PROTOCOL

A Pilot Trial of Nasogastric fluid Options in BROnchiolitis: The NOBRO study

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Statement of Compliance

This document is a protocol for a research project. This study will be conducted in compliance with all stipulations of this protocol, the conditions of the ethics committee approval, the NHMRC *National Statement on Ethical Conduct in Human Research (2007) – Updated 2018*, and the NHMRC and Universities Australia *Australian Code for the Responsible Conduct of Research (2018)*. If the project is a clinical trial, it will comply with the *Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95)*.

STUDY INVESTIGATORS

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Lead Principal Investigator:	Name: Dr Ravichandra Balakrishnamoorthy Institution: Gold Coast University Hospital Department: Paediatrics Address: 1 Hospital Boulevarde, Southport, QLD 4215 Tel: 0431663654 Email: rav4bkm@gmail.com; ravi.bala@health.qld.gov.au Role in Study: Lead Principal Investigator
Principal Investigator:	Name: Dr Tung Vu Institution: Gold Coast University Hospital Department: Paediatrics Address: 1 Hospital Boulevarde, Southport, QLD 4215 Tel: 1300 744284 Email: tung.vu@health.qld.gov.au Role in Study: Principal Investigator; Research Supervisor
Principal Investigator:	Name: A/Prof Shane George Institution: Gold Coast University Hospital Department: Emergency Medicine and Children's Critical Care Address: 1 Hospital Boulevarde, Southport, QLD 4215 Tel: 1300 744284 Email: shane.george@health.qld.gov.au Role in Study: Principal Investigator
PrincipalInvestigator	Name: Dr Kelly Weir Institution: Gold Coast University Hospital Department: Office for Research Governance and Development Address: 1 Hospital Boulevarde, Southport, QLD 4215 Tel: 1300 744284 Email: Kelly.weir@health.qld.gov.au Role in Study: Principal Investigator
Associate Investigator:	Name: Dr Ian Hughes Institution: Gold Coast University Hospital Department: Office for Research Governance and Development Address: 1 Hospital Boulevarde, Southport, QLD 4215 Tel: 1300 744284 Email: ian.hughes2@health.qld.gov.au Role in Study: Biostatistician
Associate Investigator:	Name: Nicole Ross Institution: Gold Coast University Hospital Department: Paediatrics

	Address: 1 Hospital Boulevarde, Southport, QLD 4215 Tel: 1300 744284 Email: Nicole.ross@health.qld.gov.au Role in Study: Associate Investigator
Associate Investigator:	Name: Dr Isabel Borthwick Institution: Gold Coast University Hospital Department: Paediatrics Address: 1 Hospital Boulevarde, Southport, QLD 4215 Tel: 1300 744284 Email: Isabel.borthwick@health.qld.gov.au Role in Study: Associate Investigator
Associate Investigator:	Name: Dr Nicola Bobeldyk Institution: Gold Coast University Hospital Department: Paediatrics Address: 1 Hospital Boulevarde, Southport, QLD 4215 Tel: 1300 744284 Email: Nicola.bobeldyk@health.qld.gov.au Role in Study: Associate Investigator
Mentor:	Name: Dr Caitlin Brandenburg Institution: Gold Coast University Hospital Department: Office for Research Governance and Development Address: 1 Hospital Boulevarde, Southport, QLD 4215 Tel: 1300 744284 Email: Caitlin.brandenburg@health.qld.gov.au Role in Study: Associate Investigator, mentor

STUDY SYNOPSIS

Title:	**A Pilot Trial of Nasogastric fluid Options in BROnchiolitis: The NOBRO study**
Short Title:	The NOBRO Pilot study
Study Sites:	Gold Coast University Hospital
Study Aims/Objectives/Hypothesis:	For infants with bronchiolitis who cannot tolerate oral feeds, their nutrition can be supplemented with nasogastric fluids of either milk or oral rehydration solution. There are two main regimes for nasogastric fluids; intermittent bolus fluids or continuous fluids. The NOBRO study looks to investigate in infants less than 12 months of age with bronchiolitis that require nasogastric fluid therapy, which nasogastric fluid regime (continuous fluids or intermittent bolus fluids) leads to a quicker return to normal oral feeding We hypothesise that intermittent bolus fluids lead to a quicker return to normal oral feeding compared with continuous fluids Before proceeding with this larger trial, we will first conduct a pilot trial.
Study Design:	Pilot feasibility study for a subsequent randomised control trial

Study Outcome Measures:	The primary outcome for our eventual larger scale randomised control trial will be the time taken for the patient to return to adequate oral feeding after the introduction of nasogastric fluids.
	Secondary outcomes for our larger scale trial include:
	• The tolerability of nasogastric fluids
	• Length of hospital stay
	• The number of infants requiring re-instatement of nasogastric fluids after nasogastric fluids are initially ceased
	• Adverse events, including:
	  ○ Persistent vomiting
	  ○ Pulmonary aspiration events
	  ○ Worsening of respiratory status secondary to nasogastric fluids

	The outcomes we will be measuring in this pilot feasibility trial include: • As part of this pilot trial we aim to recruit more than 80% of eligible patients, determine the appropriateness and variance of our primary outcome and to further help us determine the sample size needed for our subsequent randomised control trial • Estimation of our recruitment rate • Retention rates for those in the intervention groups • Determine the incidence of adverse events • Auditing the completeness of data reporting
Study Population:	Infants less than 1 year old
Number of participants:	30
Translation to Clinical Practice:	This study will help us determine the practicality of us proceeding with a subsequent, larger randomised control trial. This study will also hopefully provide preliminary data regarding which nasogastric fluid regime • Leads to a quicker return to normal oral feeding • Leads to better tolerance of nasogastric fluids • Leads to a shorter length of inpatient stay • Leads to a lesser incidence of re-instatement of nasogastric fluids after nasogastric fluids are initially ceased
Key Ethical and Safety Considerations:	This study will be conducted in accordance with the protocol, ICH GCP guidelines, and the ethical principles that have their origin in the Declaration of Helsinki. Patients will be closely monitored for adverse events secondary to nasogastric fluids. Patient deemed to have a severe adverse event thought to be related to nasogastric fluids will have this temporarily discontinued. Appropriate medical therapy will be initiated as per the patient treating team. Nasogastric fluids may be restarted once patient is medically stable.

Glossary of Abbreviations, Terms, and Acronyms

Abbreviation, Term, Acronym	Definition (using lay language)

1. Background

Bronchiolitis is defined as symptoms and signs of respiratory distress (tachypnoea, recessions, nasal flaring, or cyanosis) associated with symptoms of a viral respiratory tract infection[1]. It generally affects children less than 12 months of age and is the leading cause of hospital admission during the first year of life.[2,3,4].

Due to an increase in respiratory effort and work of breathing, patients with bronchiolitis can develop dehydration as a result of inadequate oral intake, fatigue with feeding and evaporative fluid losses from the lungs[5,6]. Decreased nutritional intake early in the hospital course has been associated with a longer length of stay in infants with bronchiolitis[7].

The goals of therapy in bronchiolitis are to maintain tissue oxygenation, detect respiratory failure, and provide adequate hydration. Previous studies suggest approximately a third of patients hospitalised for bronchiolitis require fluid replacement[8,9].

Depending of the degree of disease severity, fluid replacement in patients with bronchiolitis who cannot maintain hydration orally can be accomplished by enteral or parenteral routes[10]. Nasogastric fluids are a form of enteral hydration that is commonly used in infants with bronchiolitis and forms part of our hospitals' bronchiolitis guideline, as well as international guidelines [10,11,12].

The efficacy and use of nasogastric fluids in patients with bronchiolitis has previously been assessed in several studies.

- A survey of Australasian Paediatric Emergency Physicians by Oakley et al demonstrated that 48% of Emergency Physicians had used nasogastric fluids for patients with bronchiolitis[17]. Oakley et al extended their work to perform a retrospective cohort for patients less than 2 months of age with bronchiolitis amongst 3 paediatric centres over 3 bronchiolitis seasons[19]. Of those that required feeding support, almost 70% went on to have nasogastric fluids and on average spent 15 hours less in hospital than those that required intravenous fluids. A follow-up multi-centre randomized control trial was performed with patients between 2-12 months with bronchiolitis over a 2.5 year period and demonstrated a non-clinically important difference of 4.5 hours in length of stay between infants receiving nasogastric or intravenous fluids[19].
- Kugelman et al performed a randomized pilot study in Israel with patients receiving either nasogastric fluids (of breastmilk of formula) or intravenous fluids[13] and found that there was a non-statistically significant improvement in length of stay of approximately 21 hours for those receiving nasogastric fluids compared with those receiving intravenous fluids[13].
- A study by Brand & Vaessen-Verbene in the Netherlands showed that 96% of paediatricians surveyed had used nasogastric fluids in their practice of treating patients with bronchiolitis[15].
- A case series by Vogel et al in New Zealand studied 409 infants admitted to hospital with bronchiolitis, of which 21% received nasogastric fluids[16].
- A quality improvement study by Srinivasan et al demonstrated that 58% of patients admitted to hospital with bronchiolitis over a 4-month period received nasogastric hydration[18].

The safety of nasogastric fluids has been assessed in several studies

- The retrospective cohort study by Oakley et al reported an adverse event rate of 27.4% in those that received nasogastric fluids, with 21.9% of these being desaturations, 5.5% being apnoeas (with one patient requiring caffeine), 2.7% being bradycardias (with two patients

requiring inotropic support) and no aspiration events recorded[19]. 12.3% of patients receiving nasogastric fluids went on to require intravenous fluids. 19.9% of patients receiving nasogastric fluids required intensive care unit admission[19]. The subsequent randomised control trial by Oakley et al. demonstrated a 2% incidence of bradycardia and a 1% incidence of apnoeas, in patients receiving nasogastric fluids[3]. There were no episodes of epistaxis or aspiration in any of the infants studied during their time in hospital[3]. 13% of infants receiving nasogastric fluids went on to require intravenous fluids and 8.5% of patients receiving nasogastric fluids required intensive care unit admission. The difficulty with the adverse events reported in this study is that it is unclear whether the adverse events reported were directly related to the nasogastric fluids used or related to the natural history of the patient's bronchiolitis.

- The study by Kugelman et al did not demonstrate any cases of aspiration in those receiving nasogastric fluids and did not demonstrate any worsening of patients' respiratory status[13].
- A case study by Unger & Cunningham did not report any complications related to nasogastric feeding[14].
- The quality improvement study by Srinivasan et al. reported no aspiration events in patients receiving nasogastric fluids[18].
- A pilot study by Sammartino et al. (2002) described 37 patients during a seasonal epidemic of bronchiolitis that required hydration support[5]. The majority of patients tolerated nasogastric fluids well, with only 2 patients deteriorating (subsequently requiring intravenous fluids), thought to be secondary to the natural history of the illness[5].

Differing regimes for nasogastric fluids have been utilised in previous studies.

- The quality improvement study by Srinivasan et al aimed to hydrate patients with formula or breast milk via the nasogastric tube but found that the majority of patients were given Pedialyte (60%) compared with breast milk or formula (40%).
- The pilot study by Sammartino et al. (2002) describes using either gastrolyte or milk for patients receiving nasogastric fluids[5].
- Patients receiving nasogastric fluids in the randomized control trial by Oakley et al. received continuous oral electrolyte solution for the first 2 hours of therapy, followed by 1-2 hourly boluses of expressed breast milk or formula[3].
- It is difficult to determine the incidence in previous studies of patients receiving oral feeds whilst simultaneously receiving nasogastric fluids. The study by Kugelman et al. has openly disclosed that patients were allowed comfort, non-nutritive sucking for infants whilst receiving nasogastric fluid therapy[13].
- Both Local and international bronchiolitis guidelines suggest the use of either formula or expressed breast milk delivered either continuously or via intermittent boluses every 2nd to 3rd hour[6,19].
- Local guidelines suggest that the ideal volume of nasogastric fluids to maintain hydration should be 60 to 100% of maintenance fluid to prevent complications secondary to the syndrome of inappropriate ADH secretion (SIADH)[12]. This is similar to guidelines reported in other states[4] as well as used in previous studies[17, 20].

Although clinical practice guidelines and pre-existing evidence support the use of nasogastric fluids for patients with bronchiolitis, there is no consensus as to which nasogastric fluid regime should be prescribed for patients with bronchiolitis.

Both clinically, and as seen in previous studies, there are two main regimes for nasogastric fluids; intermittent bolus fluids or continuous fluids.

- Intermittent bolus fluids refers to when a patient has the same volume delivered through the nasogastric tube over a 1 hour period that they would typically have in a normal oral feed.
- Continuous fluids refers to when a patient has the same bolus fluid amount delivered through the nasogastric tube, however given at a slow continuous rate.

However, there is no consensus as to which nasogastric fluid regime should be prescribed for patients with bronchiolitis.

Anecdotally, there exists clinical equipoise, and the decision of which nasogastric fluid regime to use for patients with bronchiolitis is usually clinician dependant.

A local bronchiolitis guideline suggests that gastric distension from bolus feeds can result in worsening of respiratory symptoms, thereby suggesting the use of continuous nasogastric fluids in severe bronchiolitis. However, there is no evidence of previous studies supporting or refuting this practice within this guideline[6].

Conversely, some clinicians hypothesise that delivering nasogastric fluids via intermittent boluses is more physiologically similar to an infant's normal pre-morbid oral feeding practices and could thus improve an infants' readiness to tolerate normal oral feeding during their course of bronchiolitis..

We look to investigate in infants less than 12 months of age with bronchiolitis that require nasogastric fluid therapy, which nasogastric fluid regime (continuous fluids or intermittent bolus fluids) leads to the patient having a quicker return to normal oral feeding, as well as a range of other secondary outcome measures.

We plan to conduct a randomised controlled trial (RCT) to help inform our hypothesis. Prior to this however, we will conduct a pilot RCT, in order to test and refine the study procedures prior to beginning the main trial and to identify what might be considered a clinically important difference in our primary outcome measure and its standard deviation. This will enable reliable power calculations for the proposed RCT. The primary outcome measure is a specifically defined measure of time taken for the patient to return to adequate oral feeding. As this is not a routine or well published measure, our pilot will enable a greater understanding of it and enable assessment of its appropriateness prior to the RCT. Other feasibility related factors will also be addressed such as recruitment and retention rates, possible problems in the randomisation process, and adherence to the randomised protocol.

Trials of a similar nature to this study were not found in The Australian New Zealand Clinical Trials Registry (ANZCTR) or in the US National Library of Medicine Clinical Trials Catalogue.

2. Study Objectives

a. Research Question and Aims/objectives

Population

- Patients less than 1 year (ie. Up to 364 days) old with a clinical diagnosis of bronchiolitis that have been assessed as requiring nasogastric fluids due to poor feeding and/or dehydration

Interventions

- The use of intermittent bolus nasogastric fluids (of either breast milk, formula or oral rehydration solution) every 3 hours

Comparator

- The use of continuous nasogastric fluids (breast milk, formula or oral rehydration solution)

Outcome

- The primary outcome for the main randomized control trial will be the time taken for the patient to return to adequate oral feeding after the introduction of nasogastric fluids (see section-i for further definition of this).

- As this is a pilot trial, we aim to assess a range of outcomes to determine the practicality of progressing with a subsequent larger randomized control trial
    - As part of this pilot trial we aim to recruit more than 80% of eligible patients, determine the appropriateness and variance of our primary outcome and to further help us determine the sample size needed for our subsequent randomised control trial
    - Estimation of our recruitment rate
    - Retention rates for those in the intervention groups
    - Determine the incidence of adverse events
    - Auditing the completeness of data reporting
    - The primary investigator will collect field notes and reflections on the study process, including aspects such as
        - Identifying the willingness of clinicians to recruit patients
        - Estimation of cost and resources
        - Identification of any major issues with the study process

The primary outcome for the main randomised control trial will be the time taken for the patient to return to adequate oral feeding after the introduction of nasogastric fluids (see section-i for further definition of this).

Time

- Over a 2-month period

b. Hypothesis

As this is a pilot trial, we aim to recruit more than 80% of eligible patients, determine the appropriateness and variance of our primary outcome and to further help us determine the sample size needed for our subsequent randomised control trial.

3. Methods

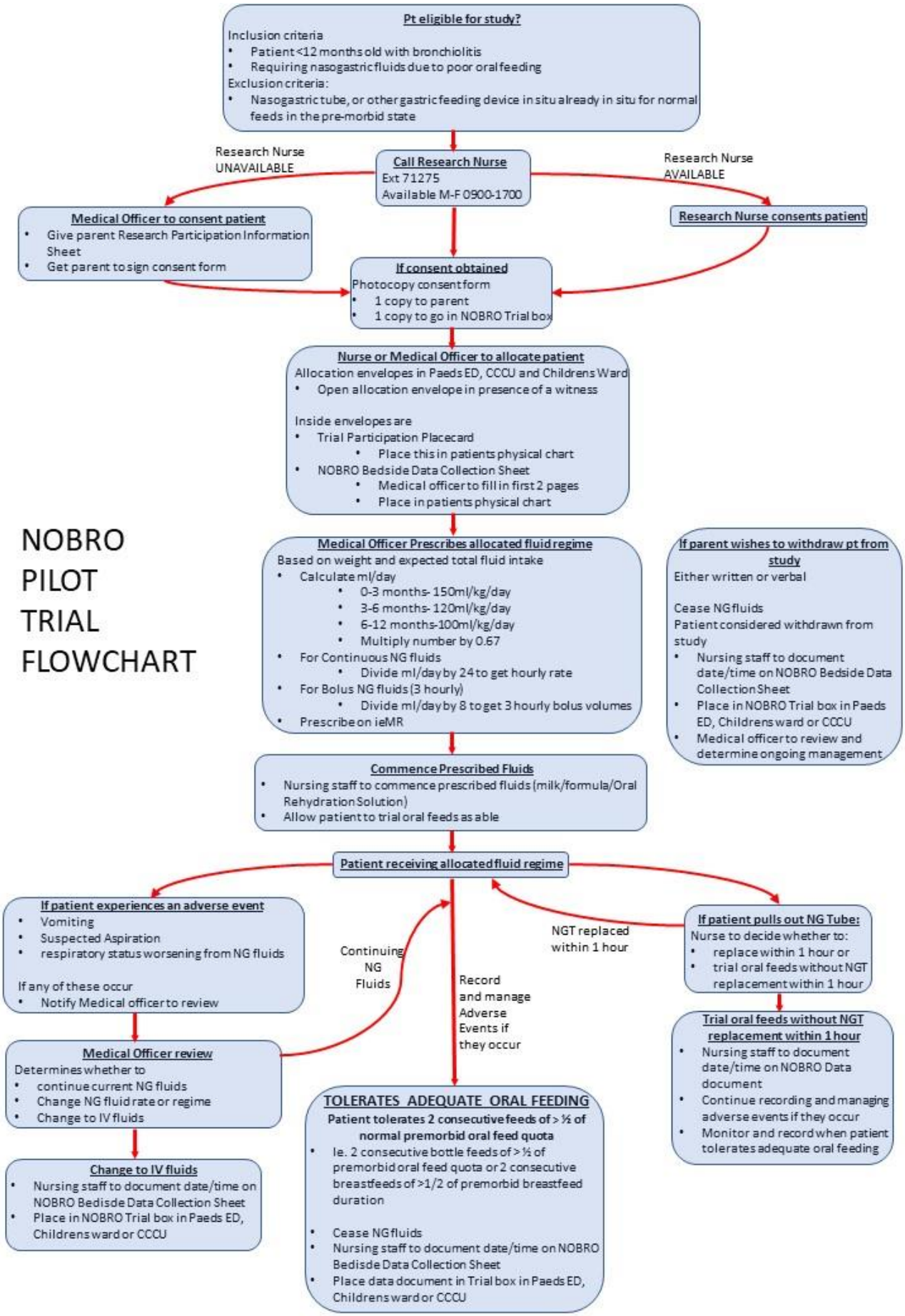
a. Methodological Approach

The NOBRO study will be conducted as an unblinded Randomised Control trial. This study design has been chosen as it will allow us to directly compare the two nasogastric fluid regimes whilst minimising the risk of confounding factors that may influence the study results.

We have chosen to perform this pilot trial in the first instance in order to inform the subsequent, larger study.

The trial flowchart that will be replicated within our pilot trial is detailed below

NOBRO PILOT TRIAL FLOWCHART



b. Study Sites/Settings

The NOBRO study will be a single-centre study performed at the Gold Coast University Hospital (GCUH) Southport Campus.

Bronchiolitis is a commonly serviced medical condition at the Gold Coast University Hospital within the Paediatric Emergency Department, Children's Inpatient Unit and Children's Critical Care Unit. In 2018, the Gold Coast University Hospital Southport Campus had 433 presentations with bronchiolitis.

For this reason, the Gold Coast University Hospital poses an ideal environment in which to recruit and manage patients with bronchiolitis that are involved with the NOBRO study.

c. Study Population

The NOBRO study will involve patients under the age of 12 months with a clinical diagnosis of bronchiolitis, who have also been deemed by their treating clinician as requiring nasogastric fluid therapy.

Patients in the study must satisfy the following inclusion and exclusion criteria

- Inclusion criteria
    - Patient under 12 months (and 0 days) chronological age
    - Patient diagnosed with bronchiolitis (regardless of the severity) as their primary diagnosis for hospital admission
    - Patient deemed by their treating clinician to require nasogastric fluids due to poor oral feeding
- Exclusion criteria:
    - Nasogastric tube, or other gastric feeding device in situ or required for a reason other than due to poor oral feeding
    - Patients requiring greater than 2L/kg of Nasal High Flow at the time of initiating nasogastric fluids
    - Patients that are receiving non invasive mask ventilation (such as CPAP or BIPAP) at the time of initiating nasogastric fluids
    - Patients that are intubated and requiring mechanical ventilation at the time of initiating nasogastric fluids
    - Patients that have a high clinical suspicion of the need for escalated respiratory support (ie. Above 2L/kg of Nasal High Flow oxygen) within the next 24 hours
    - Patients that have been transferred to GCUH from a peripheral hospital, or if there is a clear plan at the time of presentation for the patient to be back-transfered to a peripheral hospital

d. Recruitment/ Selection

<u>Sampling</u>

Parents/guardians of infants that meet inclusion/exclusion criteria will be consented to participate in the study. Participants will be sampled consecutively.

The location where patients will be identified and consented is likely to be the hospitals' emergency department, however the need for nasogastric fluids may arise at any point throughout the patients' time in hospital (in the Paediatric Emergency Department, on the Children's Inpatient Unit or the Paediatric Critical Care Unit).

Randomisation

If consent is received, the patient will then be randomised to receive their nasogastric fluids at either a continuous rate or via intermittent boluses.

A block randomization strategy will be employed using the ralloc command of the statistical software Stata 15. Randomizations will be provided in consecutively numbered opaque sealed envelopes.

Blinding and allocation concealment

Due to the nature of the interventions assigned to each group, blinding of participants and the research assistant is not feasible. However, once outcome data is collected and recorded by the research assistant, the final data set will be further coded in such a way as to deidentify which nasogastric fluid regime patients were assigned to, further ensuring that the statistician analysing the results is blinded to the patients allocation .

e. Consent

Due to the age of patients in the trial, consent will need to be obtained from the patients' parent/s or guardian.

A dedicated research assistant will be responsible for providing the study consent and information form to eligible patients, as well as obtaining consent to minimise any conflicts of interest. However, in cases where the decision to initiate nasogastric fluids occurs when the research assistant is not available (such as after-hours), this role will be performed by the patient's treating clinician or nurse.

We will mitigate the risk of coercion by providing clinical staff with training around consenting procedures for the trial, ensuring that parents and guardians will be made aware that participation in this study is completely voluntary and that refusal to participate or withdrawal from the study will not affect their child's clinical care in any way.

The information sheet provided to parents/guardians will encompass a simplified lay version of the current evidence regarding nasogastric fluid therapy in bronchiolitis, the purpose of the NOBRO study and its' methodology. The information leaflet will specify our hospitals practice regarding the use of nasogastric fluids in patients with bronchiolitis, and that all patients within the study will be managed in line with best practice as noted by the PREDICT Australasian Bronchiolitis Guideline[12]. The information sheet will also contain important information regarding patient confidentiality and disclosure of information. The information sheet will also include contact details of the investigating team and the hospitals Ethics association.

We will be gaining consent in accordance with the National Statement[24]: 4.2.7 Except in the circumstances described in paragraphs 4.2.10 and 4.2.11, specific consent to a child's or young person's participation in each research project should be obtained from: (a) the child or young person whenever he or she has the capacity to make this decision; and (b) either (i) one parent, except when, in the opinion of the review body, the risks involved in a child's participation require the consent of both parents; or where applicable (ii) the guardian or other primary care giver, or any organisation or person required by law.

In situations where parents disagree about enrolling their child in the study, the research team will have a detailed discussion with both parents to answer their questions freely and appropriately. It is likely that in these cases where parents disagree, we would suggest that they not enrol in the study

In situations where parents are separated and have joint custody of the infant, we will always encourage the parent to discuss with the other parent before signing the consent form. However, we would feel that if one parent is informed and wishes to proceed that this would be considered adequate.

Children who are under the care of child safety who have all medical decisions made by the state director general (where the biological parent/s do not have medical decision-making capability) will not be consented to participate in the study.

We posit that the risks of this study are relatively low, as both arms are established clinical practices, to consent one parent, if only one is present, or a guardian or primary caregiver, or any other organisation or person required by law in the case of an infant in state care.

f. Risk Mitigation Procedures

Adverse events that may be associated with Nasogastric fluid therapy include the following, which have been defined by the U.S Department of Health and Human Services Common Terminology Criteria for Adverse Events (CTCAE)[22].

- Vomiting
    - Defined as the ejection of stomach contents through the mouth[22].
    - Episodes of vomiting will be graded as per the CTCAE[22].
        - Grade 1: 1-2 episodes (separated by 5 minutes) in 24 hours
        - Grade 2: 3-5 episodes (separated by 5 minutes) in 24 hours
        - Grade 3: >= 6 episodes (separated by 5 minutes) in 24 hours
        - Grade 4: Life threatening consequences
        - Grade 5: Death
    - Episodes of vomiting will be detected and documented by nursing staff looking after the patient in their medical chart as part of the patient's Fluid Balance. This is no different to the standard of care which is already instituted across our hospital for patients with bronchiolitis.
    - If vomiting occurs, the patients treating nurse will cease the patients' nasogastric fluids and generate a medical officer review. Once a medical review has occurred, a clinical decision will be made as to whether nasogastric fluids should be re-started, whether an alternative form of hydration should be trialed (such as oral or intravenous fluids),

or any other medical care that should be undertaken. The management applied will be recorded in the patients' medical chart and will be reported as part of the trial.

- Pulmonary aspiration of nasogastric fluids
    - Defined as inhalation of liquids into the lung[22].
    - Episodes of aspiration will be graded as per the CTCAE[22].
        - Grade 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated
        - Grade 2: Altered eating habits; coughing or choking episodes after eating or swallowing; medical intervention indicated (e.g., suction or oxygen)
        - Grade 3: Dyspnea and pneumonia symptoms (e.g., aspiration pneumonia); hospitalization indicated; unable to aliment orally
        - Grade 4: Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated
        - Grade 5: Death
    - Episodes of aspiration will be detected and documented by nursing staff looking after the patient in their medical chart. This is no different to the standard of care which is already instituted across our hospital for patients with bronchiolitis.
    - If a pulmonary aspiration event occurs, the patients treating nurse will cease the patients' nasogastric fluids and generate a medical officer review. Once a medical review has occurred, a clinical decision will be made as to whether nasogastric fluids should be re-started, whether an alternative form of hydration should be trialed (such as oral or intravenous fluids), or any other medical care that should be undertaken. The management applied will be recorded in the patients' medical chart and will be reported as part of the trial.
- If the patient has a worsening of their respiratory status believed to be secondary to their nasogastric fluid regime
    - We have defined this adverse event as when a patient experiences a sudden increase in any of the following that occurs persistently during, or within an hour after the patients nasogastric fluid regime has commenced
        - Heart rate >20 above baseline
        - Respiratory Rate > 10 above baseline
        - Work of breathing
        - Oxygen requirement

Both nasogastric fluid regimes are essentially treatment as usual, so we expect that the study as a whole poses no foreseeable additional risk to patients. We will still perform safety analysis on the pilot data collected.

We do not anticipate any significant difference in safety between the interventions. If we do detect a significant difference in safety, we will have procedures in place to address this for the subsequent larger study.

There is no evidence in the literature to suggest that patients receiving nasogastric fluids are at risk of a serious adverse event (SAE), such as

- death during the study period
- electrolyte disturbance causing seizure
- Any other event not mentioned above that is life threatening or jeopardises the patient or requires medical or surgical intervention

We will endeavour to manage any serious adverse events with the following practice:

- SAEs need to be reported within 24 hours by telephone to the local site investigator.
- The local investigator must report the SAE to their local ethics committee within 48 hours (or in accordance with local ethics committee regulations).
- The local investigator must also report SAEs to the principal investigators who will report the event to the Data Monitoring Committee chairman.
- The principal investigator will also report the SAE to all Ethics Committees and other regulatory bodies involved in the trial as per regional regulatory requirements.
- SAEs will also be reported to the consultant of the child's treating team. The medical consultant will initiate appropriate management and inform the family if the family is not already aware of the event. This reporting is the responsibility of the site investigator

g. Participant Withdrawal Procedures

Parents/guardians of any patient enrolled in the trial are able to withdraw their consent at any point after it is initially obtained either verbally or through written means. At the point of withdrawal of consent, the treating clinician will determine the course of ongoing therapy for the patient in discussion with the patients' parent/guardian as per normal practice.

If a patient is withdrawn from the study after consent has been obtained, but before randomisation occurs, baseline demographic data and outcome data will not be collected or reported on for that participant. In cases where baseline demographic data has already been collected, this information will be deleted from any health records and destroyed.

If a patient is withdrawn from the study after randomisation, no new information will be collected from the time of withdrawal but any information that was collected prior to withdraw will still be used and kept for the purpose of this study.

Parent/guardians of patients that initially decline consent to the study will be excluded from the study and will not be able to enter the study at a later point in the patient's clinical course

h. Study Procedure

Randomisation

Treating clinicians, nurses and our research assistant will identify if a patient in the Emergency Department, Childrens Inpatient Unit or Childrens Critical Care Unit with bronchiolitis that require nasogastric fluid therapy, due to poor oral feeding or concerns of dehydration.

These patients' parents or guardian will be given an information leaflet regarding the NOBRO trial, as well as a consent form to participate in the trial.

If the parent/guardian consents to the patient being enrolled in the study, the patient will undergo randomisation.

Randomisation will be performed by the patients treating nurse and witnessed by another nursing or medical staff member to minimise any randomisation bias. All nursing staff looking after patients with bronchiolitis will undergo training in how to perform the randomisation and collect outcome data.

A block randomization strategy will be employed using the ralloc command of the statistical software Stata 15. Randomizations will be provided in consecutively numbered opaque sealed envelopes.

We will employ a research assistant to assist in identifying, recruiting and randomising eligible patients, as well as helping with providing education about the NOBRO study to medical and nursing staff working in the emergency department, inpatient paediatric ward and paediatric critical care unit.

Allocation

After the patient has been randomised to receive either continuous or intermittent bolus nasogastric fluids, the treating nurse will inform the treating medical doctor to prescribe the appropriate fluid type (oral rehydration solution, breast milk or formula) and rate (based on their randomisation group, weight and expected total fluid quota[1]).

Patients assigned to the Intermittent bolus nasogastric fluid group will receive their fluid 3 hourly intervals based on their age and weight over 1 hour via a pump.

The fluid quota that is prescribed to each patient will be as per our local bronchiolitis guideline[6].

- Patients aged 0-3 months will receive nasogastric fluids at a rate of 150ml/kg/day
- Patients aged 3-6 months will receive nasogastric fluids at a rate of 120ml/kg/day
- Patients aged 6-12 months will receive nasogastric fluids at a rate of 100ml/kg/day
- Due to the risk of fluid overload and the Syndrome of Inappropriate Anti-Diuretic Hormone (SIADH) in patients with bronchiolitis, patients will be prescribed nasogastric fluids at 2/3 (67%) of the fluid quotas stated above. This is as per recommended practice by the Australasian Bronchiolitis Guideline.[3]

The treating nurse will then initiate the prescribed fluid regime.

Patients in the study will have their nasogastric fluids ceased when they have achieved adequate oral feeding, or if determined by the treating clinician if an adverse event related to the nasogastric fluid regime occurs.

In our study, Adequate oral feeding has been defined by as when the patient tolerates two consecutive feeds of > 50% of their normal pre-morbid oral feed quotas.

- For patients that are normally formula-fed, we will be able to quantify when the patient has >50% of their normal pre-morbid oral feed quotas
- For patients that are normally breast-fed, we will assume that the patient has achieved adequate oral feeding when they have achieved two consecutive breastfeeds, each of which has lasted for >50% of their normal pre-morbid breastfeed duration.

There may be occasions where there is a clinical need to deviate from this protocol. For example;

- A patient experiences an adverse event and the medical officer deems it necessary to either change or cease the patients nasogastric fluid regime; or

If the patient pulls out their nasogastric tube and the treating doctor or nurse makes a clinical decision not to replace the nasogastric tube. In this circumstance, details of the events leading to the change in feeding will be recorded on the bedside data collection form. If the patient continues of nasogastric feeds, data collection will continue on the alternate feeding regimen to assess for ongoing feed intolerance. Where NG feeds are ceased, the time that two consecutive adequate oral feeds will also be collected.

Data Collection

A research assistant will be responsible for collecting relevant demographic and outcome data.

The demographic data we will collect on patients in the study includes:

- Age (in months)
- If the patient was born prematurely (<37 weeks gestation)
- Sex
- Weight at admission and discharge
- Oral feeding practices pre-hospital admission (breast fed, formula fed, or both) including typical duration of normal feeds pre-hospital admission
- Severity of bronchiolitis as defined by the patients Modified Tal Score[25]
- Any pre-existing risk factors that could indicate more severe bronchiolitis[6]
    - History of significant preterm delivery (<32 weeks gestation)
    - Chronological age < 6 weeks
    - Congenital cardiac disease
    - Neurological or neuromuscular disorder
    - Immunodeficiency
    - Trisomy 21
    - Chronic respiratory illness including Chronic Neonatal Lung Disease (CNLD) or Cystic Fibrosis (CF)
- Duration of illness (in days) before hospital admission
- Respiratory support during admission (type and duration).
- If the patient had an additional diagnosis eg. pneumonia

The research assistant will have access to (and have had training on how to use) NOBRO study Bedside Data Collection Form to record demographic and outcome measures on. The Bedside Data Collection Form will remain de-identified and only coded information will be transcribed on to the Bedside Data Collection Form.

If the patient is transferred to another hospital during their inpatient stay, outcome data will be reported for the patient up until they have been transferred out of the hospital. Any further outcome data will not be reported on for that patient in the study's results, though we will attempt to access information regarding the patients' outcome at their next hospital.

i. Outcome Measures

Outcome measures for pilot trial

As this is a pilot trial, we aim to assess a range of outcomes to determine the feasibility of progressing with a subsequent larger randomized control trial

- As part of this pilot trial we aim to recruit more than 80% of eligible patients, determine the appropriateness and variance of our primary outcome and to further help us determine the sample size needed for our subsequent randomised control trial
- Estimation of our recruitment rate
- Retention rates for those in the intervention groups
- Determine the incidence of adverse events
- Auditing the completeness of data reporting
- The primary investigator will collect field notes and reflections on the study process, including aspects such as
    - Identifying the willingness of clinicians to recruit patients
    - Estimation of cost and resources
    - Identification of any major issues with the study process

As part of this pilot we are also collecting data for all the intended outcomes for the larger trial to fully test the study procedures and data collection but will not use them for formal analyses. These other outcomes include:

- Time taken for the patient to return to adequate oral feeding after the introduction of nasogastric fluids. This is the primary outcome for our subsequent larger trial.
- Length of stay (in hours).
- The incidence of adverse events that may be attributed to nasogastric fluid therapy, including
    - Vomiting
    - Pulmonary aspiration of nasogastric fluids
    - Worsening of the patients respiratory status
- The number of infants requiring re-instatement of nasogastric fluids after nasogastric fluids are initially ceased
- The number of infants requiring a change from Nasogastric to intravenous fluid hydration
- The duration of supplemental oxygen requirement
- The need for admission to an Intensive Care Unit

j. Data Collection

A research assistant will be responsible for collecting relevant demographic and outcome data. Re-identifiable, coded patient information data will initially be recorded by the research assistant onto NOBRO study source document. The research assistant will then input this data into an Excel Spreadsheet. This spreadsheet will be password-protected and be located on a dedicated computer that only the research assistant has access to.

Following merging, identifiable data shall be made non-identifiable. The NOBRO study source documents will also be stored in a locked drawer in the research assistant's office.

k. Data Storage and Confidentiality

The baseline demographic, primary and secondary outcome data that we are collecting as part of the NOBRO study is already routinely collected on patients within the hospital as part of the course of routine clinical care for patients with bronchiolitis.

Information collected about participants for the study will be used in order to report on outcomes. The data collected will be recorded on paper (as part of the NOBRO study source document) and will remain confidentially within the child's physical patient file. This information in these source documents will be in the form of grouped data, with no identifying information. Data for all patients entering the study will be deidentified and will thus exist as re-identifiable (coded) information. The baseline characteristics and subsequent outcome data measures of infants in each group will not reveal any personal details that threaten the identity or safety of any of the patients

Confidentiality will be maintained by having as few people as possible being able to access the data, prior to merging. Following merging, identifiable data shall be made de-identifiable. In the dissemination of results, only grouped data will be reported. If publicised only de-identified cases will be reported.

Measures to prevent misuse and loss involve storing data on a password protected computer file on the principal researcher's computers and on a transportable flash drive (for back up and future data storage purposes) that will remain in a locked filing cabinet, in the principal researcher's office when not in use. The transportable flash drive shall only be utilised when identifiers have been removed. The primary and secondary database managers shall manage the security of this device.

The results of the research will be disseminated in the following manner:

- In a report to the districts' Human Research Ethics committee
- At > or = 1 health conference
- Submitted to a peer-review journal for publication
- Participants in the study will be provided with a website link in which a simplified version of the study's results can be viewed.
- To fulfil a Royal Australasian College of Physicians training requirement of the primary investigator (Dr Ravichandra Balakrishnamoorthy)

Following the implementation of the study, the information gathered will be used to provide baseline data to substantiate further expansion and integration of the study to other wards and specialist services who care for patients with bronchiolitis requiring nasogastric fluids.

Information collected from the study will be disposed of 5 years after the youngest patients' 18th Birthday. Any electronic records relating to study data will be deleted and paper records will be placed into appropriately labelled shredding bins

I. Data Analysis and Statistical Considerations

No formal hypothesis testing will be completed, as this is a pilot study. Descriptive statistics will be used to measure the various outcomes of the trial- e.g. data completeness, % eligible patients approached, % eligible patients approached who then consented, total number of eligible patients per week. Data analysis will be done using Microsoft Excel in consultation with the biostatistician.

Data analysis in this pilot study will primarily be related to determining an appropriate sample size and analysis methods for the subsequent RCT. Data will be collected over a 2 month period during which we anticipate to recruit 30 participants based on the current bronchiolitis presentation rate.

The primary outcome measure will be time to adequate oral feeding (TAOF) as detailed above. Descriptive and graphical statistics will be used to ascertain the nature of the frequency distribution of TAOF. Understanding the nature of the distribution of TAOF will inform the most appropriate analysis method to be used in the RCT. If the distribution is normal, or can adequately be transformed to normality, the standard deviations (SDs) of TAOF in each treatment group along with means will be calculated. The SD estimates may then be used to estimate the sample size required in the RCT. The other requirement for this sample size estimation is an understanding of what the minimal clinically important difference (MCID) in TAOF is. As this is a new and specific measure, clinical members of the team will use this preliminary TAOF data to determine a consensus MCID for TAOF. Given this information, preliminary analyses will be undertaken to detect any difference, if any, in TAOF.

Similar analyses will be undertaken with respect of secondary objectives, hospital length of stay, and tolerability though these will not inform sample size. With respect to tolerability, this preliminary data will be used to assess possible tolerability indices that may be used in the main RCT.

At the end of the pilot, a qualitative judgement will be made by all investigators as to whether the it is appropriate to proceed, in line with Abbott (2014)[23]:

- Insurmountable problems with necessary processes: stop
- Problems identified are surmountable: modifications will be necessary in full study protocol, and further pilot testing may be necessary
- Few or no major problems: a full study can proceed without modifications or further testing

4. Translation to Changes in Clinical Practice

To date, there have been no studies in patients with bronchiolitis to assess which nasogastric fluid regime (intermittent bolus or continuous nasogastric fluids) leads to a quicker return to oral feeding and a shorter duration of inpatient stay.

The NOBRO study will be the first of its kind to directly compare nasogastric fluid practices in patients with bronchiolitis. We hope that the study will help guide clinicians when determining what nasogastric fluid to prescribe for patients with bronchiolitis. We also hope that the results of the study will help supplement best practice guidelines used by our hospital with regards to the management of patients with bronchiolitis. We also hope that this research will help to inform clinicians working in other hospital and health settings and perhaps generate similar research trials.

We hope that this pilot trial will help us determine the following before proceeding with a larger scale randomised control trial:

- The validity of our research methods and primary outcome.
- Any barriers to proceeding with a larger scale randomised control trial.
- Preliminary data to assist with a power calculation for the larger scale randomised control trial

5. Timeline

After ethics and governance approvals, we aim to then start regular education sessions and awareness campaigns for the study for nursing, medical and administration staff over the following month.

We aim to start recruiting patients in January 2020 and aim to continue recruiting patients for the following 2 months.

After outcome data has been collected, we aim to collate our results, perform statistical analyses and report data outcomes over the following 2 months.

After analysing and reporting on the results of this pilot trial, we hope to proceed with running a larger, high powered randomised control trial to run for likely 18 months in duration.

6. Funding and Resources

The Paediatric Critical Care Research Group (PCCRG) will provide in-kind resources for a research assistant in this study. The research assistants from the Paediatric Critical Care Research Group are established researchers with experience in clinical trials in the paediatric environment.

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