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A single-center, non-blinded, randomized, feasibility and equivalence trial to compare post-pyloric tube and gastric tube enteral feeding in infants with bronchiolitis on High-Flow Nasal Cannula; Bronchiolitis and High-flow nasal cannula with Enteral Tube feeding Randomized (BHETR) trial

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Complete List of Authors:	Parlar-Chun, Raymond; University of Texas John P and Katherine G McGovern Medical School Lafferty-Prather, Meaghan; University of Texas John P and Katherine G McGovern Medical School Gonzalez, Veronica; University of Texas John P and Katherine G McGovern Medical School Pedroza, Claudia; McGovern Medical School at The University of Texas Health Science Center at Houston, Center for Clinical Research and Evidence-Based Medicine Gourishankar, Anand; University of Texas John P and Katherine G McGovern Medical School, Pediatrics
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Title:
A single-center, non-blinded, randomized, feasibility and equivalence trial to compare post-pyloric tube and gastric tube enteral feeding in infants with bronchiolitis on High-Flow Nasal Cannula; **B**ronchiolitis and **H**igh-flow nasal cannula with **E**nteral **T**ube feeding **R**andomized (**BHETR)** trial.

Authors: Raymond Parlar-Chun, MD, Meaghan Lafferty-Prather, MD, Veronica Gonzalez, MD, Claudia Pedroza, PhD, Anand Gourishankar, MD.

All Authors from the Department of Pediatrics at McGovern Medical School, Houston, TX

Corresponding Author:
Raymond Parlar-Chun
Address: 6410 Fannin MSE R3188, Houston TX 77030
Telephone: 713-500-5586
Email: raymond.l.chun@uth.tmc.edu

Author Emails:
Raymond Parlar-Chun: raymond.l.chun@uth.tmc.edu
Meaghan Lafferty-Prather: Meaghan.LaffertyPrather@uth.tmc.edu
Veronica Gonzalez: Veronica.M.Gonzalez@uth.tmc.edu
Claudia Pedroza: Claudia.Pedroza@uth.tmc.edu
Anand Gourishankar: Anand.Gourishankar@uth.tmc.edu

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Abstract
Introduction: High flow nasal cannula (HFNC) is a noninvasive form of respiratory support that is becoming increasingly widespread in its use for patients with bronchiolitis. HFNC provides a variable amount of positive pressure similar to CPAP. The positive pressure in CPAP can distend and loosen esophageal sphincter pressure leading to increased reflux. It is unclear if HFNC causes a similar action. Feeding tubes are used to provide nutrition and hydration to patients that are unable to safely take oral feedings. If there is increased reflux from HFNC, this would increase the risk of aspiration. Our institution places post pyloric feeding tubes (NDT) to eliminate this risk. The purpose of the study is to see if there is a difference between NDT and nasogastric tubes among outcomes of length of respiratory support, number of emesis, number of chest x-rays, and readmission/ER revisit rates.

Methods and Analysis: Patients with bronchiolitis, on high flow nasal cannula, and whose primary physicians have decided on feeding tube for nutrition/hydration will be approached for consent and enrollment. Patient's will be randomized to NG and NDT in variable block sizes and stratified into low and high risk groups. Outcomes will be analyzed by both a frequentist and Bayesian statistical approach.

Ethics and dissemination: The trial was approved by local institutional review board. Every attempt will be made to reduce to an absolute minimum the interval between completion of data collection and release of study results through appropriate dissemination mediums including abstracts, poster presentations, and journal publications

Article Summary:
Strengths and limitations
- Block Randomized trial with allocation concealment
- Few exclusion criteria with increased generalizability
- Bayesian analysis to estimate probability of benefit
- Could not be blinded

Key Words: Bronchiolitis, high flow nasal cannula, nasogastric tube, nasoduodenal tube

Trial Registration and Protocol Version available in (Supplementary Materials Appendix 1)

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Roles and Responsibilities: R.PC, A.G, M.LP, V.G, C.P
Authors' contributions

RPC conceived of the study. RPC, AG, MLP, and VG initiated the study design and implementation. C.P is conducting the primary statistical analysis. All authors contributed to refinement of the study protocol and approved the final manuscript.

Trial Sponsor: McGovern Medical School
Contact name: Raymond Parlar-Chun
Address: 6410 Fannin MSE R3188, Houston TX 77030
Telephone: 713-500-5586
Email: raymond.l.chun@uth.tmc.edu

Introduction

Bronchiolitis is a viral lower respiratory tract infection that can cause respiratory distress and failure secondary to inflammation of bronchial tissue and subsequent airway obstruction due to airway secretions and edema. This disease typically affects children less than two-years-old and is most severe in those under three months of age. Infants are at high risk of severe illness if they are born premature, or have chronic lung/heart disease, immunodeficiency, abnormal airway anatomy or neuromuscular disease. Clinical features of bronchiolitis may include nasal congestion, respiratory distress, wheezes and/or crackles, and atelectasis. Bronchiolitis hospitalization is overall declining, but remains the most common reason for hospitalization in infants in the United States; annual hospital-related charges amount to a few billion dollars in the United States.[1]

The route of nutrition and hydration in bronchiolitis remains an area of interest. For tachypneic infants, oral feeding may pose a risk for pulmonary aspiration.[2] In cases where oral feeds cannot be done safely, numerous pediatric societies such as the American Academy of Pediatrics (AAP) strongly recommends nasogastric (NG) or intravenous (IV) fluids for hydration.[3] IV fluids with nil per os (NPO) status is advantageous for the infant in imminent respiratory failure, but the choice of various tonicity of fluids and risk of iatrogenic hyponatremia (compounded by SIADH) is a concern.[4] Additionally, nutrition will suffer if prolonged IV fluids are given without any supplemental nutrition.

This question of how best to provide nutrition to patients with bronchiolitis is compounded when the patient is being supported with High-Flow Nasal Cannula (HFNC). HFNC is increasingly used in a variety of medical settings as non-invasive ventilation in infants with bronchiolitis. HFNC provides humidified air at flows that provide a variable amount of positive pressure. This positive pressure may complicate feeding in bronchiolitis. There are studies in adults on Continuous Positive Airway Pressure (CPAP) that show increased positive pressure can create a decreased esophageal sphincter tone and increased incidences of gastroesophageal reflux.[5,6] It is unclear if there is a similar effect in infants on HFNC therapy. Physiologic studies do record changes in esophageal pressure.[7] A decrease in esophageal sphincter tone and increased reflux could lead to subsequent aspiration of milk from nasogastric feeds.

Rationale for Study

At our institution, infants with bronchiolitis who are on HFNC receive ND tube feeds. As compared to NG feeds, ND feeds are thought to minimize gastric reflux and potential airway aspiration. However, ND tubes are technically more difficult to place and provide continuous feeds which are less physiologic than bolus gastric feedings. For those infants who are not ready for oral feeds, but would benefit from enteral nutrition, an NG tube, in general, is easier to place. To date, no randomized trial compares two modalities (NG vs. ND) of tube feeds in infants with bronchiolitis on HFNC.

Choice of Comparators
Our current standard of practice is placement of an ND tube in patients with bronchiolitis on HFNC. It is therefore justified as a comparator. Given NG tube feeding has been studied in infants with bronchiolitis and is supported by the AAP and other various organizations, this modality will be compared to our institution's standard of care.

Objectives

Research Hypothesis

As NG tube feeding appears to be well-tolerated in infants with bronchiolitis on HFNC, we hypothesize there will be no difference in duration of respiratory support, the number of, and peak respiratory support between patients receiving NG tube feeds compared to ND tube feeds. We also hypothesize there will be no difference in these outcomes in the subgroup of the high-risk population (as defined in "Interventions").

Primary objective

Compare the duration of respiratory support between the NG and ND tube feeding groups.

Key Secondary objectives

To determine if differences exist between the NG and ND feeding groups with regards to:

- Number of emesis
- Peak flow rates on HFNC
- Duration of HFNC
- Instances of failure of HFNC
- Occurrences of aspiration pneumonia
- Number of X-rays for tube placement
- The overall length of hospital stay
- Emergency and hospital readmissions within 7 and 30 days post discharge

Other Secondary Objectives

To determine if high-risk infants (criteria listed below in "Interventions") have differences between the NG and ND feeding groups in regards to the objectives above.

Trial design

The BHETR trial is designed as a single center, randomized, non-blinded, equivalence trial with two parallel groups and a primary outcome of the length of time requiring respiratory support.

Randomization will be in blocks stratified by low and high-risk groups with an allocation ratio of 1:1.

Study setting

The "BHETR trial" will be conducted at a single tertiary-care, academic children's hospital. We will recruit patients who are inpatients in the pediatric intermediate medical unit (IMU) of Children's Memorial Hermann Hospital affiliated with UTHealth at Houston McGovern Medical School. This randomized trial will recruit subjects from January 2018 until May 2019

Eligibility Criteria

Inclusion Criteria

Ø All infants up to 12 months of age admitted for bronchiolitis requiring HFNC for whom the treating physician has decided to place a feeding tube.

Exclusion Criteria

Ø Infants with craniofacial anomalies that prevent tube placement
Ø Infants who had surgery compromising esophageal sphincter tones such as Nissen fundoplication or congenital hiatal hernia
Ø Infants initially requiring CPAP (continuous positive airway pressure) or mechanical ventilation
Ø Infants transferred from the PICU
Ø Infants transferred from a non-Hermann facility who are already on HFNC

Interventions

For all eligible patients on HFNC ready for tube feeding, a review of their past medical history will determine which category to classify the intervention group – low-risk or high-risk. High-risk patients are those born prematurely (<37 weeks gestation), and/or a previous diagnosis of neuromuscular disorders, seizures, cerebral palsy, eosinophilic esophagitis, upper airway disorders (i.e laryngomalacia), hemodynamically unstable congenital heart disease +/- requiring cardiac-related medications, or medically managed gastroesophageal reflux as determined by consensus among pediatric gastrointestinal and pulmonary specialists. Low-risk patients, on the other hand, are that born term (≥37 weeks gestation) without any of the previously listed comorbidities. Once the caregiver consents to the study and the patient are enrolled, the University-affiliated RedCap software will be utilized to assist with stratified block randomization for NG tube or ND tube placement.

Once the patient has been randomized, the study investigators notify a member of the medical team caring for the patient which type of feeding tube should be placed. The feeding tube is subsequently placed, and an X-ray is obtained for placement confirmation (X-ray confirmation is standard of care at our hospital for both NG and ND tubes). Feeds are given continuously through an ND tube and as a bolus over 30 minutes every 3 hours through an NG tube. The total kcal/kg/day given is standardized for the patient's age and weight. The patient is provided with the same caloric density formula (or expressed breast milk) that they are given at home.

Because of practicality, neither the study investigators, medical team, nor the caregivers could be blinded to the feeding modality chosen through randomization.

Modifications

Patients typically continue to be fed via the route determined by randomization until HFNC is discontinued. We expect patients to be managed via standard bronchiolitis protocol at our institution. The caregivers can withdraw from the study at any point. Should the patient experience any adverse events, such as vomiting or aspiration, it is at the discretion of the primary physician caring for the patient to change the feeding route, hold, or discontinue feeds.

Outcomes

The difference in total duration of respiratory support between the NG and ND feeding groups was selected as the primary outcome measure. This outcome measure was selected as it is clinically relevant to both medical staff and caregivers and would serve as a surrogate measure for any worsening of the bronchiolitis disease process potentially associated with the different types of feeding routes. Secondary outcome measures include differences between the two groups in the number of documented emesis while receiving tube feeds and on HFNC, maximum respiratory support received, total duration of HFNC therapy, number of X-rays obtained to confirm tube placement, number of attempts for tube placement by the nursing staff, adverse events during placement or while the tube is in place (i.e. nosebleeds, tube dislodgement), instances of aspiration pneumonia, hospital length of stay, and emergency room visits and hospital readmissions within 7 and 30 days after discharge.

Participant Timeline

Once a patient has been enrolled in the study, the patient remains enrolled throughout the acute care hospitalization until discharged. A phone follow-up interview occurs 30 days after discharge.

Sample Size

The sample size was based on retrospective data analysis of bronchiolitis admissions at our institution over the past 3 years. Low-risk infants had an average duration of respiratory support of 86.8 hours (SD = 26), while high-risk infants had an average duration of respiratory support of 97.6 hours (SD = 39.6). Assuming $1 - \beta = 0.8$ and $\alpha = 0.05$, an $n = 36$ and $n = 86$ were calculated to be able to detect a difference at 24 hours in the duration of respiratory support in the low- and high-risk groups, respectively.

Recruitment

Patients are recruited continuously throughout the year; however, peak enrollment is expected to occur during “respiratory season”, which is typically between October and March. When patients are admitted on HFNC from the emergency room, or started on HFNC after admission to the inpatient ward and deemed ready for enteral tube feeding, the study investigators will ask the caregivers to consent to the study. If after 2 consecutive respiratory seasons, the sample size for each risk category is not achieved, enrollment will continue until Bayesian analysis, which will be performed annually for up to two years, identifies 90% or greater probability there

is a difference of respiratory support duration between the two groups, or until the planned sample size is met.

Allocation

After a patient has been identified as meeting inclusion criteria and consent is obtained, baseline data is entered into REDCap in which randomization occurs. Participants will be randomly assigned to either the NG or ND feeding group with a 1:1 allocation and will be stratified by risk level as previously defined. Investigators will be blinded to the block size and the block size will vary.

Allocation concealment will be ensured as the assigned group will not be revealed by REDCap until after the patient has been recruited into the trial and the baseline data has been entered into REDCap.

Blinding

Trial participants, caregivers, medical personnel, and investigators will not be blinded to the study group assignment due to the obvious differences in the interventions. Study group assignment will be blinded to the statistician.

Data Collection Methods

Data Collection Methods

After informed consent has been obtained, the investigator obtaining consent will gather the Baseline Parameters from the hospital EMR and from the parents. This data will be entered into UTH REDCap. The bedside nurse will be informed of the patient's enrollment and will be given a data collection form for tube placement to document the number of attempts needed to place the tube as well as any adverse events associated with the initial tube placement as well as any future tube placement needed if the tube becomes dislodged. An investigator will retrieve this form prior to the patient's discharge from the hospital. 30 days after discharge from the hospital, an investigator will assess for any subsequent emergency department visits or hospital admissions via hospital EMR and a phone call to the parent. Three attempts will be made to contact the parent. If after three attempts, the investigator is unable to contact the parent, the patient will be considered lost to follow up.

After the patient is discharged from the hospital, the Clinical Parameters data collection form will be completed in REDCap using information obtained from the nursing form, hospital EMR, and the 30-day follow up phone call using the variable definitions agreed upon by the investigators. A second investigator will independently enter the Baseline Parameters as well as the Clinical Parameters into REDCap. The principal investigator will then compare the duplicate sets of data and address any discrepancies to ensure validity.

Retention

All randomized patients will be included in an intention-to-to treat analysis. The primary treating physicians may choose to change the method of feeding at any point if they are concerned

about adverse events. Similarly, if the patient requires subsequent admission to PICU, the study will not dictate feeding methods at that time.

To maximize retention to the 30-day post-discharge follow up phone call, investigators will obtain a working phone number and/or email address from the parents at the time of consent and enrollment into the study. Parents will be told to expect a phone call and/or email 30 days after discharge.

Data Management

Paper Baseline Parameters and Nursing forms will be kept in a file cabinet in a secure office. All data will be entered electronically and stored on a UTShare account and on UTHealth REDCap, both of which are private health information protected and require 2-factor authentication. As described above, each set of data will be entered twice with each duplicate data set compared by the primary investigator, and discrepancies addressed to ensure data validity.

Within the data collection forms in REDCap, calculators have been programmed to calculate the length of time on respiratory support as well as other outcome measures from entered date/time data entries to minimize human calculation error.

Statistical Methods

Outcomes

All analyses will be intent-to-treat. Differences in total length of respiratory support between treatment groups will be assessed with a regression model including treatment and risk group (stratifying variable) as covariates. Rates of secondary outcomes will be assessed using log-binomial or logistic models, and a total number of secondary outcomes will be assessed with negative binomial models.

Additional Analyses

In this small pilot study, some treatment effects that could be considered important by family members and clinicians (reduced hospital days) may not be statistically significant. As a result, Bayesian analyses will also be performed to estimate the probability of benefit. Neutral, weakly informative priors will be used for the treatment effect, e.g. for binary outcomes, the prior relative risk will be centered at 1.0 with 95% prior interval of 0.5-2.0.

Data Monitoring

Formal Committee

Not applicable - a data monitoring committee (DMC) is not needed as risks are expected to be minimal.

Interim Analysis

An interim analysis will be performed when 50% of patients have been randomized and will be performed by an independent statistician who is blinded to the treatment allocation. A standard normal deviate test will be calculated to determine if the rate of adverse events are significantly different between the two groups ($p < 0.05$).

Harms
Adverse events related to tube placement is recorded by nurse responsible for placing the tube. The route of feeding may be changed at the discretion of the primary physician if the particular tube placed is believed to be causing harm to the patient, such as worsening respiratory distress or aspiration pneumonia.

Auditing
Independent, periodic audits will not be performed. The investigators will perform self-assessments to ensure the data collected were for patients admitted for bronchiolitis and the other inclusion criteria.

Research Ethics Approval
The protocol and the template informed consent forms contained in Appendix were approved by UTHealth's Committee For the Protection of Human Subjects (our institution's IRB) with respect to scientific content and compliance with applicable research and human subjects regulations.

Protocol Amendments
Any modifications to the protocol which may impact the conduct of the study, the safety of the patient, or any changes to the objectives, design, population, sample sizes, procedures, or significant administrative aspects will have a formal amendment to the protocol and approved by the IRB prior to implementation.

Trial Registration and Protocol Version available in (Supplementary Materials Appendix 1)

Patient and Public Involvement
Patients were not involved in the development of the research question, study design, or recruitment into the study.

Consent
Members of the study team, all who are familiar with the trial and study design, will obtain written consent from patients' caregivers. All consent and information sheets are available in English and Spanish. (Supplementary Materials Appendix 2).

Confidentiality
All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in a secured office. Electronic data will be stored on the university cloud storage that requires two-factor authentication and private health information security.

Declaration of Interests
No conflicts of interest are declared for any of the study investigators.

Dissemination Policy

Every attempt will be made to reduce to an absolute minimum the interval between completion of data collection and release of study results through appropriate dissemination mediums including abstracts, poster presentations, and journal publications.

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Supplementary Material, Appendix 1 and 2

1. Trial Registration and Protocol Revision
2. Informed Consent Documents

Trial Registration:
Registry: ClinicalTrials.gov: NCT03346850

Data Category	Information
Primary registry and trial identifying the number	ClinicalTrials.gov NCT03346850
Date of registration in the primary registry	November 16, 2017
Sources of Monetary Support/Sponsors	None
Contact for public queries	Raymond Parlar-Chun MD, raymond.l.chun@uth.tmc.edu
Contact for scientific queries	Raymond Parlar-Chun MD, McGovern Medical School, Houston, TX
Public Title	Comparison of Nasogastric and Nasoduodenal Feeding tubes in infants with bronchiolitis and on high flow nasal cannula
Scientific Title	A single-center, non-blinded, randomized, feasibility and equivalence trial to compare post-pyloric tube and gastric tube enteral feeding in infants with bronchiolitis on High-Flow Nasal Cannula; **B**ronchiolitis and **H**igh-flow nasal cannula with **E**nteral **T**ube feeding **R**andomized (**BHETR)** trial
Countries of recruitment	United States
Health conditions studied	Bronchiolitis, high flow nasal cannula therapy, tube feeding
Interventions	Active comparators: - nasoduodenal tube feeding - nasogastric tube feeding
Key Inclusion and Exclusion Criteria	Ages eligible for study: 0 - 12 months Sexes eligible for study: both Inclusion criteria: hospitalized, clinical diagnosis of bronchiolitis, on high flow nasal cannula, clinician decision to place the feeding tube Exclusion criteria: patients with craniofacial abnormalities that prevent tube placement, prior surgery compromising esophageal sphincter tones such as Nissen fundoplication, or congenital hiatal hernia surgery, patients on CPAP and mechanical ventilation are also

	excluded from the study. Patients stepped down from pediatric ICU (PICU) and patients transferred from another facility already on HFNC are also excluded.
Study Type	Interventional Allocation: randomized Intervention model: parallel assignment Masking: Statistician blinded
Date of first enrollment	February 2018
Target sample size	150
Recruitment status	Recruiting
Primary outcomes	Duration of respiratory support
Key secondary outcomes	The number of emesis, number of chest x-rays obtained, peak respiratory support, length of stay, and ER visits and/or rehospitalizations at 7 and 30 days after discharge.

Protocol Version
Issue Date: 3/21/2018
Protocol Amendment Number : 02
Authors: R.PC

Revision Chronology:

2017 - August 10	Original
2018 - January 29	Amendment 01.: Primary reason for amendment: optimization of randomization and allocation concealment
2018 - March 21	Amendment 02.: Change in primary outcome from the duration of HFNC to the duration of all respiratory support to capture the patients that had to be reinitiated to HFNC after discontinuation

University of Texas Health Science Center at Houston/Memorial Hermann Healthcare System
INFORMED CONSENT FORM TO TAKE PART IN RESEARCH
Comparison Between Gastric and Post Pyloric Feedings in Bronchiolitis Patients Requiring High Flow Nasal Cannula
HSC-MS-17-0725
Parental Consent

INVITATION TO TAKE PART

You are invited to allow your child to take part in a research project called, *Comparison Between Gastric and Post Pyloric Feedings in Bronchiolitis Patients Requiring High Flow Nasal Cannula*, conducted by Dr. Raymond Parlar-Chun of the University of Texas Health Science Center at Houston (UTHealth) and Memorial Hermann Healthcare System. For this research project, he will be called the Principal Investigator or PI.

Your decision to allow your child to take part is voluntary. You may refuse to allow your child to take part or choose to stop your child from taking part, at any time. A decision not to allow your child to take part or to stop being a part of the research project will not change the services available to your child from Dr. Parlar-Chun and research staff with the University of Texas Health Science Center at Houston (UTHealth) and Memorial Hermann Healthcare System .

You and your child may refuse to answer any questions asked or written on any forms. This research project has been reviewed by the Committee for the Protection of Human Subjects (CPHS) of the University of Texas Health Science Center at Houston as HSC-MS-17-0725.

PURPOSE

The purpose of this research study is to determine the best way to provide nutrition to infants admitted to the hospital with viral bronchiolitis. Bronchiolitis is the most common cause of hospitalization for infants < 1 year of age. High flow nasal cannula (HFNC) is being used to provide respiratory support. However, the optimal feeding strategy for patients on HFNC remains unclear. Some institutions allow these infants to feed orally by mouth. Others keep them on IV fluids for the duration of their time on HFNC. Others still institute some type of tube feedings, either nasogastric tube feeds or nasoduodenal tube feeds. Our goal is to study outcomes in patients who are fed with nasogastric (NG) tube feeds (a tube that goes from the nose into the stomach) vs. nasoduodenal (ND) tube feeds (a tube that goes from the nose, past the stomach, and into the small intestine) in patients admitted to the hospital for viral bronchiolitis who require treatment with HFNC.

Your child is being asked to participate in this study because they are being admitted to the hospital for management of viral bronchiolitis and may require high flow nasal cannula therapy. Our study runs for the duration of the current respiratory season (October 2017-April 2018).

This is a local study that will enroll approximately 230 patients.

PROCEDURES

If you agree and allow your child is able to take part in this study you will first sign the consent form before undergoing these study procedures:

Your child will qualify for inclusion in the study when 1.) They are admitted to the hospital for viral bronchiolitis, and 2.) they are started on respiratory treatment with HFNC. When both those criteria are met, he/she will be randomly assigned (similar to flipping a coin, 50% chance of either outcome) to one of two feeding strategies – NG tube vs. ND tube. Depending on which group your child is assigned to, that particular tube will be inserted for the purposes of feeding your child. The NG tube is inserted through the nose and ends in the stomach. The ND tube is inserted through the nose, goes past the stomach, and ends in the small intestine. The NG or ND tube will be inserted as soon as your child qualifies for the study. For example, if your child is admitted for bronchiolitis but originally is on room air, or on regular nasal cannula, they will only qualify for the study when and if their primary medical team decides that they require HFNC for treatment. If they stay on room air or regular nasal cannula, then they do not qualify for the study. If they are admitted to the inpatient unit with HFNC already started in the Emergency Department or at an outside facility, then we will place the NG or ND tube soon after they arrive at our inpatient unit. The placement of the tube will be confirmed by an abdominal x-ray prior to starting any feedings.

Your child will remain on NG or ND tube feeds for as long as they remain on HFNC. The decision about when to restart regular oral feedings will be made by your regular doctors. They will also determine how long your child requires HFNC, or whether they require even more breathing support such as CPAP or mechanical ventilation. If your child develops severe bronchiolitis and requires either CPAP or mechanical ventilation, they will be removed from the remainder of the study, and the decision about how/when to feed your child will be made by your primary medical doctors.

We will be collecting several measurements during the study. These include: child's age, child's gender, child's race, child's weight, number of days your child requires HFNC support, number of times they have vomiting, maximum respiratory support they require, number of xrays ordered during hospitalization, whether they received any antibiotics during the hospitalization, total number of days they are in the hospital, and whether they have to return to an emergency department or are rehospitalized 7 and/or 30 days after discharge from our facility.

If you choose to not participate in this study, and your child requires tube feedings for nutrition, they will receive a NDT, our current standard of care. Your decision to participate, or not to participate, will not affect your doctor's decisions about what is the best medical treatment for your child. He/she will still receive the appropriate level of respiratory support your child needs (room air, regular nasal cannula, HFNC, CPAP, or intubation), and feedings will be provided at the discretion of your primary doctors (IV fluids, regular oral feeds, NG tube feeds, or ND tube feeds).

TIME COMMITMENT

The total amount of time your child will take part in this research study is the total duration of time they remain on HFNC therapy. Most infants admitted for bronchiolitis who require HFNC therapy require it for approximately 1-5 days. The participation in the study will end when the child improves and is weaned oxygen via regular nasal cannula or room air, or if their bronchiolitis worsens and they require CPAP or intubation.

BENEFITS

Your child may receive no direct benefit from being in the study. However, bronchiolitis is the leading cause of hospitalization of children, and your child's participation in this study will help us understand the best way to feed the large number infants who are admitted for this disease every year.

RISKS AND/OR DISCOMFORTS

While on this study, your child is at risk for side effects. The study doctor will discuss these risks with you and your child. This study may include risks that are unknown at this time.

Inserting either an NG or ND tube can be uncomfortable for your child. They are inserted by nurses who are trained to minimize any discomfort your child may experience. The ND tube is slightly more challenging to place than an NG tube because it has to go further, but both tubes are placed every day and are common and relatively simple procedures. Once the tube is placed, your child should not feel any further discomfort, similar to after an IV is inserted. Prior to starting any feedings, the position of both tubes are verified by an abdominal xray to minimize any risk of feedings being delivered incorrectly. Your child may also continue to feel hungry while being fed via ND tube, as the sensation of hunger is satiated by being fed into the stomach, not past the stomach. However both forms of feeding are equally nutritious and will provide the same number of calories to help with your child's recovery and daily requirements.

There is a theoretical risk of reflux and aspiration while on NG tube feeds and HFNC simultaneously. Reflux is when food from the stomach moves up into the esophagus or mouth, similar to when a patient vomits. Aspiration is when food from the stomach enters the lungs. Several studies have looked at this question and determined that NG tube feeds are safe for patients with bronchiolitis, with or without HFNC. Additionally, many children's hospitals around the country only feed patients with bronchiolitis using NG tubes as their standard of care. However, no studies have directly compared patient outcomes in bronchiolitis patients fed using NG tube vs. ND tube feedings, which is what we are looking to do. If your child's primary doctor feels that your child is having worsening respiratory distress because of NG feeds, your child will be pulled from the remainder of the study and these feedings will be discontinued. Additionally, the study group will be meeting each week during the study to review the data we have collected. If we feel that the NG tube group is having more complications than the ND tube group, the study will be immediately discontinued.

As with all clinical studies, there is a possible risk of breach of confidentiality. All efforts will be made to minimize this risk. Your child's medical information will only be shared by certified members of the study team, in addition to the regular group of bedside caregivers (doctors, nurses, students, respiratory therapists, pharmacists, etc).

ALTERNATIVES

If you choose to not participate in this study, your child will still receive the same excellent care from all team members taking care of your child. Your decision to participate, or not to participate, will not affect your doctor's decisions about what is the best medical treatment for your child. We will still provide the appropriate level of respiratory support your child needs (room air, regular nasal cannula, HFNC, CPAP, or mechanical ventilation), and will provide feedings at the discretion of your primary doctors (IV fluids, regular oral feeds, NG tube feeds, or ND tube feeds). They will not be randomized to NG vs. ND feeds, but instead, will be given feeds according to the discretion of the primary doctors taking care of your child in discussion with your preferences. If the decision for tube feedings has been made, our current standard of care is placing NDTs.

STUDY WITHDRAWAL

Your decision to allow your child to take part is voluntary. You may decide to stop your child from taking part in the study at any time. A decision to decline to take part or to stop being a part of the research study will not change the services available to you and your child from Dr. Parlar-Chun and research staff, or any care providers at Children's Memorial Hermann Hospital.

Your child's doctor can stop the study at any time for any of the following reasons: if your child's doctors determine he/she requires CPAP or mechanical ventilation, or if your child's doctors feel he/she may be aspirating with NG feeds.

Should the study be stopped, we will still be able to use the data that your child provides, and the reason for withdrawal from the study will be noted in our results.

IN CASE OF INJURY

If your child suffers an injury as a result of taking part in this research study please understand that nothing has been arranged to provide free treatment of the injury or any other type of payment. However, necessary facilities, emergency treatment and professional services will be available to your child, just as they are to the general community. You should report any such injury to Dr. Parlar-Chun at 713-500-5586 and to the Committee for the Protection of Human Subjects at 713-500-7943. You will not give up any of your child's legal rights by signing this consent form.

COSTS, REIMBURSEMENT AND COMPENSATION

If you decide to allow your child to take part in this research study, you will not incur any additional costs. You and your child will not be paid for taking part in this study.

CONFIDENTIALITY

Please understand that representatives of the Food and Drug Administration (FDA), the University of Texas Health Science Center at Houston, and the sponsor of this research may review your child's research and/or medical records for the purposes of verifying research data, and will see personal identifiers. However, identifying information will not appear on records retained by the sponsor, with the exception of your child's date of birth, your child's initials, and treatment/service dates. Your child will not be personally identified in any reports or publications that may result from this study. There is a separate section in this consent form that you will be asked to sign which details the use and disclosure of your child's protected health information.

Clinical Trials.Gov Language:
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

NEW INFORMATION

While taking part in this study, the study team will notify you of new information that may become available and could affect your willingness to allow your child to stay in the study. They will notify you of this information in person during the hospitalization.

QUESTIONS

If you have questions at any time about this research study, please feel free to contact the Dr. Parlar-Chun at 713-500-5586, as they will be glad to answer your questions. You can contact the study team to discuss problems, voice concerns, obtain information, and offer input in addition to asking questions about the research.

AUTHORIZATION TO USE AND DISCLOSE
PROTECTED HEALTH INFORMATION FOR RESEARCH
UT HEALTH AND/OR MEMORIAL HERMANN HEALTHCARE SYSTEM

PATIENT NAME:_____ **DATE OF BIRTH:**_____

Protocol Number and Title: Comparison Between Gastric and Post Pyloric Feedings in Bronchiolitis Patients Requiring High Flow Nasal Cannula

Principal Investigator: *Dr. Raymond Parlar-Chun*
If you sign this document, you give permission to The University of Texas Health Science Center at Houston AND/OR Memorial Hermann Healthcare System to use or disclose (release) your child's health information that identifies your child for the research study named above.

The health information that we may use or disclose (release) for this research includes child's date of birth, child's age, child's weight, result of physical examinations of your child, your child's medical history, lab test results, and hospital course. ***Information disclosed or released is de-identified.***

The health information listed above may be used by and/or disclosed (released) to researchers and their staff. The researchers may disclose information to employees at The University of Texas Health Science Center at Houston AND/OR Memorial Hermann Healthcare System for the purposes of verifying research records. The researchers may also disclose information to the following entities:

- Food and Drug Administration

The University of Texas Health Science Center at Houston AND/OR Memorial Hermann Healthcare System is required by law to protect your child's health information. By signing this document, you authorize The University of Texas Health Science Center at Houston AND/OR Memorial Hermann Healthcare System to use and/or disclose (release) your child's health information for this research. Those persons who receive your child's health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

If all information that does or can identify your child is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes. No publication or public presentation about the research described above will reveal your child's identity without another authorization from you.

Please note that health information used and disclosed may include information relating to HIV infection; treatment for or history of drug or alcohol abuse; or mental or behavioral health or psychiatric care. In case of an adverse event related to or resulting from taking part in this study, you give permission to the researchers involved in this research to access test, treatment and outcome information related to the adverse event from the treating facility.

Please note that you do not have to sign this Authorization, but if you do not, your child may not participate in this research study. The University of Texas Health Science Center at Houston AND/OR Memorial Hermann Healthcare System may not withhold treatment or refuse treating you if you do not sign this Authorization.

You may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers may still use or disclose health information they already have obtained about your child as necessary to maintain the integrity or reliability of the current research. To revoke this Authorization, you must write to:

PI Name: Dr. Raymond Parlar-Chun
The University of Texas Health Science Center at Houston
Address:
6431 Fannin MSE R318
Houston, Texas 77030
PI Fax: 713-486-0838

Privacy Officer
Memorial Hermann Healthcare System
909 Frostwood
Houston, Texas 77024
Fax: 713-338-4542

This Authorization will expire 6 years after the end of the study.

SIGNATURES

Sign below only if you understand the information given to you about the research and you choose to allow your child to take part. Make sure that any questions have been answered and that you understand the study. If you have any questions or concerns about your child's rights as a research subject, call the Committee for the Protection of Human Subjects at (713) 500-7943. You may also call the Committee if you wish to discuss problems, concerns, and questions; obtain information about the research; and offer input about current or past participation in a research study. If you decide to allow your child to take part in this research study, a copy of this signed consent form will be given to you.

Printed Name of (Child) Subject			
Printed Name of Parent or Legally Authorized Representative	Signature of Parent or Legally Authorized Representative	Date	Time
Printed Name of Person Obtaining Informed Consent	Signature of Person Obtaining Informed Consent	Date	Time

CPHS STATEMENT: This study (HSC-MS-17-0725) has been reviewed by the Committee for the Protection of Human Subjects (CPHS) of the University of Texas Health Science Center at Houston. For any questions about research subject's rights, or to report a research-related injury, call the CPHS at (713) 500-7943.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	4
Funding	#4	Sources and types of financial, material, and other support	3
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,4,5
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	5

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	9

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	11
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	11
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	11
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Data access	#29	Statement of who will have access to the final trial dataset,	n/a

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	13
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Protocol: Randomized trial to compare nasoduodenal tube and nasogastric tube feeding in infants with bronchiolitis on High-Flow Nasal Cannula; Bronchiolitis and High-flow nasal cannula with Enteral Tube feeding Randomized (BHETR) trial

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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Respiratory medicine, Research methods, Intensive care
Keywords:	Bronchiolitis, High Flow Nasal Cannula, Nasogastric Tube, Nasoduodenal Tube, Aspiration

Title:
Protocol: Randomized trial to compare nasoduodenal tube and nasogastric tube feeding in infants with bronchiolitis on High-Flow Nasal Cannula; **B**ronchiolitis and **H**igh-flow nasal cannula with **E**nteral **T**ube feeding **R**andomized (**BHETR)** trial.

Authors: Raymond Parlar-Chun, MD, Meaghan Lafferty-Prather, MD, Veronica Gonzalez, MD, Claudia Pedroza, PhD, Anand Gourishankar, MD.

All Authors from the Department of Pediatrics at McGovern Medical School, Houston, TX

Corresponding Author:
Raymond Parlar-Chun
Address: 6410 Fannin MSE R3188, Houston TX 77030
Telephone: 713-500-5586
Email: raymond.l.chun@uth.tmc.edu

Author Emails:
Raymond Parlar-Chun: raymond.l.chun@uth.tmc.edu
Meaghan Lafferty-Prather: Meaghan.LaffertyPrather@uth.tmc.edu
Veronica Gonzalez: Veronica.M.Gonzalez@uth.tmc.edu
Claudia Pedroza: Claudia.Pedroza@uth.tmc.edu
Anand Gourishankar: Anand.Gourishankar@uth.tmc.edu

Word Count: 3405 words

Title:
Protocol: Randomized trial to compare nasoduodenal tube and nasogastric tube feeding in infants with bronchiolitis on High-Flow Nasal Cannula; **B**ronchiolitis and **H**igh-flow nasal cannula with **E**nteral **T**ube feeding **R**andomized (**BHETR)** trial.

Abstract
Introduction: High flow nasal cannula (HFNC) is a noninvasive form of respiratory support used increasingly in bronchiolitis. HFNC provides a variable amount of positive pressure similar to continuous positive airway pressure (CPAP). The positive pressure in CPAP can distend and loosen esophageal sphincter pressure leading to increased reflux. It is unclear if HFNC causes a similar action. Feeding tubes are used to provide nutrition and hydration to patients that are unable to safely take oral feedings. If there is increased reflux from HFNC, this would increase the risk of aspiration. Our institution places nasoduodenal tubes (NDT) to eliminate this risk. The purpose of the study is to infer if there is a difference between NDT and nasogastric tube (NGT) feeding with regard to length of respiratory support, number of emesis, number of chest x-rays, and readmission/ER revisit rates.

Methods and Analysis: Patients with bronchiolitis, on high flow nasal cannula, and whose primary physicians have decided on feeding tube for nutrition/hydration will be approached for consent and enrollment. Patient's will be randomized to NGT or NDT in variable block sizes and stratified into low and high risk groups. Outcomes will be analyzed by both a frequentist and Bayesian statistical approach.

Ethics and dissemination: The trial was approved by local institutional review board. Every attempt will be made to reduce to an absolute minimum the interval between completion of data collection and release of study results through appropriate dissemination mediums including abstracts, poster presentations, and journal publications.

Article Summary:
Strengths and limitations
- There has been no prior randomized control trial regarding the type of feeding tube in infants with bronchiolitis on high flow nasal cannula
- Trial is block randomized with allocation concealment
- There are few exclusion criteria resulting in increased generalizability
- Both frequentist statistical analysis and Bayesian analysis will be used to estimate the probability of benefit.
- Clinicians could not be blinded.

Key Words: Bronchiolitis, high flow nasal cannula, nasogastric tube, nasoduodenal tube

Trial Registration ClinicalTrials.gov: NCT03346850

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Roles and Responsibilities: R.PC, A.G, M.LP, V.G, C.P

Authors' contributions

RPC conceived of the study. RPC, AG, MLP, and VG initiated the study design and implementation. C.P is conducting the primary statistical analysis. All authors contributed to refinement of the study protocol and approved the final manuscript.

Trial Sponsor: McGovern Medical School
Contact name: Raymond Parlar-Chun
Address: 6410 Fannin MSE R3188, Houston TX 77030
Telephone: 713-500-5586
Email: raymond.l.chun@uth.tmc.edu

Introduction

Bronchiolitis is a viral lower respiratory tract infection that can cause respiratory distress and failure secondary to inflammation of bronchial tissue and subsequent airway obstruction due to airway secretions and edema. This disease typically affects children less than two-years-old and is most severe in those under three months of age. Infants are at high risk of severe illness if they are born premature, or have chronic lung/heart disease, immunodeficiency, abnormal airway anatomy or neuromuscular disease. Clinical features of bronchiolitis may include nasal congestion, respiratory distress, wheezes and/or crackles, and atelectasis. Bronchiolitis hospitalization is overall declining, but remains the most common reason for hospitalization in infants in the United States; annual hospital-related charges amount to a few billion dollars in the United States.[1]

The route of nutrition and hydration in bronchiolitis remains an area of interest. For tachypneic infants, oral feeding may pose a risk for pulmonary aspiration.[2] Recently, however, a study suggested the incidence of aspiration-related respiratory failure in otherwise healthy, term children with bronchiolitis on HFNC receiving oral nutrition was low.[3] Nevertheless, there are instances in which children with bronchiolitis on HFNC will not take adequate oral feeds to meet daily nutritional demands, or it cannot be done safely, and feeding tube placement is necessary. Numerous pediatric societies such as the American Academy of Pediatrics (AAP) strongly recommend nasogastric (NG) or intravenous (IV) fluids for hydration.[4] IV fluids with nil per os (NPO) status is advantageous for the infant in imminent respiratory failure, but the choice of various tonicity of fluids and risk of iatrogenic hyponatremia is a concern.[5] Additionally, nutrition will suffer if prolonged IV fluids are given without any supplemental nutrition. The timing of introduction of enteral nutrition is also vital as recent guidelines from the American Society for Parenteral and Enteral Nutrition (ASPEN) suggest introduction of enteral nutrition for critically ill children within the first 24-48 hours of an intensive care unit (ICU) admission, as well as achieving 66% of goal feeds in the beginning improves clinical outcome.[6]

This question of how best to provide nutrition to patients with bronchiolitis is compounded when the patient is being supported with High-Flow Nasal Cannula (HFNC). HFNC is increasingly used in a variety of medical settings as non-invasive ventilation in infants with bronchiolitis.

HFNC provides humidified air at flows that provide a variable amount of positive pressure. This positive pressure may complicate feeding in bronchiolitis. There are studies in adults on Continuous Positive Airway Pressure (CPAP) that show increased positive pressure can create a decreased esophageal sphincter tone and increased incidences of gastroesophageal reflux.[7,8] It is unclear if there is a similar effect in infants on HFNC therapy. Physiologic studies do record changes in esophageal pressure.[9] A decrease in esophageal sphincter tone and increased reflux could lead to subsequent aspiration of gastric contents during nasogastric feeds.

Rationale for Study

At our institution, infants with bronchiolitis who are on HFNC receive nasoduodenal (ND) tube feeds. As compared to NG tube feeds, ND tube feeds are thought to minimize gastric reflux and potential airway aspiration. However, ND tubes are technically more difficult to place and provide continuous feeds which are less physiologic than bolus gastric feeding. For those infants who are not ready for oral feeds, but would benefit from enteral nutrition, an NG tube, in general, is easier to place. To date, no randomized trial compares two modalities (NG vs. ND) of tube feeds in infants with bronchiolitis on HFNC.

Choice of Comparators

Our current standard of practice is placement of an ND tube in patients with bronchiolitis on HFNC. Given NG tube feeding has been studied in infants with bronchiolitis and is supported by the AAP and other various organizations, this modality will be compared to our institution's standard of care.

Objectives

Research Hypothesis

As NG tube feeding appears to be well-tolerated in infants with bronchiolitis on HFNC, we hypothesize there will be no difference in duration of respiratory support, the number of emeses, and peak respiratory support between patients receiving NG tube feeds compared to ND tube feeds. We also hypothesize there will be no difference in these outcomes in the subgroup of the high-risk population (as defined in "Interventions").

Primary objective

To compare the duration of respiratory support between the NG and ND tube feeding groups.

Key Secondary objectives

To determine if differences exist between the NG and ND feeding groups with regards to:

- Number of emesis as recorded by bedside nursing
- Peak flow rates on HFNC
- Duration of HFNC
- Instances of failure of HFNC – defined as escalation of respiratory support to CPAP, BIPAP or intubation with mechanical ventilation.
- Occurrences of aspiration pneumonia – defined as an outcome determined by patient's primary physician with subsequent antibiotic treatment
- Number of X-rays for tube placement

- The overall length of hospital stay
- Emergency and hospital readmissions within 7 and 30 days post discharge

Other Secondary Objectives
To determine if high-risk infants (criteria listed below in "Interventions") have differences between the NG and ND tube feeding groups in regards to the objectives above.

Trial design
The BHETR trial is designed as a single center, randomized, non-blinded, equivalence trial with two parallel groups and a primary outcome of the length of time requiring respiratory support. Randomization will be in blinded blocks and stratified by low and high-risk groups with an allocation ratio of 1:1.

Study setting
The "BHETR trial" will be conducted at a single tertiary-care, academic children's hospital. We will recruit patients who are inpatients in the pediatric intermediate medical unit (IMU) of Children's Memorial Hermann Hospital affiliated with UTHealth McGovern Medical School at Houston. This randomized trial will recruit subjects from January 2018 until May 2019.

Eligibility Criteria
Inclusion Criteria
Ø All infants up to 12 months of age admitted for bronchiolitis requiring HFNC for whom the treating physician has decided to place a feeding tube.

Exclusion Criteria
Ø Infants with craniofacial anomalies that prevent tube placement
Ø Infants who had surgery compromising esophageal sphincter tones such as Nissen fundoplication or congenital hiatal hernia
Ø Infants initially requiring CPAP (continuous positive airway pressure) or mechanical ventilation
Ø Infants transferred from the PICU
Ø Infants transferred from a non-Hermann facility who are already on HFNC

Interventions

For all eligible patients on HFNC ready for tube feeding, a review of their past medical history will determine which category to classify the intervention group – low-risk or high-risk. High-risk patients are those born prematurely (<37 weeks gestation), and/or a previous diagnosis of neuromuscular disorders, seizures, cerebral palsy, eosinophilic esophagitis, upper airway disorders (i.e laryngomalacia), hemodynamically unstable congenital heart disease, or medically managed gastroesophageal reflux as determined by consensus among pediatric gastrointestinal and pulmonary specialists. Low-risk patients, on the other hand, are that born term (≥37 weeks gestation) without any of the previously listed comorbidities. Once the caregiver consents to the

study and the patient are enrolled, the University-affiliated "RedCap" software will be utilized to assist with stratified block randomization for NG tube or ND tube placement.

Once the patient is randomized, the study investigators will notify a member of the medical team caring for the patient about the patient's assignment of feeding tube type. The feeding tube is subsequently placed, and an X-ray is obtained for placement confirmation (X-ray confirmation is standard of practice at our hospital for both NG and ND tubes). Feeds are given continuously through an ND tube and as a bolus over 30 minutes every 3 hours through an NG tube. The total kcal/kg/day given is standardized for the patient's age and weight. The patient is provided with the same caloric density formula (or expressed breast milk) that they are given at home. Because of practicality, neither the study investigators, medical team, nor the caregivers could be blinded to the feeding modality chosen through randomization.

Modifications

Patients typically continue to be fed via the route determined by randomization until HFNC is discontinued. We expect patients to be managed via standard bronchiolitis protocol at our institution. There is no specific weaning protocol off HFNC, and is typically driven at the discretion of the primary physician. The caregivers can withdraw from the study at any point. Should the patient experience any adverse events, such as vomiting or aspiration, it is at the discretion of the primary physician caring for the patient to change the feeding route, hold, or discontinue feeds.

Outcomes

The total duration of respiratory support was selected as the primary outcome measure. This outcome measure serves as a surrogate measure for clinically relevant aspiration. There is no standard definition for aspiration, and there is no gold standard to determine if aspiration has occurred. By choosing length of respiratory support, the study uses a clinically relevant outcome with the presumption that increased aspiration events would lead to longer duration of support. While aspiration is multifactorial, randomization will help nullify the confounders and isolate the role of the type of tube feeding. Secondary outcome measures include the number of documented emesis , maximum respiratory support received, total duration of HFNC therapy, number of X-rays obtained to confirm tube placement, number of attempts for tube placement by the nursing staff, adverse events during placement or while the tube is in place (i.e. nosebleeds, tube dislodgement), instances of aspiration-related respiratory events, instances of HFNC failure (need for BiPAP, CPAP, or mechanical ventilation with intubation), hospital length of stay, and emergency room visits and hospital readmissions within 7 and 30 days after discharge.

Participant Timeline

Once a patient has been enrolled in the study, the patient remains enrolled throughout the acute care hospitalization until discharged. A telephone follow-up interview occurs 30 days after discharge.

Sample Size

The sample size was based on retrospective data analysis of bronchiolitis admissions at our institution over the past 3 years. Low-risk infants had an average duration of respiratory support of 86.8 hours (SD = 26), while high-risk infants had an average duration of respiratory support of 97.6 hours (SD = 39.6). Assuming 1 -β = 0.8 and α = 0.05, an *n* = 36 and *n* = 86 were calculated to be able to detect a difference at 24 hours in the duration of respiratory support in the low- and high-risk groups, respectively.

Recruitment

Patients are recruited continuously throughout the year; however, peak enrollment is expected to occur during "respiratory season", which is typically between October and March. When patients with bronchiolitis are admitted on HFNC from the emergency room, or started on HFNC after admission to the inpatient ward and deemed ready for enteral tube feeding, the patient is eligible for enrollment and the study investigators will ask the caregivers to consent to the study.

Allocation

After a patient has been identified as meeting inclusion criteria and consent is obtained, baseline data is entered into "REDCap" in which randomization occurs. Participants will be randomly assigned to either the NG or ND tube feeding group with a 1:1 allocation and will be stratified by risk level as previously defined. Investigators will be blinded to the block size and the block size will vary.

Allocation concealment will be ensured as the assigned group will not be revealed by "REDCap" until after the patient has been recruited into the trial and the baseline data has been entered into "REDCap".

Blinding

Trial participants, caregivers, medical personnel, and investigators will not be blinded to the study group assignment due to the obvious differences in the interventions. Study group assignment will be blinded to the statistician as deidentified data will be used for analysis.

Data Collection Methods

Data Collection Methods

After informed consent has been obtained, the investigator obtaining consent will gather the Baseline Parameters from the hospital EMR and from the parents. This data will be entered into UTH REDCap. The bedside nurse will be informed of the patient's enrollment and will be given a data collection form for tube placement to document the number of attempts needed to place the tube as well as any adverse events associated with the initial tube placement as well as any future tube placement needed if the tube becomes dislodged. An investigator will retrieve this form prior to the patient's discharge from the hospital. 30 days after discharge from the hospital, an investigator will assess for any subsequent emergency department visits or hospital admissions via hospital EMR and a phone call to the parent. Three attempts will be made to contact the parent. If after three attempts, the investigator is unable to contact the parent, the patient will be considered lost to follow up.

After the patient is discharged from the hospital, the Clinical Parameters data collection form will be completed in REDCap using information obtained from the nursing form, hospital EMR, and the 30-day follow up phone call using the variable definitions agreed upon by the investigators. A second investigator will independently enter the Baseline Parameters as well as the Clinical Parameters into REDCap. The principal investigator will then compare the duplicate sets of data and address any discrepancies to ensure validity.

Retention

All randomized patients will be included in an intention-to-to treat analysis. The primary treating physicians may choose to change the method of feeding at any point if they are concerned about adverse events. Similarly, if the patient requires subsequent admission to PICU, the study will not dictate feeding methods at that time.

To maximize retention to the 30-day post-discharge follow up phone call, investigators will obtain a working phone number and/or email address from the parents at the time of consent and enrollment into the study. Parents will be told to expect a phone call and/or email 30 days after discharge.

Data Management

Paper Baseline Parameters and Nursing forms will be kept in a file cabinet in a secure office. All data will be entered electronically and stored on a UTShare account and on UTHealth REDCap, both of which are private health information protected and require 2-factor authentication. As described above, each set of data will be entered twice with each duplicate data set compared by the primary investigator, and discrepancies addressed to ensure data validity.

Within the data collection forms in REDCap, calculators have been programmed to calculate the length of time on respiratory support as well as other outcome measures from entered date/time data entries to minimize human calculation error.

Statistical Methods

Outcomes

All analyses will be intent-to-treat. Differences in total length of respiratory support between treatment groups will be assessed with a regression model including treatment and risk group (stratifying variable) as covariates. Rates of secondary outcomes will be assessed using log-binomial or logistic models, and a total number of secondary outcomes will be assessed with negative binomial models.

Additional Analyses

In this small pilot study, some treatment effects that could be considered important by family members and clinicians (reduced hospital days) may not be statistically significant. As a result, Bayesian analyses will also be performed to estimate the probability of benefit. Neutral, weakly informative priors will be used for the treatment effect, e.g. for binary outcomes, the prior relative risk will be centered at 1.0 with 95% prior interval of 0.5-2.0. Depending on the results of the pilot, the need for a larger trial will be assessed.

Data Monitoring

Formal Committee

Not applicable - a data monitoring committee (DMC) is not needed as risks are expected to be minimal.

Interim Analysis

An interim analysis will be performed when 50% of patients have been randomized and will be performed by an independent statistician who is blinded to the treatment allocation. A standard normal deviate test will be calculated to determine if the rate of adverse events are significantly different between the two groups ($p< 0.05$).

Harms

Adverse events related to tube placement is recorded by nurse responsible for placing the tube. The route of feeding may be changed at the discretion of the primary physician if the particular tube placed is believed to be causing harm to the patient, such as worsening respiratory distress or aspiration pneumonia.

Auditing

Independent, periodic audits will not be performed. The investigators will perform self-assessments to ensure the data collected were for patients admitted for bronchiolitis and the other inclusion criteria. Data for each patient is collected by two separate investigators and then verified by the principal investigator to ensure good data quality. “RedCap” is able to compare two entries for irregularities.

Research Ethics Approval

The protocol and the template informed consent forms contained in Appendix were approved by UTHealth’s Committee For the Protection of Human Subjects (our institution’s IRB) with respect to scientific content and compliance with applicable research and human subjects regulations.

Protocol Amendments

Any modifications to the protocol which may impact the conduct of the study, the safety of the patient, or any changes to the objectives, design, population, sample sizes, procedures, or significant administrative aspects will have a formal amendment to the protocol and approved by the IRB prior to implementation.

Protocol Version available in Supplementary Materials Appendix 1

Patient and Public Involvement

Patients were not involved in the development of the research question, study design, or recruitment into the study.

Consent

Members of the study team, all who are familiar with the trial and study design, will obtain written consent from patients' caregivers. All consent and information sheets are available in English and Spanish. See Supplementary Materials Appendix 2.

Confidentiality

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in a secured office. Electronic data will be stored on the university cloud storage that requires two-factor authentication and private health information security.

Declaration of Interests

No conflicts of interest are declared for any of the study investigators.

Dissemination Policy

Every attempt will be made to reduce to an absolute minimum the interval between completion of data collection and release of study results through appropriate dissemination mediums including abstracts, poster presentations, and journal publications.

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Supplementary Material, Appendix 1 and 2

1. Trial Registration and Protocol Revision
2. Informed Consent Documents

Protocol Version
Issue Date: 3/21/2018
Protocol Amendment Number : 02
Authors: R.PC

Revision Chronology:

2017 - August 10	Original
2018 - January 29	Amendment 01.: Primary reason for amendment: optimization of randomization and allocation concealment
2018 - March 21	Amendment 02.: Change in primary outcome from the duration of HFNC to the duration of all respiratory support to capture the patients that had to be reinitiated to HFNC after discontinuation

University of Texas Health Science Center at Houston/Memorial Hermann Healthcare System
INFORMED CONSENT FORM TO TAKE PART IN RESEARCH
Comparison Between Gastric and Post Pyloric Feedings in Bronchiolitis Patients Requiring High Flow Nasal Cannula
HSC-MS-17-0725
Parental Consent

INVITATION TO TAKE PART

You are invited to allow your child to take part in a research project called, *Comparison Between Gastric and Post Pyloric Feedings in Bronchiolitis Patients Requiring High Flow Nasal Cannula*, conducted by Dr. Raymond Parlar-Chun of the University of Texas Health Science Center at Houston (UTHealth) and Memorial Hermann Healthcare System. For this research project, he will be called the Principal Investigator or PI.

Your decision to allow your child to take part is voluntary. You may refuse to allow your child to take part or choose to stop your child from taking part, at any time. A decision not to allow your child to take part or to stop being a part of the research project will not change the services available to your child from Dr. Parlar-Chun and research staff with the University of Texas Health Science Center at Houston (UTHealth) and Memorial Hermann Healthcare System .

You and your child may refuse to answer any questions asked or written on any forms. This research project has been reviewed by the Committee for the Protection of Human Subjects (CPHS) of the University of Texas Health Science Center at Houston as HSC-MS-17-0725.

PURPOSE

The purpose of this research study is to determine the best way to provide nutrition to infants admitted to the hospital with viral bronchiolitis. Bronchiolitis is the most common cause of hospitalization for infants < 1 year of age. High flow nasal cannula (HFNC) is being used to provide respiratory support. However, the optimal feeding strategy for patients on HFNC remains unclear. Some institutions allow these infants to feed orally by mouth. Others keep them on IV fluids for the duration of their time on HFNC. Others still institute some type of tube feedings, either nasogastric tube feeds or nasoduodenal tube feeds. Our goal is to study outcomes in patients who are fed with nasogastric (NG) tube feeds (a tube that goes from the nose into the stomach) vs. nasoduodenal (ND) tube feeds (a tube that goes from the nose, past the stomach, and into the small intestine) in patients admitted to the hospital for viral bronchiolitis who require treatment with HFNC.

Your child is being asked to participate in this study because they are being admitted to the hospital for management of viral bronchiolitis and may require high flow nasal cannula therapy. Our study runs for the duration of the current respiratory season (October 2017-April 2018).

This is a local study that will enroll approximately 230 patients.

PROCEDURES

If you agree and allow your child is able to take part in this study you will first sign the consent form before undergoing these study procedures:

Your child will qualify for inclusion in the study when 1.) They are admitted to the hospital for viral bronchiolitis, and 2.) they are started on respiratory treatment with HFNC. When both those criteria are met, he/she will be randomly assigned (similar to flipping a coin, 50% chance of either outcome) to one of two feeding strategies – NG tube vs. ND tube. Depending on which group your child is assigned to, that particular tube will be inserted for the purposes of feeding your child. The NG tube is inserted through the nose and ends in the stomach. The ND tube is inserted through the nose, goes past the stomach, and ends in the small intestine. The NG or ND tube will be inserted as soon as your child qualifies for the study. For example, if your child is admitted for bronchiolitis but originally is on room air, or on regular nasal cannula, they will only qualify for the study when and if their primary medical team decides that they require HFNC for treatment. If they stay on room air or regular nasal cannula, then they do not qualify for the study. If they are admitted to the inpatient unit with HFNC already started in the Emergency Department or at an outside facility, then we will place the NG or ND tube soon after they arrive at our inpatient unit. The placement of the tube will be confirmed by an abdominal x-ray prior to starting any feedings.

Your child will remain on NG or ND tube feeds for as long as they remain on HFNC. The decision about when to restart regular oral feedings will be made by your regular doctors. They will also determine how long your child requires HFNC, or whether they require even more breathing support such as CPAP or mechanical ventilation. If your child develops severe bronchiolitis and requires either CPAP or mechanical ventilation, they will be removed from the remainder of the study, and the decision about how/when to feed your child will be made by your primary medical doctors.

We will be collecting several measurements during the study. These include: child's age, child's gender, child's race, child's weight, number of days your child requires HFNC support, number of times they have vomiting, maximum respiratory support they require, number of xrays ordered during hospitalization, whether they received any antibiotics during the hospitalization, total number of days they are in the hospital, and whether they have to return to an emergency department or are rehospitalized 7 and/or 30 days after discharge from our facility.

If you choose to not participate in this study, and your child requires tube feedings for nutrition, they will receive a NDT, our current standard of care. Your decision to participate, or not to participate, will not affect your doctor's decisions about what is the best medical treatment for your child. He/she will still receive the appropriate level of respiratory support your child needs (room air, regular nasal cannula, HFNC, CPAP, or intubation), and feedings will be provided at the discretion of your primary doctors (IV fluids, regular oral feeds, NG tube feeds, or ND tube feeds).

TIME COMMITMENT

The total amount of time your child will take part in this research study is the total duration of time they remain on HFNC therapy. Most infants admitted for bronchiolitis who require HFNC therapy require it for approximately 1-5 days. The participation in the study will end when the child improves and is weaned oxygen via regular nasal cannula or room air, or if their bronchiolitis worsens and they require CPAP or intubation.

BENEFITS

Your child may receive no direct benefit from being in the study. However, bronchiolitis is the leading cause of hospitalization of children, and your child's participation in this study will help us understand the best way to feed the large number infants who are admitted for this disease every year.

RISKS AND/OR DISCOMFORTS

While on this study, your child is at risk for side effects. The study doctor will discuss these risks with you and your child. This study may include risks that are unknown at this time.

Inserting either an NG or ND tube can be uncomfortable for your child. They are inserted by nurses who are trained to minimize any discomfort your child may experience. The ND tube is slightly more challenging to place than an NG tube because it has to go further, but both tubes are placed every day and are common and relatively simple procedures. Once the tube is placed, your child should not feel any further discomfort, similar to after an IV is inserted. Prior to starting any feedings, the position of both tubes are verified by an abdominal xray to minimize any risk of feedings being delivered incorrectly. Your child may also continue to feel hungry while being fed via ND tube, as the sensation of hunger is satiated by being fed into the stomach, not past the stomach. However both forms of feeding are equally nutritious and will provide the same number of calories to help with your child's recovery and daily requirements.

There is a theoretical risk of reflux and aspiration while on NG tube feeds and HFNC simultaneously. Reflux is when food from the stomach moves up into the esophagus or mouth, similar to when a patient vomits. Aspiration is when food from the stomach enters the lungs. Several studies have looked at this question and determined that NG tube feeds are safe for patients with bronchiolitis, with or without HFNC. Additionally, many children's hospitals around the country only feed patients with bronchiolitis using NG tubes as their standard of care. However, no studies have directly compared patient outcomes in bronchiolitis patients fed using NG tube vs. ND tube feedings, which is what we are looking to do. If your child's primary doctor feels that your child is having worsening respiratory distress because of NG feeds, your child will be pulled from the remainder of the study and these feedings will be discontinued. Additionally, the study group will be meeting each week during the study to review the data we have collected. If we feel that the NG tube group is having more complications than the ND tube group, the study will be immediately discontinued.

As with all clinical studies, there is a possible risk of breach of confidentiality. All efforts will be made to minimize this risk. Your child's medical information will only be shared by certified members of the study team, in addition to the regular group of bedside caregivers (doctors, nurses, students, respiratory therapists, pharmacists, etc).

ALTERNATIVES

If you choose to not participate in this study, your child will still receive the same excellent care from all team members taking care of your child. Your decision to participate, or not to participate, will not affect your doctor's decisions about what is the best medical treatment for your child. We will still provide the appropriate level of respiratory support your child needs (room air, regular nasal cannula, HFNC, CPAP, or mechanical ventilation), and will provide feedings at the discretion of your primary doctors (IV fluids, regular oral feeds, NG tube feeds, or ND tube feeds). They will not be randomized to NG vs. ND feeds, but instead, will be given feeds according to the discretion of the primary doctors taking care of your child in discussion with your preferences. If the decision for tube feedings has been made, our current standard of care is placing NDTs.

STUDY WITHDRAWAL

Your decision to allow your child to take part is voluntary. You may decide to stop your child from taking part in the study at any time. A decision to decline to take part or to stop being a part of the research study will not change the services available to you and your child from Dr. Parlar-Chun and research staff, or any care providers at Children's Memorial Hermann Hospital.

Your child's doctor can stop the study at any time for any of the following reasons: if your child's doctors determine he/she requires CPAP or mechanical ventilation, or if your child's doctors feel he/she may be aspirating with NG feeds.

Should the study be stopped, we will still be able to use the data that your child provides, and the reason for withdrawal from the study will be noted in our results.

IN CASE OF INJURY

If your child suffers an injury as a result of taking part in this research study please understand that nothing has been arranged to provide free treatment of the injury or any other type of payment. However, necessary facilities, emergency treatment and professional services will be available to your child, just as they are to the general community. You should report any such injury to Dr. Parlar-Chun at 713-500-5586 and to the Committee for the Protection of Human Subjects at 713-500-7943. You will not give up any of your child's legal rights by signing this consent form.

COSTS, REIMBURSEMENT AND COMPENSATION

If you decide to allow your child to take part in this research study, you will not incur any additional costs. You and your child will not be paid for taking part in this study.

CONFIDENTIALITY

Please understand that representatives of the Food and Drug Administration (FDA), the University of Texas Health Science Center at Houston, and the sponsor of this research may review your child's research and/or medical records for the purposes of verifying research data, and will see personal identifiers. However, identifying information will not appear on records retained by the sponsor, with the exception of your child's date of birth, your child's initials, and treatment/service dates. Your child will not be personally identified in any reports or publications that may result from this study. There is a separate section in this consent form that you will be asked to sign which details the use and disclosure of your child's protected health information.

Clinical Trials.Gov Language:
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

NEW INFORMATION

While taking part in this study, the study team will notify you of new information that may become available and could affect your willingness to allow your child to stay in the study. They will notify you of this information in person during the hospitalization.

QUESTIONS

If you have questions at any time about this research study, please feel free to contact the Dr. Parlar-Chun at 713-500-5586, as they will be glad to answer your questions. You can contact the study team to discuss problems, voice concerns, obtain information, and offer input in addition to asking questions about the research.

AUTHORIZATION TO USE AND DISCLOSE
PROTECTED HEALTH INFORMATION FOR RESEARCH
UT HEALTH AND/OR MEMORIAL HERMANN HEALTHCARE SYSTEM

PATIENT NAME:_____ **DATE OF BIRTH:**_____

Protocol Number and Title: Comparison Between Gastric and Post Pyloric Feedings in Bronchiolitis Patients Requiring High Flow Nasal Cannula

Principal Investigator: *Dr. Raymond Parlar-Chun*
If you sign this document, you give permission to The University of Texas Health Science Center at Houston AND/OR Memorial Hermann Healthcare System to use or disclose (release) your child's health information that identifies your child for the research study named above.

The health information that we may use or disclose (release) for this research includes child's date of birth, child's age, child's weight, result of physical examinations of your child, your child's medical history, lab test results, and hospital course. ***Information disclosed or released is de-identified.***

The health information listed above may be used by and/or disclosed (released) to researchers and their staff. The researchers may disclose information to employees at The University of Texas Health Science Center at Houston AND/OR Memorial Hermann Healthcare System for the purposes of verifying research records. The researchers may also disclose information to the following entities:

- Food and Drug Administration

The University of Texas Health Science Center at Houston AND/OR Memorial Hermann Healthcare System is required by law to protect your child's health information. By signing this document, you authorize The University of Texas Health Science Center at Houston AND/OR Memorial Hermann Healthcare System to use and/or disclose (release) your child's health information for this research. Those persons who receive your child's health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

If all information that does or can identify your child is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes. No publication or public presentation about the research described above will reveal your child's identity without another authorization from you.

Please note that health information used and disclosed may include information relating to HIV infection; treatment for or history of drug or alcohol abuse; or mental or behavioral health or psychiatric care. In case of an adverse event related to or resulting from taking part in this study, you give permission to the researchers involved in this research to access test, treatment and outcome information related to the adverse event from the treating facility.

Please note that you do not have to sign this Authorization, but if you do not, your child may not participate in this research study. The University of Texas Health Science Center at Houston AND/OR Memorial Hermann Healthcare System may not withhold treatment or refuse treating you if you do not sign this Authorization.

You may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers may still use or disclose health information they already have obtained about your child as necessary to maintain the integrity or reliability of the current research. To revoke this Authorization, you must write to:

PI Name: Dr. Raymond Parlar-Chun
The University of Texas Health Science Center at Houston
Address:
6431 Fannin MSE R318
Houston, Texas 77030
PI Fax: 713-486-0838

Privacy Officer
Memorial Hermann Healthcare System
909 Frostwood
Houston, Texas 77024
Fax: 713-338-4542

This Authorization will expire 6 years after the end of the study.

SIGNATURES

Sign below only if you understand the information given to you about the research and you choose to allow your child to take part. Make sure that any questions have been answered and that you understand the study. If you have any questions or concerns about your child's rights as a research subject, call the Committee for the Protection of Human Subjects at (713) 500-7943. You may also call the Committee if you wish to discuss problems, concerns, and questions; obtain information about the research; and offer input about current or past participation in a research study. If you decide to allow your child to take part in this research study, a copy of this signed consent form will be given to you.

Printed Name of (Child) Subject			
Printed Name of Parent or Legally Authorized Representative	Signature of Parent or Legally Authorized Representative	Date	Time
Printed Name of Person Obtaining Informed Consent	Signature of Person Obtaining Informed Consent	Date	Time

CPHS STATEMENT: This study (HSC-MS-17-0725) has been reviewed by the Committee for the Protection of Human Subjects (CPHS) of the University of Texas Health Science Center at Houston. For any questions about research subject's rights, or to report a research-related injury, call the CPHS at (713) 500-7943.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	4
Funding	#4	Sources and types of financial, material, and other support	3
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,4,5
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	5

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	9

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	11
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	11
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	11
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Data access	#29	Statement of who will have access to the final trial dataset,	n/a

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	13
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Protocol: Randomized trial to compare nasoduodenal tube and nasogastric tube feeding in infants with bronchiolitis on High-Flow Nasal Cannula; Bronchiolitis and High-flow nasal cannula with Enteral Tube feeding Randomized (BHETR) trial

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Title:
Protocol: Randomized trial to compare nasoduodenal tube and nasogastric tube feeding in infants with bronchiolitis on High-Flow Nasal Cannula; **B**ronchiolitis and **H**igh-flow nasal cannula with **E**nteral **T**ube feeding **R**andomized (**BHETR)** trial.

Authors: Raymond Parlar-Chun, MD, Meaghan Lafferty-Prather, MD, Veronica Gonzalez, MD, Claudia Pedroza, PhD, Anand Gourishankar, MD.

All Authors from the Department of Pediatrics at McGovern Medical School, Houston, TX

Corresponding Author:
Raymond Parlar-Chun
Address: 6410 Fannin MSE R3188, Houston TX 77030
Telephone: 713-500-5586
Email: raymond.l.chun@uth.tmc.edu

Author Emails:
Raymond Parlar-Chun: raymond.l.chun@uth.tmc.edu
Meaghan Lafferty-Prather: Meaghan.LaffertyPrather@uth.tmc.edu
Veronica Gonzalez: Veronica.M.Gonzalez@uth.tmc.edu
Claudia Pedroza: Claudia.Pedroza@uth.tmc.edu
Anand Gourishankar: Anand.Gourishankar@uth.tmc.edu

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Title:
Protocol: Randomized trial to compare nasoduodenal tube and nasogastric tube feeding in infants with bronchiolitis on High-Flow Nasal Cannula; **B**ronchiolitis and **H**igh-flow nasal cannula with **E**nteral **T**ube feeding **R**andomized (**BHETR)** trial.

Abstract
Introduction: High flow nasal cannula (HFNC) is a noninvasive form of respiratory support used increasingly in bronchiolitis. HFNC provides a variable amount of positive pressure similar to continuous positive airway pressure (CPAP). The positive pressure in CPAP can distend and loosen esophageal sphincter pressure leading to increased reflux. It is unclear if HFNC causes a similar action. Feeding tubes are used to provide nutrition and hydration to patients that are unable to safely take oral feedings. If there is increased reflux from HFNC, this would increase the risk of aspiration. Our institution places nasoduodenal tubes (NDT) to eliminate this risk. The purpose of the study is to infer if there is a difference between NDT and nasogastric tube (NGT) feeding with regard to length of respiratory support, number of emesis, number of chest x-rays, and readmission/ER revisit rates.

Methods and Analysis: Patients with bronchiolitis, on high flow nasal cannula, and whose primary physicians have decided on feeding tube for nutrition/hydration will be approached for consent and enrollment. Patient's will be randomized to NGT or NDT in variable block sizes and stratified into low and high risk groups. Outcomes will be analyzed by both a frequentist and Bayesian statistical approach.

Ethics and dissemination: The trial was approved by local institutional review board. Every attempt will be made to reduce to an absolute minimum the interval between completion of data collection and release of study results through appropriate dissemination mediums including abstracts, poster presentations, and journal publications.

Article Summary:
Strengths and limitations
- There has been no prior randomized control trial regarding the type of feeding tube in infants with bronchiolitis on high flow nasal cannula
- Trial is block randomized with allocation concealment
- There are few exclusion criteria resulting in increased generalizability
- Both frequentist statistical analysis and Bayesian analysis will be used to estimate the probability of benefit.
- Clinicians could not be blinded.

Key Words: Bronchiolitis, high flow nasal cannula, nasogastric tube, nasoduodenal tube

Trial Registration ClinicalTrials.gov: NCT03346850

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Roles and Responsibilities: R.PC, A.G, M.LP, V.G, C.P

Authors' contributions

RPC conceived of the study. RPC, AG, MLP, and VG initiated the study design and implementation. C.P is conducting the primary statistical analysis. All authors contributed to refinement of the study protocol and approved the final manuscript.

Trial Sponsor: McGovern Medical School
Contact name: Raymond Parlar-Chun
Address: 6410 Fannin MSE R3188, Houston TX 77030
Telephone: 713-500-5586
Email: raymond.l.chun@uth.tmc.edu

Introduction

Bronchiolitis is a viral lower respiratory tract infection that can cause respiratory distress and failure secondary to inflammation of bronchial tissue and subsequent airway obstruction due to airway secretions and edema. This disease typically affects children less than two-years-old and is most severe in those under three months of age. Infants are at high risk of severe illness if they are born premature, or have chronic lung/heart disease, immunodeficiency, abnormal airway anatomy or neuromuscular disease. Clinical features of bronchiolitis may include nasal congestion, respiratory distress, wheezes and/or crackles, and atelectasis. Bronchiolitis hospitalization is overall declining, but remains the most common reason for hospitalization in infants in the United States; annual hospital-related charges amount to a few billion dollars in the United States.[1]

The route of nutrition and hydration in bronchiolitis remains an area of interest. For tachypneic infants, oral feeding may pose a risk for pulmonary aspiration.[2] Recently, however, a study suggested the incidence of aspiration-related respiratory failure in otherwise healthy, term children with bronchiolitis on HFNC receiving oral nutrition was low.[3] Nevertheless, there are instances in which children with bronchiolitis on HFNC will not take adequate oral feeds to meet daily nutritional demands, or it cannot be done safely, and feeding tube placement is necessary. Numerous pediatric societies such as the American Academy of Pediatrics (AAP) strongly recommend nasogastric (NG) or intravenous (IV) fluids for hydration.[4] IV fluids with nil per os (NPO) status is advantageous for the infant in imminent respiratory failure, but the choice of various tonicity of fluids and risk of iatrogenic hyponatremia is a concern.[5] Additionally, nutrition will suffer if prolonged IV fluids are given without any supplemental nutrition. The timing of introduction of enteral nutrition is also vital as recent guidelines from the American Society for Parenteral and Enteral Nutrition (ASPEN) suggest introduction of enteral nutrition for critically ill children within the first 24-48 hours of an intensive care unit (ICU) admission, as well as achieving 66% of goal feeds in the beginning improves clinical outcome.[6]

This question of how best to provide nutrition to patients with bronchiolitis is compounded when the patient is being supported with High-Flow Nasal Cannula (HFNC). HFNC is increasingly used in a variety of medical settings as non-invasive ventilation in infants with bronchiolitis.

HFNC provides humidified air at flows that provide a variable amount of positive pressure. This positive pressure may complicate feeding in bronchiolitis. There are studies in adults on Continuous Positive Airway Pressure (CPAP) that show increased positive pressure can create a decreased esophageal sphincter tone and increased incidences of gastroesophageal reflux.[7,8] It is unclear if there is a similar effect in infants on HFNC therapy. Physiologic studies do record changes in esophageal pressure.[9] A decrease in esophageal sphincter tone and increased reflux could lead to subsequent aspiration of gastric contents during nasogastric feeds.

Rationale for Study

At our institution, infants with bronchiolitis who are on HFNC receive nasoduodenal (ND) tube feeds. As compared to NG tube feeds, ND tube feeds are thought to minimize gastric reflux and potential airway aspiration. However, ND tubes are technically more difficult to place and provide continuous feeds which are less physiologic than bolus gastric feeding. For those infants who are not ready for oral feeds, but would benefit from enteral nutrition, an NG tube, in general, is easier to place. To date, no randomized trial compares two modalities (NG vs. ND) of tube feeds in infants with bronchiolitis on HFNC.

Choice of Comparators

Our current standard of practice is placement of an ND tube in patients with bronchiolitis on HFNC. Given NG tube feeding has been studied in infants with bronchiolitis and is supported by the AAP and other various organizations, this modality will be compared to our institution's standard of care.

Objectives

Research Hypothesis

As NG tube feeding appears to be well-tolerated in infants with bronchiolitis on HFNC, we hypothesize there will be no difference in duration of respiratory support, the number of emeses, and peak respiratory support between patients receiving NG tube feeds compared to ND tube feeds. We also hypothesize there will be no difference in these outcomes in the subgroup of the high-risk population (as defined in "Interventions").

Primary objective

To compare the duration of respiratory support between the NG and ND tube feeding groups.

Key Secondary objectives

To determine if differences exist between the NG and ND feeding groups with regards to:

- Number of emesis as recorded by bedside nursing
- Peak flow rates on HFNC
- Duration of HFNC
- Instances of failure of HFNC – defined as escalation of respiratory support to CPAP, BIPAP or intubation with mechanical ventilation.
- Occurrences of aspiration pneumonia – defined as an outcome determined by patient's primary physician with subsequent antibiotic treatment
- Number of X-rays for tube placement

- The overall length of hospital stay
- Emergency and hospital readmissions within 7 and 30 days post discharge

Other Secondary Objectives
To determine if high-risk infants (criteria listed below in "Interventions") have differences between the NG and ND tube feeding groups in regards to the objectives above.

Trial design
The BHETR trial is designed as a single center, randomized, non-blinded, equivalence trial with two parallel groups and a primary outcome of the length of time requiring respiratory support. Randomization will be in blinded blocks and stratified by low and high-risk groups with an allocation ratio of 1:1.

Study setting
The "BHETR trial" will be conducted at a single tertiary-care, academic children's hospital. We will recruit patients who are inpatients in the pediatric intermediate medical unit (IMU) of Children's Memorial Hermann Hospital affiliated with UTHealth McGovern Medical School at Houston. This randomized trial will recruit subjects from January 2018 until May 2019.

Eligibility Criteria
Inclusion Criteria
Ø All infants up to 12 months of age admitted for bronchiolitis requiring HFNC for whom the treating physician has decided to place a feeding tube.

Exclusion Criteria
Ø Infants with craniofacial anomalies that prevent tube placement
Ø Infants who had surgery compromising esophageal sphincter tones such as Nissen fundoplication or congenital hiatal hernia
Ø Infants initially requiring CPAP (continuous positive airway pressure) or mechanical ventilation
Ø Infants transferred from the PICU
Ø Infants transferred from a non-Hermann facility who are already on HFNC

Interventions

For all eligible patients on HFNC ready for tube feeding, a review of their past medical history will determine which category to classify the intervention group – low-risk or high-risk. High-risk patients are those born prematurely (<37 weeks gestation), and/or a previous diagnosis of neuromuscular disorders, seizures, cerebral palsy, eosinophilic esophagitis, upper airway disorders (i.e laryngomalacia), hemodynamically unstable congenital heart disease, or medically managed gastroesophageal reflux as determined by consensus among pediatric gastrointestinal and pulmonary specialists. Low-risk patients, on the other hand, are that born term (≥37 weeks gestation) without any of the previously listed comorbidities. Once the caregiver consents to the

study and the patient are enrolled, the University-affiliated "RedCap" software will be utilized to assist with stratified block randomization for NG tube or ND tube placement.

Once the patient is randomized, the study investigators will notify a member of the medical team caring for the patient about the patient's assignment of feeding tube type. The feeding tube is subsequently placed, and an X-ray is obtained for placement confirmation (X-ray confirmation is standard of practice at our hospital for both NG and ND tubes). Feeds are given continuously through an ND tube and as a bolus over 30 minutes every 3 hours through an NG tube. The total kcal/kg/day given is standardized for the patient's age and weight. The patient is provided with the same caloric density formula (or expressed breast milk) that they are given at home. Because of practicality, neither the study investigators, medical team, nor the caregivers could be blinded to the feeding modality chosen through randomization.

Modifications

Patients typically continue to be fed via the route determined by randomization until HFNC is discontinued. We expect patients to be managed via standard bronchiolitis protocol at our institution. There is no specific flow weaning protocol off HFNC, and will be driven at the discretion of the primary physician. Respiratory viral panels will also be obtained at the discretion of the primary physician. The caregivers can withdraw from the study at any point. Should the patient experience any adverse events, such as vomiting or aspiration, it is at the discretion of the primary physician caring for the patient to change the feeding route, hold, or discontinue feeds.

Outcomes

The total duration of respiratory support was selected as the primary outcome measure. This outcome measure serves as a surrogate measure for clinically relevant aspiration. There is no standard definition for aspiration, and there is no gold standard to determine if aspiration has occurred. By choosing length of respiratory support, the study uses a clinically relevant outcome with the presumption that increased aspiration events would lead to longer duration of support. While aspiration is multifactorial, randomization will help nullify the confounders and isolate the role of the type of tube feeding. Secondary outcome measures include the number of documented emesis , maximum respiratory support received, total duration of HFNC therapy, number of X-rays obtained to confirm tube placement, number of attempts for tube placement by the nursing staff, adverse events during placement or while the tube is in place (i.e. nosebleeds, tube dislodgement), instances of aspiration-related respiratory events, instances of HFNC failure (need for BiPAP, CPAP, or mechanical ventilation with intubation), hospital length of stay, and emergency room visits and hospital readmissions within 7 and 30 days after discharge.

Participant Timeline

Once a patient has been enrolled in the study, the patient remains enrolled throughout the acute care hospitalization until discharged. A telephone follow-up interview occurs 30 days after discharge.

Sample Size

The sample size was based on retrospective data analysis of bronchiolitis admissions at our institution over the past 3 years. Low-risk infants had an average duration of respiratory support of 86.8 hours (SD = 26), while high-risk infants had an average duration of respiratory support of 97.6 hours (SD = 39.6). Assuming 1 -β = 0.8 and α = 0.05, an n = 36 and n = 86 were calculated to be able to detect a difference at 24 hours in the duration of respiratory support in the low- and high-risk groups, respectively.

Recruitment

Patients are recruited continuously throughout the year; however, peak enrollment is expected to occur during "respiratory season", which is typically between October and March. When patients with bronchiolitis are admitted on HFNC from the emergency room, or started on HFNC after admission to the inpatient ward and deemed ready for enteral tube feeding, the patient is eligible for enrollment and the study investigators will ask the caregivers to consent to the study.

Allocation

After a patient has been identified as meeting inclusion criteria and consent is obtained, baseline data is entered into "REDCap" in which randomization occurs. Participants will be randomly assigned to either the NG or ND tube feeding group with a 1:1 allocation and will be stratified by risk level as previously defined. Investigators will be blinded to the block size and the block size will vary.

Allocation concealment will be ensured as the assigned group will not be revealed by "REDCap" until after the patient has been recruited into the trial and the baseline data has been entered into "REDCap".

Blinding

Trial participants, caregivers, medical personnel, and investigators will not be blinded to the study group assignment due to the obvious differences in the interventions. Study group assignment will be blinded to the statistician as deidentified data will be used for analysis.

Data Collection Methods

After informed consent has been obtained, the investigator obtaining consent will gather the Baseline Parameters from the hospital EMR and from the parents. This data will be entered into UTH REDCap. The bedside nurse will be informed of the patient's enrollment and will be given a data collection form for tube placement to document the number of attempts needed to place the tube as well as any adverse events associated with the initial tube placement as well as any future tube placement needed if the tube becomes dislodged. An investigator will retrieve this form prior to the patient's discharge from the hospital. 30 days after discharge from the hospital, an investigator will assess for any subsequent emergency department visits or hospital admissions via hospital EMR and a phone call to the parent. Three attempts will be made to contact the parent. If after three attempts, the investigator is unable to contact the parent, the patient will be considered lost to follow up.

After the patient is discharged from the hospital, the Clinical Parameters data collection form will be completed in REDCap using information obtained from the nursing form, hospital EMR, and the 30-day follow up phone call using the variable definitions agreed upon by the investigators. A second investigator will independently enter the Baseline Parameters as well as the Clinical Parameters into REDCap. The principal investigator will then compare the duplicate sets of data and address any discrepancies to ensure validity.

Retention

All randomized patients will be included in an intention-to-to treat analysis. The primary treating physicians may choose to change the method of feeding at any point if they are concerned about adverse events. Similarly, if the patient requires subsequent admission to PICU, the study will not dictate feeding methods at that time.

To maximize retention to the 30-day post-discharge follow up phone call, investigators will obtain a working phone number and/or email address from the parents at the time of consent and enrollment into the study. Parents will be told to expect a phone call and/or email 30 days after discharge.

Data Management

Paper Baseline Parameters and Nursing forms will be kept in a file cabinet in a secure office. All data will be entered electronically and stored on a UTShare account and on UTHealth REDCap, both of which are private health information protected and require 2-factor authentication. As described above, each set of data will be entered twice with each duplicate data set compared by the primary investigator, and discrepancies addressed to ensure data validity.

Within the data collection forms in REDCap, calculators have been programmed to calculate the length of time on respiratory support as well as other outcome measures from entered date/time data entries to minimize human calculation error.

Statistical Methods

Outcomes

All analyses will be intent-to-treat. Differences in total length of respiratory support between treatment groups will be assessed with a regression model including treatment and risk group (stratifying variable) as covariates. Rates of secondary outcomes will be assessed using log-binomial or logistic models, and a total number of secondary outcomes will be assessed with negative binomial models.

Additional Analyses

In this small pilot study, some treatment effects that could be considered important by family members and clinicians (reduced hospital days) may not be statistically significant. As a result, Bayesian analyses will also be performed to estimate the probability of benefit. Neutral, weakly informative priors will be used for the treatment effect, e.g. for binary outcomes, the prior relative risk will be centered at 1.0 with 95% prior interval of 0.5-2.0. Depending on the results of the pilot, the need for a larger trial will be assessed.

Data Monitoring

Formal Committee

Not applicable - a data monitoring committee (DMC) is not needed as risks are expected to be minimal.

Interim Analysis

An interim analysis will be performed when 50% of patients have been randomized and will be performed by an independent statistician who is blinded to the treatment allocation. A standard normal deviate test will be calculated to determine if the rate of adverse events are significantly different between the two groups ($p< 0.05$).

Harms

Adverse events related to tube placement is recorded by nurse responsible for placing the tube. The route of feeding may be changed at the discretion of the primary physician if the particular tube placed is believed to be causing harm to the patient, such as worsening respiratory distress or aspiration pneumonia.

Auditing

Independent, periodic audits will not be performed. The investigators will perform self-assessments to ensure the data collected were for patients admitted for bronchiolitis and the other inclusion criteria. Data for each patient is collected by two separate investigators and then verified by the principal investigator to ensure good data quality. “RedCap” is able to compare two entries for irregularities.

Research Ethics Approval

The protocol and the template informed consent forms contained in Appendix were approved by UTHealth’s Committee For the Protection of Human Subjects (our institution’s IRB) with respect to scientific content and compliance with applicable research and human subjects regulations.

Protocol Amendments

Any modifications to the protocol which may impact the conduct of the study, the safety of the patient, or any changes to the objectives, design, population, sample sizes, procedures, or significant administrative aspects will have a formal amendment to the protocol and approved by the IRB prior to implementation.

Protocol Version available in Supplementary Materials Appendix 1

Patient and Public Involvement

Patients were not involved in the development of the research question, study design, or recruitment into the study.

Consent

Members of the study team, all who are familiar with the trial and study design, will obtain written consent from patients' caregivers. All consent and information sheets are available in English and Spanish. See Supplementary Materials Appendix 2.

Confidentiality

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in a secured office. Electronic data will be stored on the university cloud storage that requires two-factor authentication and private health information security.

Declaration of Interests

No conflicts of interest are declared for any of the study investigators.

Dissemination Policy

Every attempt will be made to reduce to an absolute minimum the interval between completion of data collection and release of study results through appropriate dissemination mediums including abstracts, poster presentations, and journal publications.

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Supplementary Material, Appendix 1 and 2

1. Trial Registration and Protocol Revision
2. Informed Consent Documents

Protocol Version
Issue Date: 3/21/2018
Protocol Amendment Number : 02
Authors: R.PC

Revision Chronology:

2017 - August 10	Original
2018 - January 29	Amendment 01.: Primary reason for amendment: optimization of randomization and allocation concealment
2018 - March 21	Amendment 02.: Change in primary outcome from the duration of HFNC to the duration of all respiratory support to capture the patients that had to be reinitiated to HFNC after discontinuation

University of Texas Health Science Center at Houston/Memorial Hermann Healthcare System
INFORMED CONSENT FORM TO TAKE PART IN RESEARCH
Comparison Between Gastric and Post Pyloric Feedings in Bronchiolitis Patients Requiring High Flow Nasal Cannula
HSC-MS-17-0725
Parental Consent

INVITATION TO TAKE PART

You are invited to allow your child to take part in a research project called, *Comparison Between Gastric and Post Pyloric Feedings in Bronchiolitis Patients Requiring High Flow Nasal Cannula*, conducted by Dr. Raymond Parlar-Chun of the University of Texas Health Science Center at Houston (UTHealth) and Memorial Hermann Healthcare System. For this research project, he will be called the Principal Investigator or PI.

Your decision to allow your child to take part is voluntary. You may refuse to allow your child to take part or choose to stop your child from taking part, at any time. A decision not to allow your child to take part or to stop being a part of the research project will not change the services available to your child from Dr. Parlar-Chun and research staff with the University of Texas Health Science Center at Houston (UTHealth) and Memorial Hermann Healthcare System .

You and your child may refuse to answer any questions asked or written on any forms. This research project has been reviewed by the Committee for the Protection of Human Subjects (CPHS) of the University of Texas Health Science Center at Houston as HSC-MS-17-0725.

PURPOSE

The purpose of this research study is to determine the best way to provide nutrition to infants admitted to the hospital with viral bronchiolitis. Bronchiolitis is the most common cause of hospitalization for infants < 1 year of age. High flow nasal cannula (HFNC) is being used to provide respiratory support. However, the optimal feeding strategy for patients on HFNC remains unclear. Some institutions allow these infants to feed orally by mouth. Others keep them on IV fluids for the duration of their time on HFNC. Others still institute some type of tube feedings, either nasogastric tube feeds or nasoduodenal tube feeds. Our goal is to study outcomes in patients who are fed with nasogastric (NG) tube feeds (a tube that goes from the nose into the stomach) vs. nasoduodenal (ND) tube feeds (a tube that goes from the nose, past the stomach, and into the small intestine) in patients admitted to the hospital for viral bronchiolitis who require treatment with HFNC.

Your child is being asked to participate in this study because they are being admitted to the hospital for management of viral bronchiolitis and may require high flow nasal cannula therapy. Our study runs for the duration of the current respiratory season (October 2017-April 2018).

This is a local study that will enroll approximately 230 patients.

PROCEDURES

If you agree and allow your child is able to take part in this study you will first sign the consent form before undergoing these study procedures:

Your child will qualify for inclusion in the study when 1.) They are admitted to the hospital for viral bronchiolitis, and 2.) they are started on respiratory treatment with HFNC. When both those criteria are met, he/she will be randomly assigned (similar to flipping a coin, 50% chance of either outcome) to one of two feeding strategies – NG tube vs. ND tube. Depending on which group your child is assigned to, that particular tube will be inserted for the purposes of feeding your child. The NG tube is inserted through the nose and ends in the stomach. The ND tube is inserted through the nose, goes past the stomach, and ends in the small intestine. The NG or ND tube will be inserted as soon as your child qualifies for the study. For example, if your child is admitted for bronchiolitis but originally is on room air, or on regular nasal cannula, they will only qualify for the study when and if their primary medical team decides that they require HFNC for treatment. If they stay on room air or regular nasal cannula, then they do not qualify for the study. If they are admitted to the inpatient unit with HFNC already started in the Emergency Department or at an outside facility, then we will place the NG or ND tube soon after they arrive at our inpatient unit. The placement of the tube will be confirmed by an abdominal x-ray prior to starting any feedings.

Your child will remain on NG or ND tube feeds for as long as they remain on HFNC. The decision about when to restart regular oral feedings will be made by your regular doctors. They will also determine how long your child requires HFNC, or whether they require even more breathing support such as CPAP or mechanical ventilation. If your child develops severe bronchiolitis and requires either CPAP or mechanical ventilation, they will be removed from the remainder of the study, and the decision about how/when to feed your child will be made by your primary medical doctors.

We will be collecting several measurements during the study. These include: child's age, child's gender, child's race, child's weight, number of days your child requires HFNC support, number of times they have vomiting, maximum respiratory support they require, number of xrays ordered during hospitalization, whether they received any antibiotics during the hospitalization, total number of days they are in the hospital, and whether they have to return to an emergency department or are rehospitalized 7 and/or 30 days after discharge from our facility.

If you choose to not participate in this study, and your child requires tube feedings for nutrition, they will receive a NDT, our current standard of care. Your decision to participate, or not to participate, will not affect your doctor's decisions about what is the best medical treatment for your child. He/she will still receive the appropriate level of respiratory support your child needs (room air, regular nasal cannula, HFNC, CPAP, or intubation), and feedings will be provided at the discretion of your primary doctors (IV fluids, regular oral feeds, NG tube feeds, or ND tube feeds).

TIME COMMITMENT

The total amount of time your child will take part in this research study is the total duration of time they remain on HFNC therapy. Most infants admitted for bronchiolitis who require HFNC therapy require it for approximately 1-5 days. The participation in the study will end when the child improves and is weaned oxygen via regular nasal cannula or room air, or if their bronchiolitis worsens and they require CPAP or intubation.

BENEFITS

Your child may receive no direct benefit from being in the study. However, bronchiolitis is the leading cause of hospitalization of children, and your child's participation in this study will help us understand the best way to feed the large number infants who are admitted for this disease every year.

RISKS AND/OR DISCOMFORTS

While on this study, your child is at risk for side effects. The study doctor will discuss these risks with you and your child. This study may include risks that are unknown at this time.

Inserting either an NG or ND tube can be uncomfortable for your child. They are inserted by nurses who are trained to minimize any discomfort your child may experience. The ND tube is slightly more challenging to place than an NG tube because it has to go further, but both tubes are placed every day and are common and relatively simple procedures. Once the tube is placed, your child should not feel any further discomfort, similar to after an IV is inserted. Prior to starting any feedings, the position of both tubes are verified by an abdominal xray to minimize any risk of feedings being delivered incorrectly. Your child may also continue to feel hungry while being fed via ND tube, as the sensation of hunger is satiated by being fed into the stomach, not past the stomach. However both forms of feeding are equally nutritious and will provide the same number of calories to help with your child's recovery and daily requirements.

There is a theoretical risk of reflux and aspiration while on NG tube feeds and HFNC simultaneously. Reflux is when food from the stomach moves up into the esophagus or mouth, similar to when a patient vomits. Aspiration is when food from the stomach enters the lungs. Several studies have looked at this question and determined that NG tube feeds are safe for patients with bronchiolitis, with or without HFNC. Additionally, many children's hospitals around the country only feed patients with bronchiolitis using NG tubes as their standard of care. However, no studies have directly compared patient outcomes in bronchiolitis patients fed using NG tube vs. ND tube feedings, which is what we are looking to do. If your child's primary doctor feels that your child is having worsening respiratory distress because of NG feeds, your child will be pulled from the remainder of the study and these feedings will be discontinued. Additionally, the study group will be meeting each week during the study to review the data we have collected. If we feel that the NG tube group is having more complications than the ND tube group, the study will be immediately discontinued.

As with all clinical studies, there is a possible risk of breach of confidentiality. All efforts will be made to minimize this risk. Your child's medical information will only be shared by certified members of the study team, in addition to the regular group of bedside caregivers (doctors, nurses, students, respiratory therapists, pharmacists, etc).

ALTERNATIVES

If you choose to not participate in this study, your child will still receive the same excellent care from all team members taking care of your child. Your decision to participate, or not to participate, will not affect your doctor's decisions about what is the best medical treatment for your child. We will still provide the appropriate level of respiratory support your child needs (room air, regular nasal cannula, HFNC, CPAP, or mechanical ventilation), and will provide feedings at the discretion of your primary doctors (IV fluids, regular oral feeds, NG tube feeds, or ND tube feeds). They will not be randomized to NG vs. ND feeds, but instead, will be given feeds according to the discretion of the primary doctors taking care of your child in discussion with your preferences. If the decision for tube feedings has been made, our current standard of care is placing NDTs.

STUDY WITHDRAWAL

Your decision to allow your child to take part is voluntary. You may decide to stop your child from taking part in the study at any time. A decision to decline to take part or to stop being a part of the research study will not change the services available to you and your child from Dr. Parlar-Chun and research staff, or any care providers at Children's Memorial Hermann Hospital.

Your child's doctor can stop the study at any time for any of the following reasons: if your child's doctors determine he/she requires CPAP or mechanical ventilation, or if your child's doctors feel he/she may be aspirating with NG feeds.

Should the study be stopped, we will still be able to use the data that your child provides, and the reason for withdrawal from the study will be noted in our results.

IN CASE OF INJURY

If your child suffers an injury as a result of taking part in this research study please understand that nothing has been arranged to provide free treatment of the injury or any other type of payment. However, necessary facilities, emergency treatment and professional services will be available to your child, just as they are to the general community. You should report any such injury to Dr. Parlar-Chun at 713-500-5586 and to the Committee for the Protection of Human Subjects at 713-500-7943. You will not give up any of your child's legal rights by signing this consent form.

COSTS, REIMBURSEMENT AND COMPENSATION

If you decide to allow your child to take part in this research study, you will not incur any additional costs. You and your child will not be paid for taking part in this study.

CONFIDENTIALITY

Please understand that representatives of the Food and Drug Administration (FDA), the University of Texas Health Science Center at Houston, and the sponsor of this research may review your child's research and/or medical records for the purposes of verifying research data, and will see personal identifiers. However, identifying information will not appear on records retained by the sponsor, with the exception of your child's date of birth, your child's initials, and treatment/service dates. Your child will not be personally identified in any reports or publications that may result from this study. There is a separate section in this consent form that you will be asked to sign which details the use and disclosure of your child's protected health information.

Clinical Trials.Gov Language:
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

NEW INFORMATION

While taking part in this study, the study team will notify you of new information that may become available and could affect your willingness to allow your child to stay in the study. They will notify you of this information in person during the hospitalization.

QUESTIONS

If you have questions at any time about this research study, please feel free to contact the Dr. Parlar-Chun at 713-500-5586, as they will be glad to answer your questions. You can contact the study team to discuss problems, voice concerns, obtain information, and offer input in addition to asking questions about the research.

AUTHORIZATION TO USE AND DISCLOSE
PROTECTED HEALTH INFORMATION FOR RESEARCH
UT HEALTH AND/OR MEMORIAL HERMANN HEALTHCARE SYSTEM

PATIENT NAME:_____ **DATE OF BIRTH:**_____

Protocol Number and Title: Comparison Between Gastric and Post Pyloric Feedings in Bronchiolitis Patients Requiring High Flow Nasal Cannula

Principal Investigator: *Dr. Raymond Parlar-Chun*
If you sign this document, you give permission to The University of Texas Health Science Center at Houston AND/OR Memorial Hermann Healthcare System to use or disclose (release) your child's health information that identifies your child for the research study named above.

The health information that we may use or disclose (release) for this research includes child's date of birth, child's age, child's weight, result of physical examinations of your child, your child's medical history, lab test results, and hospital course. ***Information disclosed or released is de-identified.***

The health information listed above may be used by and/or disclosed (released) to researchers and their staff. The researchers may disclose information to employees at The University of Texas Health Science Center at Houston AND/OR Memorial Hermann Healthcare System for the purposes of verifying research records. The researchers may also disclose information to the following entities:

- Food and Drug Administration

The University of Texas Health Science Center at Houston AND/OR Memorial Hermann Healthcare System is required by law to protect your child's health information. By signing this document, you authorize The University of Texas Health Science Center at Houston AND/OR Memorial Hermann Healthcare System to use and/or disclose (release) your child's health information for this research. Those persons who receive your child's health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

If all information that does or can identify your child is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes. No publication or public presentation about the research described above will reveal your child's identity without another authorization from you.

Please note that health information used and disclosed may include information relating to HIV infection; treatment for or history of drug or alcohol abuse; or mental or behavioral health or psychiatric care. In case of an adverse event related to or resulting from taking part in this study, you give permission to the researchers involved in this research to access test, treatment and outcome information related to the adverse event from the treating facility.

Please note that you do not have to sign this Authorization, but if you do not, your child may not participate in this research study. The University of Texas Health Science Center at Houston AND/OR Memorial Hermann Healthcare System may not withhold treatment or refuse treating you if you do not sign this Authorization.

You may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers may still use or disclose health information they already have obtained about your child as necessary to maintain the integrity or reliability of the current research. To revoke this Authorization, you must write to:

PI Name: Dr. Raymond Parlar-Chun
The University of Texas Health Science Center at Houston
Address:
6431 Fannin MSE R318
Houston, Texas 77030
PI Fax: 713-486-0838

Privacy Officer
Memorial Hermann Healthcare System
909 Frostwood
Houston, Texas 77024
Fax: 713-338-4542

This Authorization will expire 6 years after the end of the study.

SIGNATURES

Sign below only if you understand the information given to you about the research and you choose to allow your child to take part. Make sure that any questions have been answered and that you understand the study. If you have any questions or concerns about your child's rights as a research subject, call the Committee for the Protection of Human Subjects at (713) 500-7943. You may also call the Committee if you wish to discuss problems, concerns, and questions; obtain information about the research; and offer input about current or past participation in a research study. If you decide to allow your child to take part in this research study, a copy of this signed consent form will be given to you.

Printed Name of (Child) Subject			
Printed Name of Parent or Legally Authorized Representative	Signature of Parent or Legally Authorized Representative	Date	Time
Printed Name of Person Obtaining Informed Consent	Signature of Person Obtaining Informed Consent	Date	Time

CPHS STATEMENT: This study (HSC-MS-17-0725) has been reviewed by the Committee for the Protection of Human Subjects (CPHS) of the University of Texas Health Science Center at Houston. For any questions about research subject's rights, or to report a research-related injury, call the CPHS at (713) 500-7943.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	4
Funding	#4	Sources and types of financial, material, and other support	3
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,4,5
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	5

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	9

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	11
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	11
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	11
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Data access	#29	Statement of who will have access to the final trial dataset,	n/a

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	13
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a