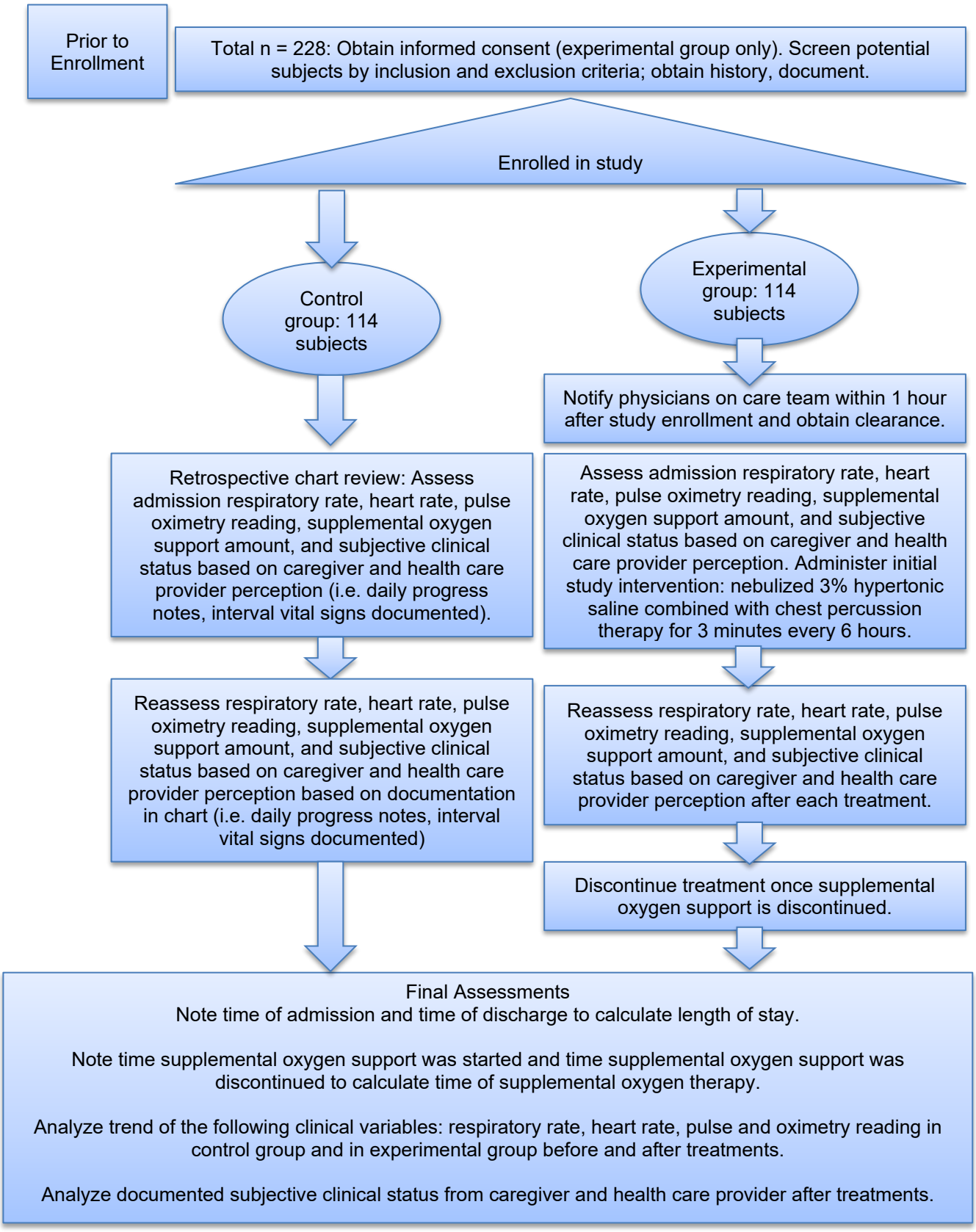
AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FFR	Federal Financial Report
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States

Protocol Summary

Title	Efficacy of combined nebulized hypertonic saline and chest percussion therapy in acute viral bronchiolitis
Short Title	Combined nebulized hypertonic saline and chest percussion in pediatric bronchiolitis
Brief Summary	This study will examine the efficacy of combined nebulized hypertonic saline with chest percussion therapy in patients age 0 to 24 months admitted to the general inpatient pediatrics unit with acute bronchiolitis. 3% nebulized hypertonic saline treatments combined with 3 minutes of chest percussion therapy will be administered every 6 hours of patients selected for the study.
Phase	N/A
Objectives	Primary outcomes measured will be length of hospital stay and time on supplemental oxygen support, both to be measured in hours. The hypothesis will be that combined nebulized hypertonic saline and chest percussion therapy will decrease length of hospital stay and time on supplemental oxygen support. Secondary outcomes measured will be clinical response (respiratory rate, heart rate, pulse oximetry reading), subjective perceptions of caregivers and health care team, and cost-benefit.
Methodology	Cross-sectional quasi-experimental, open, non-randomized clinical study
Endpoint	Primary endpoints include length of hospital stay and time on supplemental oxygen therapy. Secondary endpoints include trend of respiratory rate, heart rate, and pulse oximetry reading following treatments and subjective perceptions of patients' clinical status based on caregiver and health care team.
Study Duration	12 months
Participant Duration	The duration of participation will begin from time of admission to the general inpatient pediatrics unit until time of discharge from the general inpatient pediatrics unit. This duration may vary from patient to patient, on average will last approximately 1-5 days.
Duration of IP administration	The duration of product administration will begin from time of admission to the general inpatient pediatrics unit until time of discontinuation of supplemental oxygen therapy. This duration may vary from patient to patient, on average will last approximately 1-5 days.
Population	Pediatric patients age 0 to 24 months admitted to the general pediatrics unit admitted for acute bronchiolitis requiring supplemental oxygen therapy
Study Sites	NYU Langone Hospital – Long Island, general inpatient pediatrics unit (NP5)
Number of participants	228
Description of Study Agent/Procedure	Nebulized 3% hypertonic saline is a solution of 3% sodium chloride delivered via nebulizer and mask and is inhaled by the patient. It is FDA-approved for patients of all ages with sputum production, such as those with acute bronchiolitis. The chest percussion cup is a small, flexible cup made of vinyl that is used to provide gentle chest wall vibrations to assist with airway clearance and is utilized in patients of all ages with sputum production, such as those with acute bronchiolitis.
Reference Therapy	The 2014 American Academy of Pediatrics clinical practice guidelines for management of acute bronchiolitis does not recommend use of nebulized hypertonic saline or chest physiotherapy.
Key Procedures	N/A

Statistical Analysis	Descriptive statistics (mean ± standard deviation or median [25th, 75th percentiles] for continuous variables; frequencies and percentages for categorical variables) will be calculated separately by group. The two groups will be compared using the chi-square test or Fisher's exact test, as deemed appropriate, for categorical variables and the two-sample t-test or Mann-Whitney test for continuous data. For all analyses, the standard assumptions of Gaussian residuals and quality of variance will be tested. If the standard assumptions are not met, a transformation will be performed (i.e. logarithm transformation). Results will be brought back to the original units and reported as geometric means with their corresponding lower and upper confidence limits. For the assessment of number of days on supplemental oxygen therapy (i.e. count data), a Poisson, Negative Binomial (NB), Zero-Inflated Poisson (ZIP), or Zero-Inflated Negative Binomial (ZINB) model will be used. A result will be considered statistically significant at the $p<0.05$ level of significance. All analyses will be performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

SCHEMATIC OF STUDY DESIGN



1 Key Roles

Tuan Nguyen, DO, principal investigator
NYU Langone Hospital – Long Island
Department of Pediatrics
259 First Street, Mineola, NY 11501
516-663-3677
tuan.nguyen@nyulangone.org

Sub-investigators:
Raphael Gildengorn, M.D.
Diana Gonzalez-Golden, M.D.
Jenika Mitchell, M.D.
Zuhal Mojaddidi, M.D.
Shanta Ramsaran, D.O.

The sub-investigators are pediatric medical residents with competent knowledge in the background and relevant literate of acute bronchiolitis and the standards of care. They have had experience in interaction with this patient population and have demonstrated competence in pediatric physician milestones. All physicians listed as sub-investigators have experience in clinical research and obtaining consent, maintaining confidentiality, as well as experience with safe data handling. Per the residency program and New York State requirements, pediatric residents are not required to obtain a state medical license during their training, thus the listed sub-investigators do not have a New York State medical license number.

This study currently does not have an identified biostatistician due to no biostatistician available at NYU Langone Hospital – Long Island. A data analysis plan has been developed. Once enrollment begins, data collection will occur, but this data will not be analyzed until a biostatistician has been identified and added to this study. A biostatistician will be added at the earliest time possible pending NYU Langone Hospital – Long Island and NYU Grossman Long Island School of Medicine's administration and the biostatistic department's process on filling this position.

2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Acute bronchiolitis is a viral infection of the lower respiratory tract that primarily involves infants and young children and is only present in the pediatric population. It is the most common cause of hospitalizations in resource-rich countries. Bronchiolitis can be caused by a number of viruses, the most common being respiratory syncytial virus (RSV). [1] In the Northern Hemisphere, viral infections resulting in acute bronchiolitis increase beginning late October and will peak during the winter months of January and February and will decline through April. [2]

Bronchiolitis leads to airway inflammation, edema, and increased production of mucus. Causative viruses are spread via direct contact and inoculation at nasal mucosa or from inhalation of infective respiratory droplets. The viruses replicate in the nasopharyngeal airway and following a 4 to 6-day incubation period after transmission, the initial upper respiratory tract infection symptoms appear. Subsequent respiratory tract epithelial cell injury and necrosis occurs and this debris is aspirated into the lower respiratory tract, resulting in further inflammation, edema, and necrosis of the bronchioles, leading to airway narrowing and obstruction that is classic for acute bronchiolitis. [3]

The diagnosis of acute viral bronchiolitis is clinical, although use to molecular detection tests may help identify the causative organism. Infants and young children with acute bronchiolitis begin with upper airway symptoms of congestion, cough, and rhinorrhea that may progress to signs and symptoms of respiratory distress due to resultant lower respiratory tract obstruction such as tachypnea, accessory respiratory muscle use known as retractions, nasal flaring, grunting, or wheezing, and may also exhibit low oxygen saturations. [2] It is the resultant symptoms of lower respiratory tract obstruction that often lead to infants and young children with acute viral bronchiolitis to present to the emergency department and subsequently be admitted to the hospital.

The American Academy of Pediatrics (AAP) published guidelines in 2014 to help guide pediatricians in management of pediatrics patients with acute bronchiolitis. The strongest recommendations lie in supportive management measures, including oxygen supplementation, intravenous fluids if needed, and suctioning of the nose and/or mouth to relieve congestion. The AAP currently recommends against other treatments such as albuterol, antibiotics, steroids, saline nebulization, or chest physiotherapy, citing little to no significant efficacy of these treatment regimens. Over the years, there have been emerging studies investigating the use of these treatments and there has been some evidence demonstrating benefit in using nebulized saline treatments. Because of the non-invasiveness and low side effect profiles of nebulized hypertonic saline breathing treatments and chest percussion therapy, and their potential of improving severity of symptoms in children with acute viral bronchiolitis, it is reasonable to investigate treatment regimens that are outside the bounds of the current clinical practice guidelines, and this study intends combine these two treatments to investigate their efficacy as a combined treatment regimen for acute viral bronchiolitis.

2.2 Name and Description of the Investigational Agent

Nebulized 3% hypertonic saline is an inhaled respiratory solution composed of sodium chloride. It is dispensed as single 4 milliliter vials that are sterile, preservative-free, and non-pyrogenic. It is administered through a nebulizer via mask or inhalation tube apparatus. It is FDA-approved for patients of all ages with sputum production, such as those with acute bronchiolitis. However, there is no specific labeled use of this medication for pediatric patients with acute bronchiolitis.

The chest percussion cup is a commercially-available device used for chest physiotherapy. It is made of vinyl and shaped like a cup with an open end that provides percussion and a handle on the other end. It is utilized by gentle and repeated motions of percussion on the chest wall to create chest wall vibrations to induce airway clearance and is used in patients of all ages with sputum production, such as those with acute bronchiolitis. However, there is no specific labeled use of this device for pediatric patients with acute bronchiolitis.

2.2.1 Clinical Data to Date

Hypertonic saline nebulization

Hypertonic saline nebulization is one of the adjuvant therapies that has been used for management of acute viral bronchiolitis. Theories behind its efficacy lie within the proposed effects of airway hydration and reduction of edema as well as mucus clearance. [1] A 2017 Cochrane systematic review showed that patients with acute bronchiolitis who received hypertonic saline nebulization treatments had a significantly shorter length of stay in comparison with patients who received normal saline nebulization treatments. This shows that there may be some benefit in using hypertonic saline nebulization in the management of acute bronchiolitis. The review however did show a low quality in evidence as well as large variations between studies. [5] The 2014 American Academy of Pediatrics clinical practice guidelines has a moderate recommendation against the use of hypertonic saline nebulization in treatment for acute bronchiolitis, with the notion that new information may arise as further evidence on this treatment option emerges. [4] Because of the limited evidence and low quality of studies, the need for standardized and multi-centered studies remains in regards to the use of hypertonic saline nebulization in acute bronchiolitis.

The side effect profile of hypertonic saline nebulization treatments remains low. There is some concern with treatments causing bronchospasm, but a retrospective cohort studied showed a 0.3% rate of occurrence of this side effect. The concern for bronchospasm seems to increase with the increase in concentration of hypertonic saline nebulization treatments, as formulations range from 3% to 7%. Other adverse events were reported in this study and showed a 1.0% rate of occurrence, and these events involved excessive coughing, which was transient. [6] Other side effects that have been reported such as hypernatremia, desaturation, bradycardia, vomiting and diarrhea were minor and spontaneously resolved. [5]

Given the evidence of potential benefits of nebulized hypertonic saline in improvement of airway hydration, edema and clearance in conjunction with a very low side effect profile, its use in a study to determine its efficacy is justifiable.

Chest percussion therapy

Chest physiotherapy is a group of airway clearance techniques that may assist with clearance of mucus. These techniques include chest vibration or percussion, assisted coughing devices, and forced expiratory techniques.

A non-invasive and gentle chest physiotherapy device that can be used in pediatric patients such as those in the age group for this study is a chest percussion cup. The chest percussion cup is usually made of vinyl and shaped like a suction cup with a small handle on the closed end. The technique involves tapping/percussion of the chest with this cup to cause vibration of the chest wall. The theory behind this technique is that it will loosen mucus trapped in the lower respiratory tract and allow for ease of expectoration and airway clearance. This method has been used in treatment for acute bronchiolitis given the pathophysiology of mucus build-up and debris in the lower respiratory tract of patients with acute bronchiolitis who are often have difficulty clearing this mucus. [7]

In a systematic review evaluating the effects of airway clearance techniques in treatment for acute bronchiolitis, while concluding that respiratory therapy techniques such as chest percussion did not reduce the severity of the disease, the review did note that there were newer studies with positive results that had not been included. Furthermore, several studies in this review showed several positive outcomes, such as improvement in clinical scores, positive perception from caregivers on patients' clinical status, and improved oxygen saturation. One study also found that there was a noted decreased length of stay in patients with moderate disease. [8] However, due to the heterogenicity of these studies the use of chest physiotherapy in acute bronchiolitis remains controversial and need for further randomized controlled trials remains.

In regards to the side effect profile of chest percussion therapy, adverse effects of concern include excessive coughing and irritability. There were two case reports of rib fractures in children who received chest physiotherapy; however these were related to the more invasive forced expiratory techniques. Overall, the evidence lacked any statistically significant adverse outcomes following use of chest percussion therapy in children. [7] It can be concluded that chest percussion therapy is the least invasive of the chest physiotherapy techniques and the potential adverse effects of chest percussion therapy remain very low.

2.2.2 Dose Rationale

The dose for nebulized 3% hypertonic saline is a 1 vial (4 milliliters) every six hours. The timing of nebulized hypertonic saline is discussed in a Cochrane systematic review conducted for patients with cystic fibrosis, where the review concluded that hypertonic saline nebulization treatments every 6 hours may maximized airway clearance and perceived effectiveness.[9] Rationale for dosing in acute bronchiolitis was not found in literature for this dosing.

The frequency of chest percussion therapy with a chest percussion cup will be every six hours to pair with nebulized treatments. Chest percussion therapy will be provided for 3 minutes. There is currently no rationale available in literature for this dosing or duration.

2.3 Rationale

Over the years, many different interventions have been trialed for bronchiolitis, including antibiotics, glucocorticoids, antivirals, nebulized treatments, positive end-expiratory pressure respiratory support, and chest physiotherapy. The American Academy of Pediatrics published clinical practice guidelines for the diagnosis and management of acute viral bronchiolitis in 2014 which recommended minimal interventions and mainly focuses on hydration and oxygenation and did not recommend use of such interventions listed previously. [4] Despite these published guidelines, there remains a discordance and inconsistency in the care and management of patients admitted to pediatric units for acute viral bronchiolitis. Furthermore, there are some newer studies and evidence finding some value in a few of these interventions while other studies continue to lack evidence in the value of these interventions.

2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks

The side effect profile of hypertonic saline nebulization treatments remains low. There is some concern with treatments causing bronchospasm, but a retrospective cohort studied showed a 0.3% rate of occurrence of this side effect. The concern for bronchospasm seems to increase with the increase in concentration of hypertonic saline nebulization treatments, as formulations range from 3% to 7%. Other adverse events were reported in this study and showed a 1.0% rate of occurrence, and these events involved excessive coughing, which was transient. [6] Other side effects that have been reported such as hypernatremia, desaturation, bradycardia, vomiting and diarrhea were minor and spontaneously resolved. [5] There are no long-term risks associated with nebulized hypertonic saline and it is considered safe and inexpensive.

The side effect profile of chest percussion therapy, adverse effects of concern include excessive coughing and irritability. There were two case reports of rib fractures in children who received chest physiotherapy; however these were related to the more invasive forced expiratory techniques. Overall, the evidence lacked any statistically significant adverse outcomes following use of chest percussion therapy in children. [7] It can be concluded that chest percussion therapy is the least invasive of the chest physiotherapy techniques and the potential adverse effects of chest percussion therapy remain low.

There are no foreseeable physical, psychological, social, legal, or economic risks to participants by virtue of participation in this study. The value of information to be gained from this study may further guide clinicians on a more evidence-based approach to treatment of acute bronchiolitis in pediatric patients.

Because the study involves pediatrics, it is considered a study on a vulnerable population. There are no additional risks than those described previously.

Minimizing Risks
Because the study involves pediatrics, it is considered a study on a vulnerable population. There are no additional risks than those described previously.

Standard of care monitoring will be conducted for all study participants to minimize risk. This will include routine monitoring vital signs every 4 hours and routine care team monitoring from physician providers and nurses. As with all patients admitted to the general inpatient pediatrics unit, the call bell will always be within reach for the parents or legal guardians caring for the child, and whenever they have any concerns or questions, they are oriented to use the call bell to alert the care team. Respiratory therapists will be present while providing treatments and will alert the care team of any concerns or noted adverse events. Because of the low side effect profile of both nebulized 3% hypertonic saline and chest percussion therapy, these measures are deemed sufficient to minimize risks to subjects.

2.4.2 Known Potential Benefits
The potential benefits of nebulized 3% hypertonic saline treatments is improved airway clearance. A 2017 Cochrane systematic review showed that patients with acute bronchiolitis who received hypertonic saline nebulization treatments had a significantly shorter length of stay in comparison with patients who received normal saline nebulization treatments. This shows that there may be some benefit in using hypertonic saline nebulization in the management of acute bronchiolitis. [5]

The potential benefit of chest percussion therapy is improved airway clearance. Several studies in this review showed several positive outcomes, such as improvement in clinical scores, positive perception from caregivers on patients' clinical status, and improved oxygen saturation. One study also found that there was a noted decreased length of stay in patients with moderate disease. [8].

3 Objectives and Purpose
3.1 Primary Objective
The primary objectives of this study of nebulized 3% hypertonic saline treatments combined with chest percussion therapy in treatment of acute bronchiolitis in pediatric patients age 0 to 24 months admitted to the general inpatient pediatrics unit is to assess their efficacy on length of hospital stay and time on supplemental oxygen therapy.

3.2 Secondary Objectives
The secondary objectives of this study of nebulized 3% hypertonic saline treatments combined with chest percussion therapy in treatment of acute bronchiolitis in pediatric patients at 0 to 24 months admitted to the general inpatient pediatrics unit is to assess their efficacy on disease severity and subjective perceptions on effectiveness.

4 Study Design and Endpoints
4.1 Description of Study Design

Groups:
1. Control group: Patients meeting criteria as above prior to start date, beginning 12 months prior to start date of study, will be examined via retrospective chart review

2. Experimental group: All patients meeting criteria as above beginning start date of study will be enrolled in study to receive adjuvant therapy with 3% hypertonic saline nebulization treatments combined with 3 minutes of chest physiotherapy.

Statistical Methods:
Descriptive statistics (mean ± standard deviation or median [25th, 75th percentiles] for continuous variables; frequencies and percentages for categorical variables) will be calculated separately by group. The two groups will be compared using the chi-square test or Fisher's exact test, as deemed appropriate, for categorical variables and the two-sample t-test or Mann-Whitney test for continuous data.

For all analyses, the standard assumptions of Gaussian residuals and quality of variance will be tested. If the standard assumptions are not met, a transformation will be performed (i.e. logarithm transformation). Results will be brought back to the original units and reported as geometric means with their corresponding lower and upper confidence limits.

For the assessment of number of days on supplemental oxygen therapy (i.e. count data), a Poisson, Negative Binomial (NB), Zero-Inflated Poisson (ZIP), or Zero-Inflated Negative Binomial (ZINB) model will be used.

A result will be considered statistically significant at the $p<0.05$ level of significance. All analyses will be performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Sample Size Considerations:
The proposed sample size for this study is 228 subjects (n=114 per group). Based on data published by Gajdos, et al., the mean duration of hospitalization for bronchiolitis recorded in the study hospitals during previous years was 6.5 days and standard deviation = 3.5 days. For a type I error of 0.05 and a power of 0.80, for detecting a 20% decrease in duration of hospitalization, a total of 228 subjects would be included (114 subjects in each group).

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

The primary study endpoints with be length of hospital stay expressed in days and the time on supplemental oxygen support expressed in days, and these endpoints will be compared between the control and experimental group.

4.2.2 Secondary Study Endpoints

The secondary study endpoints will be clinical variables including respiratory rate, heart rate, and pulse oximetry reading and these endpoints will be compared between the control and experimental group. Other secondary study endpoints will be subjective clinical impressions based on caregiver and physician report, and these endpoints will be compared between the control and experimental group. A cost-benefit analysis may also be a potential secondary study endpoint. Because data collected from surveys will reflect the pediatric patients enrolled in the study only, the parents/caregivers and physicians who answer the surveys are not considered research subjects.

4.2.3 Exploratory Endpoints

There are no exploratory endpoints in this study.

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

In order to be eligible to participate in this study (experimental arm), an individual must meet all of the following criteria:

1. Age 0 to 24 months
2. Admitted to the general inpatient pediatrics unit
3. Has a diagnosis of acute bronchiolitis
4. Receiving supplemental oxygen support

Data collected for the control arm will be obtained via retrospective chart review for patients meeting the following inclusion criteria:

1. Age 0 to 24 months
2. Admitted to the general inpatient pediatrics unit

3. Has a diagnosis of acute bronchiolitis
4. Receiving supplemental oxygen support

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Admitted to the pediatric intensive care unit
2. Has an underlying pre-existing condition that may affect the respiratory system (includes bronchopulmonary dysplasia, reactive airways disease, asthma, restrictive lung diseases, other chronic lung diseases, etc.)
3. Has other comorbid conditions upon admission that may affect the respiratory system (includes pneumonia or other bacterial or fungal lung infections, acute exacerbation of reactive airways disease, acute exacerbation of asthma, pulmonary edema, pleural effusion, etc.)
4. Has an absolute contraindication to nebulized 3% hypertonic saline, for example, a history of an allergic or anaphylactic reaction
5. Is receiving other respiratory treatments such as bronchodilator treatments (i.e. albuterol or levalbuterol)
6. Is receiving other adjuvant therapy such as antibiotics, antivirals, glucocorticoids, corticosteroids, or diuretics

A potential study subject in the control arm via retrospective chart review who meets any of the following criteria will be excluded from this study:

1. Admitted to the pediatric intensive care unit
2. Has an underlying pre-existing condition that may affect the respiratory system (includes bronchopulmonary dysplasia, reactive airways disease, asthma, restrictive lung diseases, other chronic lung diseases, etc.)
3. Has other comorbid conditions upon admission that may affect the respiratory system (includes pneumonia or other bacterial or fungal lung infections, acute exacerbation of reactive airways disease, acute exacerbation of asthma, pulmonary edema, pleural effusion, etc.)
4. Has an absolute contraindication to nebulized 3% hypertonic saline, for example, a history of an allergic or anaphylactic reaction
5. Is receiving other respiratory treatments such as bronchodilator treatments (i.e. albuterol or levalbuterol)
6. Is receiving other adjuvant therapy such as antibiotics, antivirals, glucocorticoids, corticosteroids, or diuretics

5.3 Vulnerable Subjects

This study involves the pediatric population and will thus include vulnerable subjects.

Under Code of Federal Regulation guidelines, in accordance to 45 CFR 46.405, this study has been determined as a research study that involves greater than minimal risk with potential of direct benefit to individual subjects.

This study utilizes nebulized 3% hypertonic saline treatments and chest percussion therapy, both as previously described in section 2 of this protocol, have very minimal and transient side effects, if any, and are not associated with any serious adverse events.

Because this study involves pediatric participants age 0 to 24 months, assent cannot be assessed or given. Permission and consent from parents or legal guardians will be obtained as set forth in HHS regulations at 45 CFR 46.408.

This proposed research poses a greater than minimal risk with the potential for direct benefit to subjects. 3% hypertonic saline nebulization treatments have been used and studied previously in children with acute bronchiolitis and have not been shown to cause any serious adverse effects and may improve severity of illness. Chest physiotherapy via a chest percussor cup is a non-invasive and gentle technique that has been used and studied previously in children with acute bronchiolitis and have not been shown to cause any serious adverse effects.

5.4 Strategies for Recruitment and Retention

Recruitment strategies include identifying patients upon admission to the general inpatient pediatrics unit with the primary diagnosis of acute bronchiolitis that do not meet exclusion criteria for this study. No media services will be required. If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact research-contact-optout@nyumc.org or 1-855-777-7858.

Informed consent will be obtained at time of admission within private space of patient room and will be conducted in a sensitive manner, allowing consent to be provided in a clearly explained manner. Ample time will be provided for caregivers to decide on consent.

Information collected will be from the patient's medical chart to include age and gender. No other personal information will be required for this study. Only the primary investigator and any future added co-investigators of this study will receive this information. The target sample size for this experimental arm will be 114 patients and it is anticipated that approximately 200 patients will be screened to achieve this number. The source of participants will only be in the general inpatient pediatrics unit.

Upon patients' enrollment into the study, physicians on the patients' care team will be notified via in person or secure chat through the electronic medical record within 1 hour from patients' enrollment into the study and investigators will obtain clearance from these providers to begin the study treatments.

These physicians will also be notified at this time that they will be asked to answer subjective surveys assessing their patients' response to the study treatment. See Appendix 3.

Parents or caregivers or legal guardians of patients enrolled in this study will be approached at least once by the principal investigator or co-investigators while their child is undergoing study treatments. The timing of this encounter may vary and this encounter is to serve as a means to conduct the subjective caregiver interview. See Appendix 4. Investigators will aim to conduct the subjective caregiver survey at least once while their child is enrolled in the study and ideally will aim to conduct this interview once the child has received the study treatment for at least 24 hours. Parents/caregivers/legal guardians will be approached in a sensitive and calm manner by the principal investigator or co-investigators, and investigators will coordinate this timing with the care team as to not disrupt patient care responsibilities of physicians or nurses.

5.4.1 Use of DataCore/Epic Information for Recruitment Purposes

This study will utilize the institutional electronic medical record, Epic, to identify subjects.

The following elements will be submitted in the recruitment process via DataCore:

- Study personnel will subject a request to NYU Langone Health DataCore via iLab
- Study team members by role who will have access to search results
- Study eligibility criteria that include age, gender, admission diagnosis of acute bronchiolitis
- Data will be discarded 30 days after use and will be discarded by shredding paper documents and any electronic data obtained will be deleted.
- The study team is projected to search DataCore/Epic monthly bi-monthly over the course of the study and queries regarding eligible cases will run bi-month during the course of the study.

5.5 Duration of Study Participation

The duration of study participation will be from beginning of admission to the general inpatient pediatrics unit until the time of discharge from the general inpatient pediatrics unit. No follow up time period is required. This is a single phase pilot study.

5.6 Total Number of Participants and Sites

Recruitment will end when approximately 114 participants are enrolled. It is expected that approximately 200 participants will be enrolled in order to produce 114 evaluable participants.

5.7 Participant Withdrawal or Termination

5.7.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant

- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

5.7.2 Handling of Participant Withdrawals or Termination

There is no follow up period required in this study after patients are discharged from the general inpatient pediatrics unit and participation in the study has been completed. Participants may choose to withdraw from the study at any time and no information prior to or after withdrawal will be collected from this participant to be utilized in this clinical study. Upon participant withdrawal or termination, every effort will be made to undertake protocol-specific safety follow up procedures to capture adverse events, serious adverse events, and unanticipated problems. Given the safe profile of the medication (nebulized 3% hypertonic saline) and device (chest percussion cup) used, there is no anticipated risk of adverse events or serious adverse events.

5.8 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to principal investigator. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

6 Study Agent (Study drug, device, biologic, vaccine etc.) and/or Procedural Intervention

6.1 Study Agent(s) and Control Description

Nebulized 3% sodium chloride solution.

6.1.1 Acquisition

Study agent is readily available and acquired from the hospital pharmacy.

6.1.2 Formulation, Appearance, Packaging, and Labeling

Formulation:	inhaled solution
Active Ingredients:	Sodium Chloride
Inactive Ingredients:	Water
Appearance:	4 mL vial, clear solution
Packaging:	60 x 4 mL sterile unit single-dose vials in 1 carton
Labeling:	Sodium Chloride Inhalation Solution
Manufactured by:	Nephron Pharmaceuticals Corporation

This product is available through prescription only and commercially marketed.

6.1.3 Product Storage and Stability

Product is stored at room temperature 15° to 30° C (59° to 86° F). Avoid excessive heat and protect from freezing.

6.1.4 Preparation

Each single-use vial contains 4mL of sterile, preservative-free, non-pyrogenic Sodium Chloride 3% for respiratory therapy.

Directions for use: Hold vial, gently twist and pull off top. Invert and squeeze to dispense prescribed volume into nebulizer cup. Discard any unused solution and any unused solution in the nebulizer cup.

6.1.5 Dosing and Administration
Standardized dose of nebulized 3% sodium chloride will be provided from 4 mL vial and administered be every 6 hours.

6.1.6 Route of Administration
Nebulized, inhaled.

6.1.7 Starting Dose and Dose Escalation Schedule
Standard dose is from 4 mL vial. There is no dose escalation schedule.

6.1.8 Dose Adjustments/Modifications/Delays
There is no dose adjustment, modification, or anticipated delays.

6.1.9 Duration of Therapy
Duration of therapy will be while participants require supplemental oxygen support from the beginning of admission to the general inpatient pediatric unit until prior to discharge from the general inpatient pediatrics unit.

6.1.10 Tracking of Dose
Tracking of dose will be reviewed from documentation in the electronic medical record under medication administration record.

6.1.11 Device Specific Considerations
Chest percussion cups will be used in this study.

- Device size: 47 mm
- Device model: MC-2247 Pediatric Manual Percussor Cup
- Duration of treatment: 3 minutes
- Frequency of treatments: Every 6 hours while on supplemental oxygen therapy

6.2 Study Agent Accountability Procedures
Regular study medication reconciliation will be performed to document medication assigned, administered, and remaining. This reconciliation will be logged on the medication reconciliation on the medication orders.

7 Study Procedures and Schedule
7.1 Study Procedures/Evaluations
7.1.1 Study Specific Procedures

- Medical history will be obtained from interview and review of electronic medical records with consideration of time from patient's birth to current age upon admission
- Medication history, to include prescription and over-the-counter medications. Assessment of eligibility should include a review of permitted and prohibited medications.
- Physical examination, to include vital signs (including height and weight) and comprehensive examination of organ systems upon admission that includes constitutional, head, eyes, nose, mouth, neck, cardiovascular and circulatory, respiratory, gastrointestinal, and musculoskeletal. Targeted physical examinations on subsequent visits will include cardiovascular and respiratory systems. particularly respiratory and cardiovascular.
- Assessment of study agent adherence

7.1.2 Standard of Care Study Procedures
Regular standard of clinical care will be adhered during this study. Pediatric patients with acute bronchiolitis will often require supplemental oxygen support, as with all proposed participants in this study. Standard of clinical care in regards to providing supplemental oxygen support, escalation, weaning, and discontinuation of supplemental oxygen support, will be followed. Pediatric patients with acute bronchiolitis may also require fluid hydration via intravenous, subcutaneous, or nasogastric route. Standard of clinical care in regards to maintenance of intravenous, subcutaneous, or nasogastric tube lines and administration of fluids.

7.2 Laboratory Procedures/Evaluations

7.2.1 Clinical Laboratory Evaluations

There are no laboratory evaluations to be included in this study.

7.2.2 Other Assays or Procedures

Some pediatric patients with acute bronchiolitis may have a respiratory pathogen panel via PCR from nasopharyngeal swab. This information may be collected for additional data to be included in this study but is not required.

7.3 Study Schedule

7.3.1 Screening

Screening Visit Encounter (Day 0)

- Obtain informed consent of potential participant verified by signature on written informed consent for screening form.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria.
- Schedule study visits for participants who are eligible and available for the duration of the study.
- Provide participants with information regarding medication and device used.

7.3.2 Enrollment/Baseline

Patients enrolled in the study will be based on history and physical examination and diagnosis. No additional procedures are required to assess or confirm whether the patients still meet the eligibility criteria.

Patients, based on history, physical examination, and diagnosis, who are receiving any additional treatments or have other underlying comorbidities affecting their respiratory system will be excluded from the study.

Enrollment/Baseline Visit (Visit 1, Day 0)

- Obtain informed consent of potential participant verified by signature on study informed consent form.
- Verify inclusion/exclusion criteria.
- Obtain demographic information, medical history and medication history.
- Record vital signs, results of examinations, other assessments.
- Administer the study treatment.
- Study participants will be provided information on the continued study treatment schedule as well as the process of evaluation and surveying on response to study treatments.

7.3.3 Intermediate Visits

7.3.3.1 Intermediate visits

Intermediate visits will vary from participant to participant depending on their length of stay during their inpatient at admission.

Intermediate visits (once per shift during duration of admission)

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs, to include respiratory rate, heart rate, and oxygen saturation.
- Record current supplemental oxygen support settings.
- Administer the study agent or provide additional medication to the participant, in accordance with schedule – nebulized 3% hypertonic saline treatments combined with 3 minutes of chest percussion therapy every 6 hours while on supplemental oxygen support.
- Record participant's adherence to treatment program.
- Record subjective responses from providers and caretakers on participants' clinical response to treatment.

7.3.4 Final Study Visit

Final Study Visit (Day of hospital discharge)

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs to include respiratory rate, heart rate, and oxygen saturation.
- Record time of supplemental oxygen support order discontinuation.
- Record subjective responses from providers and caretakers on participants' clinical response to treatment.
- Record participant's adherence to treatment regimen.

7.3.5 Withdrawal/Early Termination Visit

At time of withdrawal or early termination of the visit, the following information will be collected:

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs to include respiratory rate, heart rate, and oxygen saturation.
- Record current supplemental oxygen support settings.
- Record subjective responses from providers and caretakers on participants' clinical response to treatment.
- Record participant's adherence to treatment regimen.

7.3.6 Unscheduled Visit

There are no unscheduled visits anticipated.

7.4 Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

8 Assessment of Safety

8.1 Specification of Safety Parameters

8.1.1 Definition of Adverse Events (AE)

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event

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

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

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

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

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Agent

The clinician's assessment of an AE's relationship to study agent (drug, biologic, device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used:

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals

or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.3 Expectedness

Tuan Nguyen, the primary investigator, will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study.

8.4 Reporting Procedures – Notifying the IRB

8.4.1 Adverse Event Reporting

Adverse event reporting will be recorded in Patient Safety Intelligence (PSI) electronic self-reporting database and to be reviewed by departmental adverse drug event committee and principal investigator. Once the adverse event is reported in the PSI system, the medication-related event will be automatically routed to all members of the adverse drug event committee to review the incident. All incidents reviewed will be examined by the committee and principal investigators in collaboration.

8.4.2 Serious Adverse Event Reporting

Adverse event reporting will be recorded in Patient Safety Intelligence (PSI) electronic self-reporting database and to be reviewed by departmental adverse drug event committee and principal investigator. Once the adverse event is reported in the PSI system, the medication-related event will be automatically routed to all members of the adverse drug event committee to review the incident. All incidents reviewed will be examined by the committee and principal investigators in collaboration.

According to CFR 21 CFR 312.32(c)(1), “the sponsor must notify FDA and all participating investigator in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies reporting … In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information. The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

1. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, anaphylaxis, anaphylactic shock);

Furthermore, according to 21 CFR 312.32(c)(2), “the sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor’s initial receipt of the information.”

As noted previously, an unanticipated adverse device effect could be considered an SAE (Section 8.1.2, Definition of Serious Adverse Event). For IDE studies, according to 21 CFR 812.150(a)(1), “an investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.” In addition, according to 21 CFR 812.150(b)(1), “A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.”

8.4.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator’s responsibility to report UPs to their IRB and to the study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI’s name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the study sponsor within 7 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the study sponsor within 7 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution’s written reporting procedures), the supporting agency head (or designee), and OHRP within 7 days of the IR’s receipt of the report of the problem from the investigator.

8.5 Reporting Procedures – Notifying the Study Sponsor

The study clinician will complete a SAE Form within the following timelines:

- All serious adverse events, whether related or unrelated, will be recorded on the SAE Form and submitted to the DCC/study sponsor within 24 hours of site awareness. See Section 1, Key Roles for contact information.
- Other SAEs regardless of relationship will be submitted to the study sponsor within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the DCC/study sponsor and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor contact information is provided in Section 1, Key Roles.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to FDA and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

8.6 Reporting Procedures – Notifying the FDA

The study sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND/IDE safety reports.

The following describes the IND safety reporting requirements by timeline for reporting and associated type of event:

- **Within 7 calendar days** (via telephone or facsimile report)
  Any study event that is:
  - associated with the use of the study drug
  - unexpected,
  - fatal or life-threatening

- **Within 15 calendar days** (via written report)
  Any study event that is:
  - associated with the use of the study drug,
  - unexpected, and
  - serious, but not fatal or life-threatening
    -or-
  - a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

The following describes the IDE safety reporting requirements by timeline for reporting and associated type of event:

- **Within 10 working days** (via telephone or facsimile report)
  Any study event that is:
  - associated with the use of the study device, and
  - unanticipated,
    regardless of the seriousness of the event.

- **Within 5 working days** (via written report)
  - Protocol deviation to protect the life of the subject in emergency
  - Withdrawal of IRB approval
  - Lack of informed consent

Additional reporting requirements
Sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Reporting Process
Adverse events may be submitted on FDA Form 3500A, or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 8.3. The contact information for submitting IND safety reports is noted below:

MedWatch - Central Triage Unit
5600 Fishers Lane
Rockville, MD 20852-9787
1-888-463-6332 or 1-301-796-3400

8.7 Data Safety Monitoring
The primary investigator is responsible for data safety monitoring reviews. This includes conducting systematic and periodic reviews of aggregate data and adverse events. These specific data and events include: adverse events reported following administration of medication (nebulized 3% hypertonic saline) that would include serious allergic reactions, anaphylaxis, or bronchospasms; or following administration of the device (chest percussor cup). However there are no foreseeable or specific adverse events anticipated with use of the chest percussor cup.

No predefined stopping rules will be used due to the low side effect profile of nebulized 3% hypertonic saline and chest percussion therapy and no foreseeable serious adverse events are anticipated to occur to any study participants during the duration of this study.

A summary of the outcomes of these safety reviews along with accumulated adverse events and deviations will be submitted to the IRB as part of an annual progress report at the time of the Continuing Review submission.

9 Clinical Monitoring
Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the principal investigator.
- On-site monitoring will be occurring continuously while participants are participating in the study. Participants will be assessed with vital signs (temperature, heart rate, blood pressure, respiratory rate, and oxygen saturation) every 4 hours per institution protocol and as needed in addition.

10 Statistical Considerations
10.1 Statistical and Analytical Plans (SAP)
A formal SAP will be utilized.

10.2 Statistical Hypotheses
The statistical hypotheses are as follows:

- Null hypothesis: combined nebulized hypertonic saline nebulization with chest percussion therapy in patients age 0 to 24 months admitted to the general inpatient pediatrics unit with acute bronchiolitis will not have any significant effects on primary outcomes (length of stay and number of days on supplemental oxygen therapy) and secondary outcomes (objective clinical responses included respiratory rate, heart rate, and oxygen saturation and subjective clinical responses from physicians and caregivers).
- Alternative hypotheses: combined nebulized hypertonic saline nebulization with chest percussion therapy in patients age 0 to 24 months admitted to the general inpatient pediatrics unit with acute bronchiolitis will have clinically significant effects on primary outcomes (length of stay and number of days on supplemental oxygen therapy) and secondary outcomes (objective clinical responses included respiratory rate, heart rate, and oxygen saturation and subjective clinical responses from physicians and caregivers).

10.3 Analysis Datasets
Control group: Patients meeting criteria as above prior to start date, beginning 12 months prior to start date of study, will be examined via retrospective chart review.

Experimental group: All patients meeting criteria as above beginning start date of study will be enrolled in study to receive adjuvant therapy with 3% hypertonic saline nebulization treatments combined with 3 minutes of chest physiotherapy.

10.4 Description of Statistical Methods

10.4.1 General Approach

Descriptive statistics (mean ± standard deviation or median [25th, 75th percentiles] for continuous variables; frequencies and percentages for categorical variables) will be calculated separately by group. The two groups will be compared using the chi-square test or Fisher's exact test, as deemed appropriate, for categorical variables and the two-sample t-test or Mann-Whitney test for continuous data.

10.4.2 Analysis of the Primary Efficacy Endpoint(s)

For all analyses, the standard assumptions of Gaussian residuals and quality of variance will be tested. If the standard assumptions are not met, a transformation will be performed (i.e. logarithm transformation). Results will be brought back to the original units and reported as geometric means with their corresponding lower and upper confidence limits.

For the assessment of number of days on supplemental oxygen therapy (i.e. count data), a Poisson, Negative Binomial (NB), Zero-Inflated Poisson (ZIP), or Zero-Inflated Negative Binomial (ZINB) model will be used.

A result will be considered statistically significant at the $p<0.05$ level of significance. All analyses will be performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

10.4.3 Analysis of the Secondary Endpoint(s)

For all analyses, the standard assumptions of Gaussian residuals and quality of variance will be tested. If the standard assumptions are not met, a transformation will be performed (i.e. logarithm transformation). Results will be brought back to the original units and reported as geometric means with their corresponding lower and upper confidence limits.

For the assessment of number of days on supplemental oxygen therapy (i.e. count data), a Poisson, Negative Binomial (NB), Zero-Inflated Poisson (ZIP), or Zero-Inflated Negative Binomial (ZINB) model will be used.

A result will be considered statistically significant at the $p<0.05$ level of significance. All analyses will be performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

10.4.4 Safety Analyses

Adverse events will be coded via Medical Dictionary for Regulatory Activities (MedDRA) and each adverse event will be counted once for occurrence. The severity, frequency and relationship of the adverse event to the study agent will be presented by the System Organ Class (SOC) and preferred term groupings. Information that will be reported about each adverse event will include start date and time of study agent, stop date and time of study agent, severity, relationship to event to study agent, and outcome. Adverse events will be ascertained and reported by the primary investigator. Adverse events leading to premature discontinuation from the study and serious adverse events requiring emergent treatment will be presented in a summarized listing.

10.4.5 Adherence and Retention Analyses

Adherence to the study protocol will be assessed via audits by the principal investigator. Measure of participation and study retention will be assessed when collecting data and reviewing study participants medical records to see if study agent was administered as scheduled based on the study protocol. Any participants with adverse events or any other reasons leading to early withdrawal or termination from the study will be discounted from the study.

10.4.6 Baseline Descriptive Statistics

Baseline descriptive statistics will include participant age and gender.

10.4.7 Planned Interim Analysis

Not applicable.

10.4.7.1 Safety Review
Study enrollment will cease upon participant/participant's caregiver's voluntary request to do so or should a serious adverse event occur. No statistical rules will be used for safety review.

10.4.7.2 Efficacy Review
Descriptive statistics (mean ± standard deviation or median [25th, 75th percentiles] for continuous variables; frequencies and percentages for categorical variables) will be calculated separately by group. The two groups will be compared using the chi-square test or Fisher's exact test, as deemed appropriate, for categorical variables and the two-sample t-test or Mann-Whitney test for continuous data.

For all analyses, the standard assumptions of Gaussian residuals and quality of variance will be tested. If the standard assumptions are not met, a transformation will be performed (i.e. logarithm transformation). Results will be brought back to the original units and reported as geometric means with their corresponding lower and upper confidence limits.

For the assessment of number of days on supplemental oxygen therapy (i.e. count data), a Poisson, Negative Binomial (NB), Zero-Inflated Poisson (ZIP), or Zero-Inflated Negative Binomial (ZINB) model will be used.

A result will be considered statistically significant at the $p<0.05$ level of significance. All analyses will be performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). The proposed sample size for this study is 228 subjects (n=114 per group). The mean duration of hospitalization for bronchiolitis recorded in the study hospitals during previous years was 6.5 days and standard deviation of 3.5 days. For a type I error of 0.05 and a power of 0.80, for detecting a 20% decrease in duration of hospitalization, a total of 228 subjects would be included (114 subjects in each group).

10.4.8 Tabulation of Individual Response Data
Individual participant data will be listed by primary and secondary outcomes measures and respective time points.

10.5 Sample Size
The proposed sample size for this study is 228 subjects (n=114 per group). Based on data published by Gajdos, et al., the mean duration of hospitalization for bronchiolitis recorded in the study hospitals during previous years was 6.5 days and standard deviation = 3.5 days. For a type I error of 0.05 and a power of 0.80, for detecting a 20% decrease in duration of hospitalization, a total of 228 subjects would be included (114 subjects in each group).

10.6 Measures to Minimize Bias
This study is not blinded. All patients who meet the inclusion criteria are eligible to enroll in the study and would be receiving the investigational therapy of nebulized 3% hypertonic saline combined with chest percussion therapy. These participants will be part of the experimental arm of the study. No masking or randomization is required. It is expected that at least 114 subjects in this group will be required to accommodate for a type I error of 0.05 and a power of 0.80. An estimate of approximately 200 participants will be required to be enrolled in this study to account for early withdrawal from the study for any reason.

11 Source Documents and Access to Source Data/Documents
Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the

procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A”. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 Institutional Review Board

The protocol, informed consent form(s), and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. A standardized informed consent form is provided upon enrollment process.

13.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual’s agreeing to participate in the study and continues throughout the individual’s study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the

course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

13.4 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust. This confidentiality is extended to cover the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

13.5 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should

be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into TrialMaster, a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

The principal investigator will routinely conduct safety monitoring quarterly and review of data to ensure data is secured and protected.

13.6 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

13.7 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

13.8 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have

questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric post-market surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

14 Study Administration

14.1 Study Leadership

The Steering Committee will govern the conduct of the study. The Steering Committee will be composed of the principal investigator.

15 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

16 References

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17 Schedule of Events

Activity	Enrollment	Treatment Visits (assessed once per shift per participant for each hospital admission day; number of visits will vary)
Study team procedures		
Consent	X	
Demographics: age and gender	X	
Medical History	X	
Physical Exam	X	X
Study treatment		
Administer nebulized 3% hypertonic saline + 3 minutes chest percussion therapy every 6 hours while on supplemental oxygen therapy		X
Respiratory assessments		
Respiratory rate	X	X
Heart rate	X	X
Oxygen saturation	X	X
Supplemental oxygen setting	X	X
Subjective assessments		
Caregiver survey		X
Provider survey		X